Depression in adults: treatment and management

Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

ID	Type	Stakeholder	Document	Page No	Line No	Comments	Developer's response

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

1	SH	Stakeholder coalition	All evidence reviews	General	General	Long-term follow-up data We welcome the recognition in this draft that long-term effectiveness is indeed an important outcome and applaud the efforts made to include such data where it was available. We regret to learn that very few studies of those included in the reviews report long-term follow-up data. We acknowledge, therefore, the decision that prioritisation of these outcomes is not possible. However, we notice that this was not consistently followed through. We do not think it appropriate and ethical practice to refer to some but not all of these outcomes and ask for this to be amended. For example, as highlighted in Table 13 on p.39 of Evidence Review B, for less severe depression, 4 studies showed a statistically significant effect at their respective follow-up point. However, only the two studies on group CBT and the one study on group problem-solving were considered whereas the study in STPP was not. Another example pertains to the further-line treatment recommendations, where the statistically significant benefit of LTPP at follow-up was not considered whilst for other treatments it was (Evidence Review D, p. 113).Moreover, it appears that only studies that yielded a statistically significant effect at the relevant follow-up point were considered, whilst those that did not find an effect were not, especially in the reviews for new episodes. Again, the findings of all of these studies would need to be taken into account as they provide important information as to whether a treatment has been found to lose its effect after treatment ended. For example, for less severe depression, 55 out of 127 studies included in the NMA had follow-up data (43%). Of	Thank you for your comment. The committee agree that long-term follow-up is important and share your disappointment that this is not more routinely measured and reported. Long-term follow-up is included in the research recommendations in the guideline. As highlighted in table 13 of Evidence report B and the corresponding 'committee discussion of the evidence' section, group CBT and group problem-solving showed benefits on depression symptoms at follow-up compared to treatment as usual, and CBT with antidepressants showed benefits compared to antidepressants alone. The committee agreed that this provided a useful indication that the results seen from the NMA for group CBT and group problem-solving may be maintained over a longer period. A 6-month follow-up of short-term psychodynamic psychotherapy (STPP) compared to non-directive counselling found a benefit for STPP for the outcomes of depression symptoms and remission at 6 months, but the committee noted that this small amount of evidence did not change their view, based on the NMA results, that these treatments had similar levels of

						those, 4 were found to show statistically significant effects at their respective follow-up point (Evidence B, Table 13, p.39). This means that 51 studies did not show a statistically significant effect. Similarly, for those with more severe depression, 27 studies were identified with follow-up data and, out of those, 8 were found to have a statistically significant effect (Evidence Review B, Table 27, p.109). Again, this means that 19 studies showed no sustained effect. We cannot find where these important findings (of lack of treatment efficacy in longer-term follow ups) were both emphasised and considered in terms of the treatment recommendations. Given the importance of long term follow up data, both in demonstrating enduring clinical benefits and more accurate indications of cost effectiveness, we are concerned that it is not mentioned in the section on research recommendations. As stressed within the various documents of this draft, two thirds of patients do not currently benefit from treatments. This equates to more than 2 million individuals in the UK each year. As such we would want the guideline to stress that any studies concerning depression should aim to include and report their outcomes over the long-term follow-up.	effectiveness. In the further-line treatment evidence report (D), under the 'committee discussion of the evidence' section the committee highlight the sparsity of follow-up data from further-line treatment studies. The committee noted that a small number of studies could be combined in meta-analyses for outcomes up to 6 months after endpoint, however, beyond this point it was predominantly single-study analyses. The committee considered this limited evidence and noted that a small number of studies showed evidence for sustained benefits on depression outcomes associated with augmenting antidepressants with CBT (up to 40 months), IPT (up to 12 months), short-term psychodynamic psychotherapy (up to 12 months), and long-term psychodynamic psychotherapy (up to 2 years). The committee agreed that the effects on depression outcomes at follow-up were generally in line with the effects observed at endpoint, and this strengthened their confidence in the recommendations.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

2	SH	Stakeholder coalition	All evidence reviews	General	General	Quality of life and functioning outcomes We are particularly pleased about the inclusion of functioning and quality of life measures. We regret to learn that of those studies included in the reviews, only a few had reported on these outcomes. We would like to suggest that a sentence be added in the relevant sections in all documents referring to the importance of (a) future studies reporting on such outcomes, and (b) existing studies to publish these findings where the data was collected, especially given that these are the measures of greatest priority to service users.	Thank you for your comment. The committee agree that quality of life and functioning outcomes are important. The committee noted the limited evidence for these outcomes and included quality of life and functioning outcomes for the research recommendations in the guideline.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

3	SH	Stakeholder coalition	All evidence reviews	General	General	Appropriate methods for determining treatment effect We are pleased that the third draft of the guideline includes continuous changes in scores on depression scales in every review question. However, we remain concerned that full recovery is still a critical outcome and that partial recovery, as we had advised, has not been added. It furthermore appears that the decisions for treatment recommendation have been influenced by these recovery rates. Moreover, the economic analysis focuses primarily on full remission. As previously pointed out, full remission or recovery from a severe depression baseline might be difficult or impossible to achieve, yet smaller positive changes might still be clinically meaningful. Treatment which helps some service users move from severe depression to mild or moderate depression (i.e., 'partial recovery'), for example, would be worth recommending. Failing to do so risks the wellbeing of service users who may otherwise be denied these potentially transformative changes. We therefore recommend refining the interpretation of the evidence to inform treatment recommendation accordingly.	Thank you for your comment. The guideline includes continuous changes in scores on depression scales as a critical outcome for every treatment question, which will show changes for people who have both fully and partially recovered. This was agreed by the committee to be a better way to capture this data than the use of a dichotomous outcome for partial recovery. The economic analysis does not focus primarily on full remission. The economic analysis of treatments for a new episode of less severe depression has modelled only response (defined as at least 50% improvement in depressive symptoms) which may reflect full remission or not (depending on the starting point of depressive symptoms). Full remission was not considered in this population, due to lack of sufficient data in the respective NMA. The economic analysis of treatments for a new episode of more severe depression has considered full remission (i.e., a score on a depressive symptom scale that was below the cut-off point for a depression diagnosis) and also response that did not reach full remission (i.e. 50% improvement in depressive symptoms that

							was however not adequate to reach the scale cut-off point characterising full remission). The utility data attached to the model health states also reflected, as relevant, symptom improvement not reaching remission and/or symptom improvement reaching remission. Therefore, partial remission has been considered in the economic analysis for both populations.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

4	SH	UK Council for Psychotherapy	All evidence reviews	General	General	Long-term follow-up data We welcome the recognition in this draft that long-term effectiveness is indeed an important outcome and applaud the efforts made to include such data where it was available. We regret to learn that very few studies of those included in the reviews report long-term follow-up data. We acknowledge, therefore, the decision that prioritisation of these outcomes is not possible. However, we notice that this was not consistently followed through. We do not think it appropriate and ethical practice to refer to some but not all of these outcomes and ask for this to be amended. For example, as highlighted in Table 13 on p.39 of Evidence Review B, for less severe depression, 4 studies showed a statistically significant effect at their respective follow-up point. However, only the two studies on group CBT and the one study on group problem-solving were considered whereas the study in short-term psychodynamic psychotherapy (STPP) was not. Another example pertains to the further-line treatment recommendations, where the statistically significant benefit of long-term psychodynamic psychotherapy (LTPP) at follow-up was not considered whilst for other treatments it was (Evidence Review D, p. 113).Moreover, it appears that only studies that yielded a statistically significant effect at the relevant follow-up point were considered, whilst those that did not find an effect were not, especially in the reviews for new episodes. Again, the findings of all of these studies would need to be taken into account as they provide important information as to whether a treatment has been found to lose its effect after treatment ended. For example, for less severe	Thank you for your comment. The committee agree that long-term follow-up is important and share your disappointment that this is not more routinely measured and reported. Long-term follow-up is included in the research recommendations in the guideline. As highlighted in table 13 of Evidence report B and the corresponding 'committee discussion of the evidence' section, group CBT and group problem-solving showed benefits on depression symptoms at follow-up compared to treatment as usual, and CBT with antidepressants showed benefits compared to antidepressants alone. The committee agreed that this provided a useful indication that the results seen from the NMA for group CBT and group problem-solving may be maintained over a longer period. A 6-month follow-up of short-term psychodynamic psychotherapy (STPP) compared to non-directive counselling found a benefit for STPP for the outcomes of depression symptoms and remission at 6 months, but the committee noted that this small amount of evidence did not change their view, based on the NMA results, that these treatments had similar levels of

						depression, 55 out of 127 studies included in the network meta-analysis (NMA) had follow-up data (43%). Of those, 4 were found to show statistically significant effects at their respective follow-up point (Evidence B, Table 13, p.39). This means that 51 studies did not show a statistically significant effect. Similarly, for those with more severe depression, 27 studies were identified with follow-up data and, out of those, 8 were found to have a statistically significant effect (Evidence Review B, Table 27, p.109). Again, this means that 19 studies showed no sustained effect. We cannot find where these important findings (of lack of treatment efficacy in longer-term follow- ups) were both emphasised and considered in terms of the treatment recommendations. Given the importance of long-term follow-up data, both in demonstrating enduring clinical benefits and more accurate indications of cost effectiveness, we are concerned that it is not mentioned in the section on research recommendations. As stressed within the various documents of this draft, two thirds of patients do not currently benefit from treatments. This equates to more than 2 million individuals in the UK each year. As such we would want the guideline to stress that any studies concerning depression should aim to include and report their outcomes over the long-term follow-up.	effectiveness. In the further-line treatment evidence report (D), under the 'committee discussion of the evidence' section the committee highlight the sparsity of follow-up data from further-line treatment studies. The committee noted that a small number of studies could be combined in meta-analyses for outcomes up to 6 months after endpoint, however, beyond this point it was predominantly single-study analyses. The committee considered this limited evidence and noted that a small number of studies showed evidence for sustained benefits on depression outcomes associated with augmenting antidepressants with CBT (up to 40 months), IPT (up to 12 months), short-term psychodynamic psychotherapy (up to 12 months), and long-term psychodynamic psychotherapy (up to 2 years). The committee agreed that the effects on depression outcomes at follow-up were generally in line with the effects observed at endpoint, and this strengthened their confidence in the recommendations.

5	SH	Stakeholder coalition	All review	General	General	Limiting the evidence to RCTs As stressed during the previous stakeholder consultations, given the various limitations of RCTs specifically in the field of mental health that have been pointed out repeatedly by experts from many scientific disciplines and positions - irrespective of any modality allegiance - creating sound policy requires that we draw on a diverse range of evidence. We are disappointed that the evidence reviewed in this draft guideline continues to be limited to RCTs. We strongly uphold that this is a restrictive science and therefore leads to limiting patients' choice. We would like to signpost you to the NICE manual where it is states: "In order to formulate recommendations, the guideline Committee needs to consider a range of evidence about what works generally, why it works, and what might work (and how) in specific circumstances. The Committee needs evidence from multiple sources, extracted for different purposes and by different methods." (p.67)We would like to stress that the exclusion of available "important and well-known" UK-based pragmatic trials and real-world data collected from millions of patients treated for depression within the NHS in the very setting where the evidence from the guideline must closely followed, cannot be justified.The guideline itself makes reference to these studies, however, only appears to consider these partially to aid interpretation of clinical and cost effectiveness. We therefore ask that this draft is amended by the inclusion of such evidence from real-world data and pragmatic trials into the review. At the very least, we ask that their results are not merely used partially and selectively in order to justify the	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. The committee were also aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to name all UK-based studies which were excluded on this basis but which the

						arbitrary treatment hierarchy (e.g. p. 141, l. 21f; and p.146, l.31f of the evidence review B).	committee were aware of when making recommendations. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.

6	SH	Society for Psychotherapy Research	All reviews	General	General	Limiting evidence to RCTs only As per your repeated responses to this critique point of ours, we acknowledge that the guideline committee follows the guidance set out in the NICE manual, in limiting evidence to RCTs in this guideline. However, we would like to stress, once again, our concern with a guideline that limits itself to evidence derived from RCTs. As stressed during all stakeholder consultations, given the various limitations of RCTs specifically in the field of mental health that have been pointed out repeatedly by experts from many scientific disciplines and positions irrespective of therapeutic modality, creating sound policy requires that we draw on a diverse range of evidence. We would like to signpost you to the NICE manual where it is states: “In order to formulate recommendations, the guideline Committee needs to consider a range of evidence about what works generally, why it works, and what might work (and how) in specific circumstances. The Committee needs evidence from multiple sources, extracted for different purposes and by different methods.” (p.67)We would like to stress that there exist important UK-based pragmatic trials and real-world data. Given the apparent lack of evidence from the UK (for example, on p.80 (l.21) of evidence review B only 34 of the included RCTs in the NMA were UK-based, and as emphasised throughout the various documents, the systematic search for UK-based health economic studies produced only a few relevant studies) it would only make sense to add important evidence from the studies that we have at our disposal, and that are most relevant not only in terms of clinical evidence,	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. The committee were also aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to name all UK-based studies which were excluded on this basis but which the

						but also in terms of providing important information about cost-effectiveness. We would like to point out that, as stated on p. 58, l 45f of the evidence review B document, the committee decided despite their exclusion to take some of the results of these "important and well known" pragmatic trials into account. However, it appears that the committee was rather partial with respect to which results they were taking into account when considering treatment recommendation, seemingly considering the effects of CBT and behavioural treatments in order to justify their superiority (see for example p. 141, l. 21f; p.146, l.31f). We therefore ask to amend this draft to include a more balanced consideration of pragmatic trials in order to adhere to the scientific principles of consistency and transparency. Given the lack of studies included in the guideline review from the UK/conducted within the NHS, it is particularly relevant that there is also real-world data collected through routine outcome monitoring (i.e., the IAPT data set) collected from millions of patients treated for depression within the NHS and carried out in the very setting where the evidence from the guideline will be applied. As such, it seems absurd not to include these in full in the present review, especially when this guideline continues to emphasise the need to for health care professionals to collect ROM data (see e.g., guideline, p. 12, p. 84).We therefore ask to amend this draft by including such evidence from real-world data and pragmatic trials.	committee were aware of when making recommendations. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

7	SH	Society for Psychotherapy Research	Economic analyses for Evidence review D, E, F	General	General	Economic analyses for more complex depression We question why the committee decided not to develop economic models for the other review questions, in particular further-line treatment, which includes complex depression. The reason given stated: “because the committee agreed that other topics were higher priorities for economic evaluation”. We do consider a robust cost analysis for the treatments of more complex forms of depression to be a priority. In addition, we are concerned with the fact that in the absence of the economic modelling, the committee decided to refer to the findings from the economic modelling carried out for first-line treatment. See, for example: “The committee acknowledged that the economic evidence in this area is rather sparse and has limitations and decided to draw additional information from the economic analysis of treatments of a new depressive episode that was undertaken for the guideline” (evidence review D, p. 180).	Thank you for your comment. As for all other review questions, systematic reviews of economic literature for interventions for further line treatment of depression, chronic depression and depression with a co-existing personality disorder were also conducted. The systematic review of economic evaluations of interventions for further-line treatment included 17 studies that met inclusion criteria. These studies were considered alongside respective clinical evidence when formulating recommendations. No economic studies on chronic depression and depression with a co-existing personality disorder were identified. Regarding primary economic modelling, this was not possible to conduct across all areas due to the model complexity required and time restrictions. Thus, in accordance with NICE guideline methods, an economic plan was prepared in collaboration with the committee, which prioritised review questions for primary economic analysis, using as criteria the expected resource implications as well as the quality and the relevance of available clinical and economic evidence. Using these criteria, the area of treatments for a new episode of depression as well as the area of

							relapse prevention were identified as high priorities for de-novo economic modelling (as they were considered to have major resource implications and clinical and economic data were of adequate quality to allow robust modelling to be conducted). The area of further line treatment was not prioritised for de-novo economic modelling, however, the committee agreed that this is an area that needs to be considered for primary economic analysis in future guideline updates. It is noted, though, that this area is expected to require complex economic modelling, that may not be possible to capture all relevant sub-groups, as this area includes a heterogeneous population that may follow very diverse treatment sequences and pathways. When formulating recommendations, the committee considered the existing clinical and economic evidence in the area of further line treatment. As the economic evidence in this area was limited and of variant quality, the committee looked at the economic evidence on treatments for a new episode of depression only to check and confirm whether it supports recommendations for further-line treatment, as an intervention that is cost-

							effective in treating a new episode gives more confidence that it may also be cost-effective in further-line treatment of depression.

8	SH	UK Council for Psychotherapy	Economic Analysis, Evidence Review B	General	General	Treatment ranking – as derived from NMA If all assumptions are met, NMA is a useful technique for the purpose of ranking treatment outcome. As stressed in this guideline as well as in the NICE method guideline, it is one of the primary reasons as to why NICE recommends its usage. However, treatment ranking can be affected by small differences that are not clinically important (Faltinsen et al., 2018), which indeed seems to be the case in the current analyses.Furthermore, treatment rankings by NICE based on the NMA may be affected by small differences that are not clinically important. In more severe depression, for example, bias-adjusted analysis for comparison with placebo yielded a standardized mean difference (SMD) of -0.78 (rank: 17.28) for individual CBT/CT and of -0.58 (rank: 22.08) for short-term psychodynamic therapy (STPP), corresponding to a difference in effect sizes of -0.20. This difference is below the difference defined by NICE as clinically important (SMD=0.50), (Evidence Review B, p. 14) but rankings differ considerably. This applies to other rankings as well, e.g. of individual interpersonal therapy (IPT, SMD=-0.50 , rank 16.93) and individual CBT/CT (SMD= -0.73, rank 13.14) compared to TAU in less severe depression and also to the ranking of CT/CBT and counselling in more severe depression, with SMDs of -0.78 (rank 17.28) and -0.67 (rank 19.96) compared to pill placebo, showing no clinically significant differences between individual CT/CBT and counselling (difference in SMD=-0.11).For CBT “good evidence” of efficacy was concluded by NICE, for STPP the conclusion was that there was only “some evidence” of efficacy. If this judgment is based on the number of studies	Thank you for your comment. The committee agreed that treatment rankings in the NMA suggested uncertainty in the results. However, the treatment rankings in the NMA were not the only criterion when assessing the evidence and making recommendations. Regarding the results of the NMAs, the committee considered the mean effects of each treatment class vs the reference treatment, the uncertainty around them (as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of the pairwise meta-analysis. The committee also considered the relative cost-effectiveness of interventions, as suggested by the guideline economic analysis. Other factors such as implementation issues (step 2 and current structure of IAPT services), treatment acceptability (expressed in discontinuation rates, which were incorporated into the economic analysis), side effects (drugs), and applicability of the evidence in the UK context (relating to problem solving, and

						available, it is necessary to emphasise that a larger number of studies does not imply higher efficacy. Following, for example, Chambless and Hollon (1998), two RCTs are sufficient for a treatment to be classified as efficacious. In the Evidence Review B, the committee concedes that the 95% credible intervals (CrI) around the rankings of interventions were characterised by 'considerable uncertainty' (p.61). For example, the mean ranking of group CBT, which was shown to be the most cost-effective intervention, was 2.76; however, its 95% CrI were 1 to 12, suggesting high uncertainty around the result for group CBT. Similar uncertainty was shown for all interventions included in the analysis. In other words, the Crls show that the NMA rankings are 'uncertain' and thus likely should be treated with significant caution.	also acupuncture and antidepressant combination) were also taken into consideration. All this information on the evidence and committee's considerations are provided in Evidence review B. Regarding more severe depression, the committee agreed that the difference in the mean effects (SMD) between individual CT/CBT and short-term psychodynamic psychotherapy (STPP) on the SMD outcome was small (-0.20). The magnitude of the difference in the mean ranking (by almost 5 places) cannot be judged as 'large' in absolute terms but should take into account the fact that the ranking involved 43 treatment classes. The difference in ranking can only be judged in relative terms. For example, if only individual CT/CBT and STPP were included in the ranking, their maximum difference in the mean ranking could be 1 (if the one intervention always ranked first and the other always ranked second), and this would be a very considerable difference in their mean ranking, although it would only be 1 place. In any case, the difference in ranking between individual CT/CBT was not

							determined exclusively by their difference in mean effects, but also by the uncertainty around each treatment's mean effect: the 95%CrI around the relative effect of individual CT/CBT vs TAU were narrower than those around the relative effect of STPP vs TAU. It is also noted that the former did not cross the no effect line, whereas the latter did. Similar observations apply to the comparison of the results between individual CT/CBT and counselling in more severe depression, as well as individual CT/CBT and IPT in less severe depression (where the ranking involved 32 treatment classes). It should be noted that the committee made recommendations on the above interventions taking into account their relative cost-effectiveness. STPP was found to be less cost-effective than GP care (reference treatment) in both less and more severe depression, and this is why it was ranked in low places in Tables 1 and 2 of the guideline. IPT in less severe depression ranked as the 12th most cost-effective option out of the 16 interventions, just

							above GP care (reference treatment). In more severe depression, it ranked below GP care (i.e., it was found to be less cost-effective than GP care). Counselling in less severe depression was also found to be less cost-effective than GP care. In more severe depression it ranked as the 14th most cost-effective intervention out of the 20, just above GP care. Judgements on 'good' evidence or 'some evidence' were made on the basis of 1) the magnitude of the effect and 2) the available evidence base regarding the number of people tested on each treatment, rather than the number of trials testing each treatment. The committee felt more confident to recommend treatments that had been tested on several hundreds of people and found to be effective (such as individual CT/CBT) rather than interventions tested on few people and found to be effective. For this reason, the committee decided not to consider interventions that had been tested on N<50 people, even though some of them (e.g., combined CT/CBT group + exercise group in less severe depression; mindfulness or meditation group in more severe

							depression) had shown very high effects in the NMA. In less severe depression, group CBT showed wide 95%CrI around its mean ranking in the economic analysis, however it is noted that these were very skewed and that in most iterations group CBT ranked in a high place among other treatments (since its mean ranking was 2.76 in an analysis involving 16 interventions). It is noted that group CBT was found to be dominant in its comparison with group BA (which ranked 2nd most cost-effective), i.e., it was less costly and more effective, and, in their in-between comparison, group CBT had an 85% probability of being more cost-effective than group BA (data not shown in the report). Similarly, it was shown to have an ICER of £1,466/QALY versus group exercise (3rd most cost-effective option), which is well below the NICE lower cost-effectiveness threshold of £20,000/QALY, and a probability of being cost-effective of 81%. Therefore, the uncertainty expressed in the rankings reflects uncertainty in the overall results across the 16 interventions included in the analysis, but not necessarily uncertainty in the relative cost-

							effectiveness of each intervention within the analysis.

9	SH	The Federation of Holistic Therapists	Evidence review D	6	General	Depression evidence review I (nice.org.uk) - Patient choice review question - What are the facilitators and barriers that can enhance or inhibit choice of treatment for adults with depression? (p.6) "there are a range of pharmacological treatments and physical interventions such as electroconvulsive therapy and acupuncture. Many of these treatments are often used in combination, and may be delivered in a variety of settings (for example, individually or in groups, in primary care or secondary care), adding further complexity to the choice of treatment." There is significant evidence of the benefits to mental health from touch therapies. However, these therapies are not yet routinely used in the UK and Northern Ireland within the public and National Health Services (NHS), with access often triggered by the recipient rather than a medical professional. As highlighted earlier, NICE has previously stated that the existing body of evidence on the legitimacy and efficacy of touch therapy as a form of treatment is not robust enough with large enough sample sizes. It is therefore recommended that a number of trials are carried out which expect will demonstrate the benefits and value for money of these treatments versus those traditionally used in the UK. It is also recommended that integrated health improvements should be seen as part of the toolkit for solutions and social prescribing with existing medical services to support the NHS - with a clear strategy, policy and funding for Primary Care Trusts to access. Qualified therapists undertake in excess of 90 hours of training in anatomy physiology and pathologies as part of their nationally regulated qualification for entry into	Thank you for your comment. The committee did not consider touch therapies to be interventions that were in regular clinical use for the treatment of depression. Therefore, these interventions were not specified in any of the review protocols. As such the evidence on touch therapies has not been appraised and we are not able to make any recommendations on their use.

						the workforce. They subsequently undertake additional continual professional development training in cancer touch therapy, stress management and other touch therapies. The sector is well placed to support the NHS and Public Health to relieve issues and symptoms relating to Functional neurological disorders (FND) and physical health and wellbeing through a range of therapies, improved selfcare and preventative healthcare.	
10	SH	NHS England and Improvement	Evidence review	Evidence review F	General	The evidence base for the recommendation for 'Depression with coexisting personality disorder' is weak.	Thank you for your comment. The committee noted that although, based on the evidence, treatments combining an antidepressant with a high-intensity psychological intervention appeared to be the most effective, the evidence base for this question was limited in volume, with only small RCTs of low or very low quality. Consequently, they were only able to recommend combination treatment be 'considered' and they were not able to recommend a specific antidepressant or

							psychological therapy but agreed that this would depend on the person's preference.
11	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Evidence Review 2	18	Table 1	It does not look as though Guided Self Help as an intervention is part of this. The name/content of those interventions does not fit within the Psychological Wellbeing Practitioner/guided self-help remit (except for Computerised Cognitive Behaviour Therapy (cCBT) with support). It is not clear if data on which this recommendation is based takes into consideration any Increasing Access to Psychological Therapies (IAPT) specific therapies/ways of working/stepped care model. The recommendations appear ambiguous in terms of who would be delivering those interventions given that the table content does not include the scope of practice of Psychological Wellbeing Practitioners.	Thank you for your comment. Different self-help approaches (with or without support) were searched for and were eligible for inclusion. In addition to computerised approaches, there are also RCTs of cognitive bibliotherapy, behavioural bibliotherapy, expressive writing, mindfulness meditation CD, relaxation training CD, and third-wave cognitive therapy CD, included in the network meta-analyses (NMAs) for treatment of a new episode of depression. One intervention per class was used as an exemplar in the economic analysis, as it was not feasible to model all interventions included in the NMA. Computerised CBT (cCBT) was selected as the exemplar from the class of self-help with support as it had a large evidence base and a high effect compared with other interventions in the

							same class. Thus, the clinical evidence and resource use data used to inform the economic analysis were specific to cCBT; consequently, the results of the economic analysis were specific to cCBT (but could also be extrapolated to any other intervention with similar acceptability, effectiveness and resource use). However, the treatment class effect size for self-help (with or without support) that was estimated from the NMA and reported in the clinical evidence sections of evidence review B, was informed by evidence from all interventions included in the treatment class. In addition, individual intervention effects have been reported in the evidence review B for all interventions within each class for the SMD outcome (for both less and more severe depression). In response to stakeholder comments, self-help with support has been relabelled as guided self-help, has been placed earlier in the treatment pathway, and the description of guided self-help has been amended to clarify that this is not restricted to cCBT.

12	SH	University of South Wales	Evidence review A	30	34	No distinction is made between studies that have used 'gold standard' diagnostic interviews to determine the presence of depression according to DSM or ICD and those that have used only a psychometric test. The former studies should be the foundation for recommendations, low quality studies should not be added to the mix. Service delivery assessments are almost invariably based solely on psychometric test scores alone and it should be made clear that any recommendations flowing from this data should be given much less weighting than given to therapies evaluated in rct's.	Thank you for your comment. As pre-specified in the review protocols, the population included adults with clinically important symptoms of depression (as defined by a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by baseline depression scores on validated scales). Studies using depression symptom scales were included (in addition to studies that limited inclusion to those with a diagnosis of depression) on the basis that such scales are widely used in RCT research and clinical practice and are validated in the diagnosis of depression and the assessment of depression symptom severity. The committee were concerned that excluding studies that did not use diagnostic interviews would result in the exclusion of a large number of studies, would have a disproportionate impact on the evidence base for some interventions for example for self-help studies, and would not allow examination of those with subthreshold symptoms of depression which were included in the review question and protocol.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

13	SH	UK Council for Psychotherapy	Evidence Review B	8	4	Couple interventions, including behavioural couple's therapy, were considered only in pairwise comparisons (and not included in the network meta-analysis) due to the incorrect assumption (see earlier comment 8) that they were considered more appropriate for subgroups of adults with depression, namely for people with problems in their relationship with their partner. We request that the studies excluded on this basis are included and that couples therapy.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).
14	SH	Association for Family Therapy and Systemic Practice	Evidence Review B	8	4	Couple interventions, including behavioural couple's therapy, were considered only in pairwise comparisons (and not included in the network meta-analysis) due to the incorrect assumption (see earlier comment 8) that they were considered more appropriate for subgroups of adults with depression, namely for people with problems in their relationship with their partner. We request that the studies excluded on this basis are included and that couples therapy.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).
15	SH	UK Council for Psychotherapy	Evidence Review B	9	11	Table 1: Summary of the protocol (PICO table) contains what appear to be an error. Behavioural couple therapy instead of being listed as a psychological intervention was listed as a psychosocial intervention.	Thank you for your comment. This was a copy and paste error in creating the summary of the protocol from the full protocol in Appendix A. It has now been amended.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

16	SH	Association for Family Therapy and Systemic Practice	Evidence Review B	9	11	Table 1: Summary of the protocol (PICO table) contains what appear to be an error. Behavioural couple therapy instead of being listed as a psychological intervention was listed as a psychosocial intervention.	Thank you for your comment. This was a copy and paste error in creating the summary of the protocol from the full protocol in Appendix A. It has now been amended.

17	SH	Society for Psychotherapy Research	Evidence review B	10	15	The distinction between less severe and more severe depression We uphold that the categorisation system of first episode depression into 'less severe' and 'more severe' is concerning. As stated in all previous responses made by us to the prior consultations, there is no evidence of either the methodological/statistical or clinical validity of such a dichotomisation of individuals suffering from depression. We agree with the guideline authors that many years of clinical practice and research have yielded that depression is not a unitary phenomenon. And while, as one of the authors you cite put it: "no standardized nomenclature for different depression severity levels is agreed on" most researchers and clinicians have a common understanding that depression severity levels fall into the three broad categories of mild, moderate and severe (Wahl et al., 2014, p. 82). Indeed, the guideline itself refers to these as "traditional subcategories" (e.g., p.10, l.26). So why would the guideline divert from a tradition that has found both some clinical resonance as well as psychometric validity and reliability? In your last response to this concern of ours, you responded that "these have been updated and are now based on published work". You cite the following: Carmody, 2006; Rush, 2003; Uher, 2008; Wahl, 2014, and indicate on p. 10 l. 18 that "these thresholds were derived using standardization of depression measurement crosswalk tables" from the four referenced studies. Firstly, it is not clear which crosswalk table you have used as there appear to be differences between the four studies that you cite. Secondly, your categorisation into two groups is not based on,	Thank you for your comment. The committee considered the current NICE classifications of mild to moderate and moderate to severe depression and agreed that although these classifications have been adopted quite widely there is potential uncertainty with regards to the management of moderate depression. The committee agreed that a dichotomy of less and more severe depression was clearer, and the guideline includes definitions (that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression includes the traditional categories of moderate and severe depression) in order to improve practical utility. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line

						or recommended by, any of these authors. Wahl et al (2014), which is the latest published study, provide threshold values for mild, moderate and severe depression (see their Table 3). According to them the cut-off for moderate depression on the PHQ-9 is 10 and for severe depression 20. Your anchor point of 16 falls in the middle of that. Moreover, it appears you have changed that cut-off from 18 in the second draft guideline. Your justification for setting the anchor point at such a value was "on the basis of alignment with the clinical judgement of the committee and eligibility criteria in published studies." We would like to point out that it does not appear to be based on criteria in these published studies, and that seeking clinical judgement on such a psychometric matter and decision is highly questionable. We stress again, that any treatment recommendations based on methodological choices that have not been validated need to be viewed with caution.	presentations of depression are managed in primary care). Based on this distinction, an anchor point of 16 on the PHQ-9 was selected as the cut-off between less severe and more severe depression, on the basis of alignment with the clinical judgement of the committee and eligibility criteria in the studies included in the NMAs. The change in cut-offs between the current and earlier versions of this updated guidance was based on previous stakeholder concerns that because many of the included studies reported a mean severity score that was very close to the threshold the distinction appeared arbitrary. The committee also considered it more appropriate to group subthreshold and less severe, and moderate and severe, as this was more in line with how depression is conceptualised and with the distinction between different treatment options that might be considered appropriate. Published standardization of depression measurement crosswalk tables (Carmody 2006; Rush 2003; Uher 2008; Wahl 2014) were used in order to 'read-across' different symptom severity scales that were used in different studies. All of these crosswalk

							papers were referred to as they included different scale comparisons.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

18	SH	UK Council for Psychotherapy	Evidence Review B	13	39	Here again it is wrongly stated that couple interventions are only appropriate for sub-groups of people with depression specifically those with problems in the relationship with their partner leading to the inappropriate exclusion of some studies and the couple evidence not being included in the NMA.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).
19	SH	Association for Family Therapy and Systemic Practice	Evidence Review B	13	39	It is wrongly stated that couple interventions are only appropriate for sub-groups of people with depression specifically those with problems in the relationship with their partner leading to the inappropriate exclusion of some studies and the couple evidence not being included in the NMA.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).
20	SH	UK Council for Psychotherapy	Evidence Review B	14	23	As comment above Here again it is wrongly stated that couple interventions are only appropriate for sub-groups of people with depression specifically those with problems in the relationship with their partner leading to the inappropriate exclusion of some studies and the couple evidence not being included in the NMA.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in

							the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).
21	SH	Association for Family Therapy and Systemic Practice	Evidence Review B	14	23	As comment above	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).
22	SH	UK Council for Psychotherapy	Evidence Review B	41	5	As comment above Here again it is wrongly stated that couple interventions are only appropriate for sub-groups of people with depression specifically those with problems in the relationship with their partner leading to the inappropriate exclusion of some studies and the couple evidence not being included in the NMA.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

23	SH	Association for Family Therapy and Systemic Practice	Evidence Review B	41	5	As comment above	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA).

24	SH	University of Exeter Medical School	Evidence Review B	58	43	THIS COMMENT IS IDENTICAL TO THAT REFERRING TO PAGE 147 BUT IS REPEATED HERE AS PER THE INSTRUCTIONS REGARDING NOT CROSS REFERENCING COMMENTS The statement: "the committee were aware that a number of important and well-known, often pragmatic trials, were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression…... the committee used their knowledge of these trials in the round when interpreting the evidence from the systematic review and making recommendations" is genuinely perplexing. The trials referred to (and cited specifically elsewhere in the guideline evidence reviews) are NHS facing trials of real world populations likely to be encountered by clinicians delivering treatments. They also represent the largest number of people with depression. Most of these trials were funded by public agencies supported by taxpayers' money (NIHR for example). Many hundreds of people with depression volunteered to suspend their right to treatment choice in order to participate randomised treatment allocation. It is simply not enough to cite these trials and the selfless efforts of these participant populations as 'in the round' evidence. These are the people who most need help and are the population who present daily to primary care. The £2m NIHR HTA COBRA trial of two psychological treatments, for example, included 440 participants with diagnosed depression. NICE has chosen to exclude these data (including 18m follow up) because most of the participants were also taking antidepressants as a so called 'first line' treatment (even though this treatment was not working). This is hardly	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

						surprising, given that they were people with multiple episodes of depression and histories of treatment lasting over 300 weeks prior to the trial. This is the usual behaviour of people struggling to overcome and manage their mood disorders. The evidence review criteria used by NICE has instead, derived evidence from an artificial cohort of participants that in no way represent the clinical and behavioural treatment seeking characteristics of the vast majority of people with depression. Had the COBRA trial excluded these people or asked them to halt their pharmacological treatment we would have a) struggled to find people who were not treating their depression, b) faced the accurate critique that the trial was not generalisable to the public at large c) faced real ethical difficulties in removing existing treatments from vulnerable adults. As noted in a previous comment, the decision to exclude this trial has removed the health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world. In summary, the decision to exclude some of the largest, pragmatic health services research trials from this guideline cannot be assuaged by a side comment that they somehow back up the committee decisions. What would NICE have done, one wonders had these excluded trials NOT been	estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

						consistent with the evidence reviews? Tax payers' money, patient volunteers and the efforts of hundreds of health services researchers cannot be dismissed in this cavalier manner. It also makes a mockery of the extensive peer review systems in place including at funder, trial governance and publication levels to treat this scientific endeavour with such disdain. The guideline has based its decision making on artificial criteria that do not represent the populations and the clinical situations faced by the NHS. We face a post-pandemic mental health emergency. These HSR pragmatic trials should be included as exactly the type of evidence that we are now so desperate to work with in order to advise our long-suffering and harassed clinical colleagues in their decision making. And of course, these data should be in the public domain so that patients and their closest significant others are enabled to make life changing decisions about their care.	used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

25	SH	Society for Psychotherapy Research	Evidence review B	67	7	Differentiation between interventions – the role of qualitative evidence The committee call for 'identifying the mode of action of psychological interventions' for less severe depression as this would 'allow greater differentiation between the interventions and aid patient choice.' We welcome this call and recognise the need for greater differentiation between the interventions. Furthermore, we argue that a greater differentiation would be welcome for treatments for other, more severe forms of depression. What are described as modes of action in the draft Guideline, may be translated in psychotherapy research as 'mechanisms of action', or 'mechanisms of change' (Kazdin, 2007; 2009). We believe that qualitative evidence and evidence from case reports may be utilised to this end, in the form of a discrete evidence synthesis, such as performed for Evidence Review I. Section 6.2 of 'Developing NICE guidelines: the manual' identifies different approaches to qualitative evidence synthesis including the use of meta-ethnography and meta-synthesis which would be appropriate vehicles for incorporating qualitative evidence including case study to identify modes of action, and these approaches are already established in psychology and psychotherapy research (Timulak, 2009; Iwakabe and Gazzola, 2009; Levitt, 2018). The subsequent results could be distilled into talking points to be presented alongside the existing 'menu' of treatments set out in the Guideline, adding context to the dialogue between practitioner and patient in their arrival at a collaborative decision.	Thank you for your comment. The experience of care section from the 2009 guideline was not included in this update (as specified in the scope). However, as your comment recognises, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment. The committee considered RCTs as the most appropriate study design to assess clinical and cost effectiveness. This is consistent with the NICE guidelines manual which recognises RCTs as the most valid evidence of the effects of interventions, and this was outlined a priori in the review protocols. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context so that the 'reality' for people experiencing depression was taken into consideration and recommendations were made that were relevant to the populations that clinicians typically encounter. The committees' discussions on this are documented in 'The committee's discussion of the evidence' sections. The committee

							considered that the contextual features that you describe as requiring qualitative evidence to address, are taken into account by this interpretation of the clinical context by the committee.

26	SH	Tavistock and Portman NHS Foundation Trust	Evidence review B	102032	Table 23Table 9	No effect size differences For severe depression, bias-adjusted analysis for comparison with placebo yielded a standardized mean difference (SMD) of -0.78 (rank: 17.28) for individual CBT/CT and of -0.58 (rank: 22.08) for short-term psychodynamic therapy (STPP), corresponding to a difference in effect sizes of -0.20. For less severe depression, similar observation is found as pointed out in point 5 above. The bias-adjusted analysis for comparison for individual CBT vs. TAU is MD=-0.73, and for STPP vs. TAU, the bias-adjusted is SMD=-0.48.	Thank you for your comment. The committee agreed that there is not very large difference in the effects sizes between individual CT/CBT vs pill placebo and STPP vs pill placebo, and this uncertainty in the NMA results is stated in several places in evidence review B, including the committee's discussion. It was not feasible to comment on the differences in effect between all pairs of treatments examined (this was also one of the reasons why NMA was employed, in order to synthesise available evidence and summarise results by ranking a large number of treatments and providing effects of each treatment versus a common reference treatment). However, full results on the relative effects between all pairs of classes and interventions are provided in Supplements B5 and B6, for less and more severe depression, respectively. It is noted that, for less severe depression, the effect on the SMD vs TAU was based on N=481 for individual CBT and N=49 for STPP. Also, the 95%CrI were much wider for STPP than for individual CBT. As stated in the evidence review B, the committee considered insufficient evidence on any treatment class that was derived from N<50 people across RCTs on each NMA outcome

							(after looking at the total size of the evidence base in this area and noticing that there were several treatment classes with larger volume of evidence), and did not consider those treatment classes for a practice recommendation, however, they made an exception for treatment classes already available on the NHS, such as STPP. For more severe depression, the effect on the SMD vs pill placebo was based on N=1044 for individual CBT and N=267 for STPP. There was evidence for effect vs pill placebo for individual CBT (as the 95%CrI did not cross the zero line) but not for the STPP class (however, effects for interventions within the STPP class did marginally show effect vs pill placebo). The recommendations and the ranking of treatments for a new episode of depression were also affected by the results of the guideline economic modelling, which was informed by additional outcomes, such as discontinuation, response in completers and remission in completers. The guideline economic analysis results, which were also characterised by uncertainty, suggested that individual CBT was more cost-effective than GP care, but STPP was less cost-effective than GP care in both less and more

							severe depression. For less severe depression, this result was partly attributable to the fact that the effects modelled in the economic analysis for each intervention were achieved with fewer CBT sessions (8 for individual CBT vs. 12 for STPP, reflecting reported resource use in the trials informing the NMA and the economic analysis – see new Appendix N added in evidence review B for more details). [In more severe depression, 16 sessions were modelled for both interventions based on reported resource use in respective RCTs.]

27	SH	University of Exeter Medical School	Evidence Review B	140-141	045-002	THIS COMMENT IS IDENTICAL TO THAT REFERRING TO PAGE 147 BUT IS REPEATED HERE AS PER THE INSTRUCTIONS REGARDING NOT CROSS REFERENCING COMMENTS The statement: "the committee were aware that a number of important and well-known, often pragmatic trials, were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. The committee used their knowledge of these trials in the round when interpreting the evidence from the systematic review and making recommendations" is genuinely perplexing. The trials referred to (and cited specifically elsewhere in the guideline evidence reviews) are NHS facing trials of real world populations likely to be encountered by clinicians delivering treatments. They also represent the largest number of people with depression. Most of these trials were funded by public agencies supported by taxpayers' money (NIHR for example). Many hundreds of people with depression volunteered to suspend their right to treatment choice in order to participate randomised treatment allocation. It is simply not enough to cite these trials and the selfless efforts of these participant populations as 'in the round' evidence. These are the people who most need help and are the population who present daily to primary care. The £2m NIHR HTA COBRA trial of two psychological treatments, for example, included 440 participants with diagnosed depression. NICE has chosen to exclude these data (including 18m follow up) because most of the participants were also taking antidepressants as a so called 'first line' treatment (even though this treatment was not working). This is hardly	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

						surprising, given that they were people with multiple episodes of depression and histories of treatment lasting over 300 weeks prior to the trial. This is the usual behaviour of people struggling to overcome and manage their mood disorders. The evidence review criteria used by NICE has instead, derived evidence from an artificial cohort of participants that in no way represent the clinical and behavioural treatment seeking characteristics of the vast majority of people with depression. Had the COBRA trial excluded these people or asked them to halt their pharmacological treatment we would have a) struggled to find people who were not treating their depression, b) faced the accurate critique that the trial was not generalisable to the public at large c) faced real ethical difficulties in removing existing treatments from vulnerable adults. As noted in a previous comment, the decision to exclude this trial has removed the health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world. In summary, the decision to exclude some of the largest, pragmatic health services research trials from this guideline cannot be assuaged by a side comment that they somehow back up the committee decisions. What would NICE have done, one wonders had these excluded trials NOT been	estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

						consistent with the evidence reviews? Tax payers' money, patient volunteers and the efforts of hundreds of health services researchers cannot be dismissed in this cavalier manner. It also makes a mockery of the extensive peer review systems in place including at funder, trial governance and publication levels to treat this scientific endeavour with such disdain. The guideline has based its decision making on artificial criteria that do not represent the populations and the clinical situations faced by the NHS. We face a post-pandemic mental health emergency. These HSR pragmatic trials should be included as exactly the type of evidence that we are now so desperate to work with in order to advise our long-suffering and harassed clinical colleagues in their decision making. And of course, these data should be in the public domain so that patients and their closest significant others are enabled to make life changing decisions about their care.	used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

28	SH	University of Exeter Medical School	Evidence Review B	141	21	THIS COMMENT IS IDENTICAL TO THAT REFERRING TO PAGE 147 BUT IS REPEATED HERE AS PER THE INSTRUCTIONS REGARDING NOT CROSS REFERENCING COMMENTS The statement: "Furthermore, the committee were aware that important trials comparing CBT and behavioural activation to controls, other psychological interventions, and antidepressant medication were excluded from the NMA principally because they were pragmatic trials and the samples in the trials were <80% first-line treatment or <80% non-chronic depression (including De Rubeis 2005; Dimidjian 2006; Driessen 2013; Ekers 2011; Hollon 2014; Luty 2007; Richards 2016). The committee considered that the evidence from these studies was consistent with the evidence from the systematic review and also supported this interpretation." is genuinely perplexing. The trials referred to (and cited specifically elsewhere in the guideline evidence reviews) are NHS facing trials of real world populations likely to be encountered by clinicians delivering treatments. They also represent the largest number of people with depression. Most of these trials were funded by public agencies supported by taxpayers' money (NIHR for example). Many hundreds of people with depression volunteered to suspend their right to treatment choice in order to participate randomised treatment allocation. It is simply not enough to cite these trials and the selfless efforts of these participant populations as 'consistent' evidence. These are the people who most need help and are the population who present daily to primary care. The £2m NIHR HTA COBRA trial of two psychological treatments, for example, included 440 participants with	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

						diagnosed depression. NICE has chosen to exclude these data (including 18m follow up) because most of the participants were also taking antidepressants as a so called 'first line' treatment (even though this treatment was not working). This is hardly surprising, given that they were people with multiple episodes of depression and histories of treatment lasting over 300 weeks prior to the trial. This is the usual behaviour of people struggling to overcome and manage their mood disorders. The evidence review criteria used by NICE has instead, derived evidence from an artificial cohort of participants that in no way represent the clinical and behavioural treatment seeking characteristics of the vast majority of people with depression. Had the COBRA trial excluded these people or asked them to halt their pharmacological treatment we would have a) struggled to find people who were not treating their depression, b) faced the accurate critique that the trial was not generalisable to the public at large c) faced real ethical difficulties in removing existing treatments from vulnerable adults. As noted in a previous comment, the decision to exclude this trial has removed the health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world. In	estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

						summary, the decision to exclude some of the largest, pragmatic health services research trials from this guideline cannot be assuaged by a side comment that they somehow back up the committee decisions. What would NICE have done, one wonders had these excluded trials NOT been consistent with the evidence reviews? Tax payers' money, patient volunteers and the efforts of hundreds of health services researchers cannot be dismissed in this cavalier manner. It also makes a mockery of the extensive peer review systems in place including at funder, trial governance and publication levels to treat this scientific endeavour with such disdain. The guideline has based its decision making on artificial criteria that do not represent the populations and the clinical situations faced by the NHS. We face a post-pandemic mental health emergency. These HSR pragmatic trials should be included as exactly the type of evidence that we are now so desperate to work with in order to advise our long-suffering and harassed clinical colleagues in their decision making. And of course, these data should be in the public domain so that patients and their closest significant others are enabled to make life changing decisions about their care.	used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

29	SH	Society for Psychotherapy Research	Evidence review B	143	General	Couples psychotherapy In line with the previous guideline couples' psychotherapy has been considered as a treatment option and we welcome this. Based on a wealth of empirical research (e.g. Beach, Fincham, & Katz, 1998; Benazon & Coyne, 2000; Coyne, Thompson, Palmer, 2002; Johnson & Jacob, 1997, 2000; Scott & Cordova, 2002; Whisman, 2007), the direct pathway between couple relationship distress and depression has been well documented. However, we are surprised to learn that a very narrow definition and as such narrow inclusion criteria has been used in this draft, changing it completely from the previous guideline. Here only studies are considered where individuals report relationship problems. However, couple therapy for depression has been found to be effective for individuals suffering from depression with and without relationship problems (e.g. Baucom et al., 2018). Moreover, these stringent inclusion criteria meant that only 1 study was included, which dates from 1992 and includes cognitive therapy (Beech, 1992, see page 111). Consequently, many studies showing effectiveness of a variety of modalities of couples therapy were not reviewed, which in fact were included in the previous guideline (see list below).We strongly recommend refining the inclusion/exclusion criteria for couple therapy and amend this review according. The fact that only one study was identified reflects the methodology chosen rather than available evidence and this provides further support for our request that the exclusion/inclusion criteria for the analysis is amended. Related to this we are surprised by the inconsistency here to recommend a treatment on the review	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee considered the pairwise analysis of behavioural couples therapy for people with depression and problems in the relationship with their partner. As you indicate in your comment, this evidence was based on a small, single study which indicated that compared to waitlist, couples' therapy demonstrated benefits in terms of depression symptoms and marital adjustment, but when compared to CBT it did not show a benefit in depression symptoms but did with marital adjustment. CBT compared to waitlist demonstrated benefits only in terms of depression symptoms. The committee discussed that although this was limited evidence, behavioural couples therapy was included in

						of one study alone, that has in addition been rated as a “very weak study”. To further specify, it is inconsistent to include a treatment on the basis of one study while excluding (not recommending in the guideline) other treatments that have been shown to be effective in single. Studied that were excluded in this draft but had been included previously: Beach SRH, O'Leary KI. Treating depression in the context of marital discord: outcome and predictors of response of marital therapy versus cognitive therapy. Behav Ther 1992;23:507-528.Emanuels-Zuurveen L, Emmelkamp PMG. Individual behavioural cognitive therapy vs. marital therapy for depression in maritally distressed couples.. Br J Psychiatry 1996;169:181-188.Foley SH, Rounsaville BJ, Weissman MM, Sholomskas D, Chevron E. Individual versus conjoint interpersonal psychotherapy for depressed patients with marital disputes. International Journal of Family Psychiatry 1989;10(1-2):29-42. O'Leary KD, Beach SR. Marital therapy: a viable treatment for depression and marital discord. American Journal of Psychiatry 1990;147(2):183-186. Leff J, Vearnals S, Brewin CR, Wolff G, Alexander B, Asen E, Dayson D, Jones E, Chisholm D, Everitt B. The London Depression Intervention Trial. Randomised controlled trial of antidepressants v. couple therapy in the treatment and maintenance of people with depression living with a partner: clinical outcome and costs. [see comments.] [erratum appears in Br J Psychiatry 2000 Sep;177:284.]. British Journal of Psychiatry 2000;177:95-100.Bodenmann, G., Plancheral, B., Beach, S.R., et al. (2008). Effects of coping-orientated couples therapy on depression: A randomised clinical trial. Journal of Consulting and Clinical	the range of interventions offered by the IAPT services and that it was useful in the specific population and so recommended its use for this group of people.

						Psychology, 76(6), 944-954 Jacobson, NS., Fruzzetti, A.E., Dobson, K., Whisman, M., & Hops, H. (1993). Couple therapy as a treatment for depression: II. The effects of relationship quality and therapy on depressive relapse	

30	SH	University of Exeter Medical School	Evidence Review B	147	008-012	THIS COMMENT IS IDENTICAL TO THAT REFERRING TO PAGE 68 BUT IS REPEATED HERE AS PER THE INSTRUCTIONS REGARDING NOT CROSS REFERENCING COMMENTSThe statement: “the committee were aware that a number of important and well-known,often pragmatic trials, were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. The committee used their knowledge of these trials in the round when interpreting the evidence from the systematic review and making recommendations” is genuinely perplexing. The trials referred to (and cited specifically elsewhere in the guideline evidence reviews) are NHS facing trials of real world populations likely to be encountered by clinicians delivering treatments. They also represent the largest number of people with depression. Most of these trials were funded by public agencies supported by taxpayers’ money (NIHR for example). Many hundreds of people with depression volunteered to suspend their right to treatment choice in order to participate randomised treatment allocation. It is simply not enough to cite these trials and the selfless efforts of these participant populations as ‘in the round’ evidence. These are the people who most need help and are the population who present daily to primary care. The £2m NIHR HTA COBRA trial of two psychological treatments, for example, included 440 participants with diagnosed depression. NICE has chosen to exclude these data (including 18m follow up) because most of the participants were also taking antidepressants as a so called ‘first line’ treatment (even though this treatment was not working). This is hardly	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

						surprising, given that they were people with multiple episodes of depression and histories of treatment lasting over 300 weeks prior to the trial. This is the usual behaviour of people struggling to overcome and manage their mood disorders. The evidence review criteria used by NICE has instead, derived evidence from an artificial cohort of participants that in no way represent the clinical and behavioural treatment seeking characteristics of the vast majority of people with depression. Had the COBRA trial excluded these people or asked them to halt their pharmacological treatment we would have a) struggled to find people who were not treating their depression, b) faced the accurate critique that the trial was not generalisable to the public at large c) faced real ethical difficulties in removing existing treatments from vulnerable adults. As noted in a previous comment, the decision to exclude this trial has removed the health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world. In summary, the decision to exclude some of the largest, pragmatic health services research trials from this guideline cannot be assuaged by a side comment that they somehow back up the committee decisions. What would NICE have done, one wonders had these excluded trials NOT been	estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

						consistent with the evidence reviews? Tax payers' money, patient volunteers and the efforts of hundreds of health services researchers cannot be dismissed in this cavalier manner. It also makes a mockery of the extensive peer review systems in place including at funder, trial governance and publication levels to treat this scientific endeavour with such disdain. The guideline has based its decision making on artificial criteria that do not represent the populations and the clinical situations faced by the NHS. We face a post-pandemic mental health emergency. These HSR pragmatic trials should be included as exactly the type of evidence that we are now so desperate to work with in order to advise our long-suffering and harassed clinical colleagues in their decision making. And of course, these data should be in the public domain so that patients and their closest significant others are enabled to make life changing decisions about their care.	used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

31	SH	UK Council for Psychotherapy	Evidence Review B	207	Appendix A Review protocol	Couple therapy is again listed as a psychosocial intervention when it is a psychological intervention and again incorrectly described as more appropriate for sub-groups of people with depression specifically those with problems in the relationship with their partner.	Thank you for your comment. This was not intended to be listed as a psychosocial intervention but was in a separate section at the end. However, in response to your comment, it has been moved under the psychological interventions heading for greater clarity.
32	SH	Association for Family Therapy and Systemic Practice	Evidence Review B	207	Appendix A Review protocol	Couple therapy is again listed as a psychosocial intervention when it is a psychological intervention and again incorrectly described as more appropriate for sub-groups of people with depression specifically those with problems in the relationship with their partner.	Thank you for your comment. This was not intended to be listed as a psychosocial intervention but was in a separate section at the end. However, in response to your comment, it has been moved under the psychological interventions heading for greater clarity.

33	SH	Society for Psychotherapy Research	Evidence review B	Appendix L	General	We welcome these research recommendations, in particular the one investigating mechanisms of change. We would like to request for the following crucial additions to these research recommendations: The investigation of long-term treatments, especially for chronic and complex forms of depression. A request that all future studies need to include a meaningful long-term follow-up period and report these outcomes as a critical outcome. With regard to depression, we would suggest a minimum of a 2-year follow-up. A request for psychological studies to include therapists' effects. A request that future studies need to include quality of life and functioning measures alongside symptom-based measures.	Thank you for your comment. The committee agree that quality of life and functioning outcomes, and long-term follow-up, are important. The committee noted the limited evidence for quality of life and functioning outcomes and for longer-term follow-up, and included these outcomes and follow-up timepoints for the research recommendations in the guideline. The number of research recommendations that the committee can develop is limited and unfortunately long-term treatments were not prioritised for a research recommendation. The research recommendation on the mechanisms of action of effective psychological interventions includes the recommendation that psychological interventions should be analysed in terms of generic therapeutic components (for example therapeutic relationship, rationale; remoralization), in addition to therapy structure (for example session duration, frequency), and specific ingredients. The committee did not prioritise therapist

							effects for a stand-alone research recommendation.

34	SH	Society for Psychotherapy Research	Evidence review B & Cost analysis	General	General	Class models In this third iteration of the draft guideline, we continue to be concerned about the class models that have been adopted. The guideline states: "Each class consisted of interventions with a similar mode of action or similar treatment components or approaches so that interventions within a class were expected to have similar (but not necessarily identical) effects." There is no evidence that this similarity is in fact the case. Moreover, we were concerned about the lack of an explanation or definition as to how similarity between and within classes was assessed and we recommend the inclusion of a more thorough and transparent explanation alongside a Table or Figure in the main document that summarises these. As far as we could discern, the only place where the information can be found is in the supplementary excel spreadsheet (Supplement B1).The decision that an estimate for variance was borrowed from other interventions where it was not available needs to be made more transparent and justified adequately. For example, Exercise borrowed variance from Counselling; Sort-term Psychodynamic Psychotherapy, Psychoeducation, and Interpersonal Psychotherapy, Self-help, and Behavioural Therapies borrowed variance from Cognitive Behavioural Therapy. It is currently not clear as to why this approach was chosen and we recommend the inclusion of a plausible rationale. We consider this especially crucial as treatment costs were extrapolated from some interventions to others within a class for the economic analysis (see point 22 for our comments on that).	Thank you for your comment. The committee drew on their clinical knowledge and experience to categorise interventions into classes. In response to your comment. a cross-reference to Supplement B1 has been added to Evidence review B to highlight where the full list of intervention and class categorisations can be found. The decision about the borrowing of variance estimates was clearly stated in the protocol, which is available in PROSPERO (CRD42019151328) and also in Appendix A of Evidence review B. Details of the process are provided in the NMA report in Appendix M of Evidence review B under THE 'Class models' section, which has now been slightly edited to further clarify the rationale for the adopted approach. As stated, the borrowing of variance from other classes was only needed for classes which did not have enough evidence to estimate within-class variability of effects (i.e. classes with just 1 or 2 interventions) and only for analyses where the evidence for a class did not allow estimation of within-class variability of effects. E.g., if a class included

							3-4 interventions in one analysis and was thus possible to estimate its within-class variability of effect, then it did not borrow variance from another class. However, if in another analysis (e.g., for a different population/outcome) it had inadequate evidence (1-2 interventions in the class), then it did borrow variance from another class with adequate relevant evidence. The assumptions around which classes to borrow variance from for classes with inadequate relevant evidence was made by the committee, based on their expertise on the expected variability of effects across interventions within a class (i.e., how similar or diverse effects interventions within a particular class were expected to have). It is noted that this process did not affect the mean class effect, but the spread/uncertainty around the class effect and across the effects of interventions within the class with inadequate evidence. It obviously did not affect in any way classes with adequate evidence regarding the estimation of the within-class variance of effects. Borrowing/sharing variance from/with another class was necessary to retain the

							individual treatment effects within classes formed by 1-2 interventions, and can be considered a conservative assumption, since the alternative would be to assume no variance within the class, which would mean that all interventions in the class would have the same treatment effect, which is a much stronger assumption. The fit of all models was tested and was found to be adequate so that there was no evidence that the data were in conflict with the assumptions underpinning the analysis. The process of borrowing variance for some classes in some of the NMAs is not related at all with processes and assumptions underpinning the economic modelling. Moreover, treatment costs were not extrapolated from any intervention to any other interventions within the class. It was conclusions on cost-effectiveness of an intervention within a class that, where appropriate (i.e., where interventions shared similar effectiveness and resource intensity), were extrapolated to other interventions within the class, as it was not feasible to model every single intervention in the class. This is stated in Appendix J of Evidence report B, under Discussion:

							"Specific interventions were used as exemplars within each class, so that results of interventions can be extrapolated to other interventions of similar effectiveness and resource intensity within their class."

35	SH	Tavistock and Portman NHS Foundation Trust	Evidence review B &Guideline	11114 3169	General	Couples Therapy We notice that the review of couples therapy only includes one study (Beech, 1992, see p. 111) and that on the basis of the results of this study alone. a study has been identified as "very weak"; cognitive couples' therapy is being recommended. This is very concerning, not only because it is inconsistent with other decisions the committee appears to have made where a decision was made not recommend a treatment based on the quality of a trial, or the lack of further evidence, but also because it appears that many other studies assessing its efficacy were excluded based on the rather narrow definition to exclude trials because individuals with depression did not have relationship problems. We want to emphasise that couple therapy for depression has been found to be effective for individuals suffering from depression with and without relationship problems (e.g. Baucom et al., 2018). Subsequently 4 of the 27 studies reviewed were excluded because they did not have relationship problems. We strongly suggest this to be amended. References cited:Baucom, D., Fischer, M., Worrell, M., Corrie, S., Belus, J., Molyva, E. and Boeding, S. (2018) Couple-based intervention for depression: an effectiveness study in the national health service in England. Family Process, 57: 275–92	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee considered the pairwise analysis of behavioural couples therapy for people with depression and problems in the relationship with their partner. As you indicate in your comment, this evidence was based on a small, single study which indicated that compared to waitlist, couples' therapy demonstrated benefits in terms of depression symptoms and marital adjustment, but when compared to CBT it did not show a benefit in depression symptoms but did with marital adjustment. CBT compared to waitlist demonstrated benefits only in terms of depression symptoms. The committee discussed that although this was limited evidence, behavioural couples therapy was included in

							the range of interventions offered by the IAPT services and that it was useful in the specific population and so recommended its use for this group of people.

36	SH	Stakeholder coalition	Evidence review B &Economic Cost analysis	General	General	Network Meta-Analysis (NMA) We appreciate the inclusion of pair-wise meta-analyses alongside the NMA for the review of first episode depression. However, we remain very concerned about the fact that NMA continues to be the primary data analysis and that, in the end, pair-wise analyses were only used for comparison reasons. As stated on p.39 in evidence review B, the decision was made to utilise only the NMA results based on the finding that there were only very few differences in the comparison of findings between both. A problem with such a comparison, however, is that it can only be made for those comparisons for which direct evidence is available. As we have emphasised during all consultations on this guideline, the validity or trustworthiness of statistical evidence derived from NMA is highly controversial (Faltlinsen et al., 2018; Leucht et al., 2016). Given that it has no formal expert consensus, such an analytical approach can be viewed only as an experimental technique, and we believe that a national health treatment guideline should not be based on an experimental technique.In line with leading scientists, we strongly maintain that NMA should only be used when certain conditions are met. As repeatedly pointed out, these conditions seem not to have been met adequately here, showing evidence that transitivity and consistency assumptions are violated. Our concerns are supported by various statements within the draft guideline that point to these limitations. Moreover, given that the economic modelling carried out in this draft guideline is heavily influenced by the NMA (and therefore its limitations), we are similarly concerned about the trustworthiness of the	Thank you for your comment. NMA was the main method used to synthesise evidence on pharmacological, psychological, psychosocial, physical and combined interventions, consistently with previous drafts of this guideline, in order to allow estimation of the relative effectiveness, acceptability and tolerability across all treatments for a new episode of less severe or more severe depression. Pairwise meta-analysis was employed to synthesise data on all critical outcomes of the clinical analysis in order to compare the results of the NMA with those of pairwise meta-analysis (MA) and explore any differences between them and possible reasons for any differences. Moreover, pairwise MA was used to synthesise follow-up data as well as data on functioning and quality of life. However, the decision was (right at the start rather than in the end of the process) that results of pairwise MAs on critical outcomes would not be considered as the primary source of evidence when formulating recommendations. This decision is stated under Summary of methods, Evidence synthesis, in Evidence review B. Nowhere on page 39 is it stated that there was a decision to utilise only the NMA results

						outcome of the economic analysis of treatments. We therefore reiterate our advice that until there is consensus and evidence of the validity of such a statistical analysis for this type of complex dataset that combines three different modalities of treatment (pharmacological, psychological and physical), the primary method to synthesise the evidence should be through direct comparison (standard meta-analysis).	based on the finding that there were only very few differences in the comparison of findings between NMA and standard pairwise MA. It is only stated that, where relevant, results were overall consistent between the NMA and the pairwise meta-analysis. This finding was reassuring for the committee and increased its confidence in the NMA results. It is true that the comparison between NMA and pairwise MA results cannot be made for comparisons between treatments for which direct evidence is not available, and this is an important advantage of NMA over pairwise MA: that it allows estimation of effects between interventions that have not been directly compared in a head-to-head comparison, via indirect comparisons. This is essential in order to estimate the relative effectiveness of all pairs of treatments assessed in the review. It also allows simultaneous comparison of the effects and ranking of all treatments. Interestingly, Faltinsen et al. (2018) report that WHO have started advocating the use of NMA to inform clinical guidelines and that the scientific production of network meta-analyses is increasing rapidly over the

							world. (They also report that NICE guidelines typically prefer direct evidence from RCTs and conventional meta-analyses to indirect evidence – this is not entirely true, as NICE prefer RCTs to indirect evidence, but "when multiple competing options are being appraised, a network meta-analysis should be considered" according to the NICE Guidelines Manual.) The authors recommend further methods for reporting and statistical testing of NMAs – which is fully agreed. Full reference to Leucht et al. (2016) could not be identified in your comments, but perhaps you refer to the paper "Network meta-analyses should be the highest level of evidence in treatment guidelines" (EUR ARCH PSY CLIN N 2016; 266, 477–480) where the authors conclude: "in our opinion, systematic reviews based on network meta-analyses should generally be the highest level of evidence in treatment guidelines, but we need to assess them carefully and in certain situations (such as if a meta-analysis is mainly composed of small trials)". In the area of mental health only, there are several NMAs published on treatments for depression, anxiety, PTSD, schizophrenia etc. NICE has used NMA in the past to

							inform other mental health guidelines, including PTSD, bipolar disorder and schizophrenia, and in several other diverse disease areas such as epilepsy, acne, and induction of labour. There are also several NMAs published in the area of psychotherapies for Depression (e.g. Barth et al, PLOS Medicine 2013, 10(5): e1001454; Cuijpers et al, JAMA Psychiatry 2019, 76(7):700-707; Cuijpers et al, World Psychiatry 2020, 19(1):92-107; Cuijpers et al, World Psychiatry 2021, 20(2):283-293; Zhou et al, World psychiatry 2015, 14(2):207–222; López-López et al, Psychological medicine 2019, 49(12):1937–1947), many of which have compared different types of therapy such as pharmacological vs psychological interventions, online vs. face-to-face interventions, etc. There are also published NMAs of psychotherapies for anxiety disorders (Mayo-Wilson et al, Lancet Psychiatry 2014, 1(5):368–376; Chen et al, Journal of psychiatric research 2019, 118:73–83), panic disorder (Pompoli et al, The Cochrane database of systematic reviews 2016, 4(4):CD011004), and PTSD (Merz et al, JAMA Psychiatry 2019, 76(9):904–913; Mavranezouli et al,

							Psychological medicine 2020, 50(4): 542–555; Coventry et al, PLoS medicine 2020, 17(8):e1003262; Mavranezouli et al, J Child Psychol Psychiatry 2020, 61(1):18-29). The above suggest that NMA is recognised as an established method of evidence synthesis and not as an experimental technique. Consistency between direct and indirect evidence and transitivity are met when the distribution of the effect modifiers is the same across treatment comparisons. It is correct that, for a valid analysis, due consideration must be given to the evaluation of effect modifiers across all comparisons. Balanced distribution of effect modifiers cannot happen when there is heterogeneity in populations and/or interventions. This heterogeneity, however, can be a problem in both pairwise MA and NMA and should be considered prior to conducting the meta-analysis, and when interpreting the results. In the guideline NMA a large part of heterogeneity was controlled by splitting populations with less and more severe depression, using detailed treatment definitions [including treatment intensity and mode of delivery for psychological interventions] and

							categorising them using a class random effects model. Heterogeneity was assessed by examining for model fit and checking for inconsistency between direct and indirect evidence. Other parameters, such as sex, socio-economic factors, therapist factors, may also contribute to heterogeneity, in particular in such a large and complex dataset, but this would also be a problem had exclusively pairwise MA of the 142 RCTs for less severe depression and 534 RCTs for more severe depression included in the systematic review been conducted. Considering heterogeneity when assessing the hundreds of pairwise, independent comparisons of this dataset would make interpretation of the findings and conclusions as to which interventions are the best options highly problematic. Between-study heterogeneity in the NMA was formally assessed for each network; results of this assessment were taken into account when interpreting the results of the NMA and making recommendations. Moreover, for the SMD outcome, a non-pharmacological subgroup of the overall dataset was analysed separately as a sensitivity analysis, to explore whether transitivity issues between pharmacological

							and non-pharmacological trials might have impacted on the results of the NMA. In addition, also for the SMD outcome, a sub-group analysis including only studies at low risk of bias for the attrition domain in the RoB tool has now been conducted. Detailed results of inconsistency checks and comparison between mixed (NMA) and direct evidence as well as additional sensitivity and sub-group analyses have been provided in Appendix M of Evidence review B, and supplements B5 and B6. The committee considered all these issues when making recommendations alongside the results of the pairwise MA, the economic modelling results and newly reviewed qualitative evidence. Recommendations take also into account individual patient needs and preferences, which might be argued to be an effect modifier the distribution of which could potentially differ across pharmacological, psychological and physical treatment trials. Consideration of cost-effectiveness is an essential element of NICE guidelines. The economic analysis assessed concurrently the relative cost-effectiveness of all effective treatments with an adequate

							evidence base, both for less and more severe depression. Economic modelling would not be possible to carry out had the guideline utilised only pairwise MA and not NMA. This is because, in order to assess the relative cost-effectiveness across all treatments, the economic model must be informed with data on the relative effects (e.g. discontinuation, response, remission in this particular model) across all treatments, and this simultaneous reference to relative effects is only possible with NMA and not with pairwise MA.

37	SH	Society for Psychotherapy Research	Evidence review B & cost analysis	General	General	Network meta-analysis (NMA) We appreciate that the committee listened to our concerns and that it included pair-wise meta-analyses alongside the NMA for the review of first episode depression. However, we are disappointed that the committee decided to stick with their decision to utilise the NMA as the primary analysis, and in the end only used the pair-wise analyses for comparison reasons. As stated on p.39 of the evidence review B the decision was made to utilise only the NMA results based on the finding that there were only very few differences in the comparison of findings between both. A problem with such a comparison, however is, that it can only be made for those comparisons for which direct evidence is available! In line with leading scientists, we strongly maintain that NMA should only be used when certain conditions are met. We have stated the various reasons why we believe that these conditions were not met in the previous two drafts and outline these once more below with respect to the current draft on the grounds that they are still highly pertinent. As shown, there are numerous violations of assumptions and other methodological shortcomings in this analysis plan that warrant our concerns that the resulting treatment recommendations have to be viewed with absolute caution and may not even be valid. Moreover, the health economic analyses are also impacted, given that they are based on the results derived from the NMA.As emphasised in all consultations, the validity or trustworthiness of statistical evidence derived from NMA is controversial (Faltlinsen et al., 2018; Leucht et al., 2016). Given that it has no formal expert	Thank you for your comment. NMA was the main method used to synthesise evidence on pharmacological, psychological, psychosocial, physical and combined interventions, consistently with previous drafts of this guideline, in order to allow estimation of the relative effectiveness, acceptability and tolerability across all treatments for a new episode of less severe or more severe depression. Pairwise meta-analysis (MA) was employed to synthesise data on all critical outcomes of the clinical analysis in order to compare the results of the NMA with those of pairwise MA and explore any differences between them and possible reasons for any differences. Moreover, pairwise MA was used to synthesise follow-up data as well as data on functioning and quality of life. However, the decision was (right at the start rather than in the end of the process) that results of pairwise MAs on critical outcomes would not be considered as the primary source of evidence when formulating recommendations. This decision is stated under Summary of methods, Evidence synthesis, in Evidence review B. Nowhere on page 39 is it stated that there was a decision to utilise only the NMA results

						consensus, such an analytical approach can be viewed only as an experimental technique, and we believe that a national health treatment guideline should not be based on an experimental technique. Assumption of transitivity and consistency likely not metResults drawn from indirect comparisons can only be valid when the assumptions of transitivity and consistency are met (e.g., Cipriani et al.,2013; Faltlinsen et al., 2018). Possible modifiers affecting the outcome need therefore to be controlled for between the studies. As with the previous two analyses, again, not all sensitivity analyses appeared to have been carried out in the current analyses. These were only conducted for participants in pharmacological vs. non-pharmacological treatments. Thus, whether the transitivity assumption holds, for example, for the comparison of different non-pharmacological treatments is not clear. A general limitation of NMA is that the statistical power to detect inconsistencies between direct and indirect evidence may be insufficient in comparisons including few studies with small samples, especially if heterogeneity is large (Faltinsen et al., 2018, Veroniki et al., 2014). Despite trying to circumvent the problem by including a class model, existing inconsistencies may still have not been detected as several studies included show small sample sizes, with N≤ 20 per condition (e.g., Albornoz, 2011, Bowman et al., 1995, Costa and Barnhofer, 2016, Covi and Lipman, 1987, Doyne et al., 1987, Gerber et al., 2020, Singh et al., 1997), also calling into question the effect of randomization (Hsu, 1989).Treatment ranking If all assumptions are met, NMA is a useful technique for the purpose of ranking treatment outcome. As stressed in	based on the finding that there were only very few differences in the comparison of findings between NMA and standard pairwise MA. It is only stated that, where relevant, results were overall consistent between the NMA and the pairwise meta-analysis. This finding was reassuring for the committee and increased its confidence in the NMA results. It is true that the comparison between NMA and pairwise MA results cannot be made for comparisons between treatments for which direct evidence is not available, and this is an important advantage of NMA over pairwise MA: that it allows estimation of effects between interventions that have not been directly compared in a head-to-head comparison, via indirect comparisons. This is essential in order to estimate the relative effectiveness of all pairs of treatments assessed in the review. It also allows simultaneous comparison of the effects and ranking of all treatments, without breaking randomisation and without making implicit assumptions and calculations. Another advantage of the NMA is that it increases precision by combining direct with indirect evidence.

						this guideline as well as in the NICE method guideline, it is one of the primary reasons as to why NICE recommends its usage. However, treatment ranking can be affected by small differences that are not clinically important (Faltinsen et al., 2018), which indeed seems to be the case in the current analyses.For more severe depression, for example, bias-adjusted analysis for comparison with placebo yielded a standardized mean difference (SMD) of -0.78 (rank: 17.28); for individual CBT/CT and of -0.58 (rank: 22.08); for short-term psychodynamic therapy (STPP). In other words, the difference between these three corresponds to a difference in effect sizes of -0.20. This difference is below the MID (minimally important difference) of SMD=0.50 defined by NICE as clinically important (Evidence file B, p.14), but rankings differ considerably. This applies to other rankings as well, e.g. of individual interpersonal therapy (IPT, SMD=-0.50, rank 16.93) and individual CBT/CT (SMD= -0.73, rank 13.14) compared to TAU in less severe depression and also to the ranking of CT/CBT and counselling in more severe depression, with SMDs of -0.78 (rank 17.28) and -0.67 (rank 19.96) compared to pill placebo, showing no clinically significant differences between individual CT/CBT and counselling (difference in SMD=-0.11).This is true for less severe depression as well (individual CBT vs. TAU: bias-adjusted SMD=-0.73, STPP vs. TAU: bias-adjusted SMD=-0.48, e.g., below the SMD deemed clinically important by NICE). Ranking treatments for less severe depression according to clinically insignificant differences in efficacy is (again) highly questionable. For CBT “good evidence” of efficacy was concluded by NICE, for STPP the	Interestingly, Faltinsen et al. (2018) report that WHO have started advocating the use of NMA to inform clinical guidelines and that the scientific production of network meta-analyses is increasing rapidly over the world. (They also report that NICE guidelines typically prefer direct evidence from RCTs and conventional meta-analyses to indirect evidence – this is not entirely true, as NICE prefer RCTs to indirect evidence, but “when multiple competing options are being appraised, a network meta-analysis should be considered” according to the NICE Guidelines Manual). The authors recommend further methods for reporting and statistical testing of NMAs – which is fully agreed. Full reference to Leucht et al. (2016) could not be identified in your comments, but perhaps you refer to the paper “Network meta-analyses should be the highest level of evidence in treatment guidelines” (EUR ARCH PSY CLIN N 2016; 266, 477–480) where the authors conclude: “in our opinion, systematic reviews based on network meta-analyses should generally be the highest level of evidence in treatment guidelines, but we need to assess them carefully and in certain situations (such as if a meta-analysis is

						conclusion was that there was only “some evidence” of efficacy. If this judgment is based on the number of studies available (which is not clear, indicating a lack of transparency), it is necessary to emphasize that a larger number of studies does not imply higher efficacy. Following, for example, Chambless and Hollon (1998), two RCTs are sufficient for a treatment to be classified as efficacious. In the Evidence file B, on p.61, the committee conceded that the 95% credible intervals (CrI) around the rankings of interventions were characterized by considerable uncertainty. For example, the mean ranking of group CBT, which was shown to be the most cost-effective intervention, was 2.76, however its 95% CrI were 1 to 12, suggesting high uncertainty around the result for group CBT. Similar uncertainty was shown for all interventions included in the analysis. In other words, the CrIs show that the NMA rankings are ‘uncertain’ and thus likely should be treated with significant caution. Head-to-head comparisons It is furthermore not clear to us whether the analyses included the comparisons between the different psychotherapies and as such whether these analyses found any statistically significant differences between them. From the documents provided, it seems that only effect sizes and their CrL´s resulting from the comparisons with placebo or TAU were calculated, which were then compared for the different treatments. No head-to-head comparisons of treatments were reported which are usually presented in the NMA tables including all comparisons. It is, however, a common statistical fallacy to assume difference between two treatments if, for example, one treatment is superior to a	mainly composed of small trials)”. In the area of mental health only, there are several NMAs published on treatments for depression, anxiety, PTSD, schizophrenia etc. NICE has used NMA in the past to inform other mental health guidelines, including PTSD, bipolar disorder and schizophrenia, and in several other diverse disease areas such as epilepsy, acne, and induction of labour. There are also several NMAs published in the area of psychotherapies for Depression (e.g. Barth et al, PLOS Medicine 2013, 10(5): e1001454; Cuijpers et al, JAMA Psychiatry 2019, 76(7):700-707; Cuijpers et al, World Psychiatry 2020, 19(1):92-107; Cuijpers et al, World Psychiatry 2021, 20(2):283-293; Zhou et al, World psychiatry 2015, 14(2):207–222; López-López et al, Psychological medicine 2019, 49(12):1937–1947), many of which have compared different types of therapy such as pharmacological vs psychological interventions, online vs. face-to-face interventions, etc. There are also published NMAs of psychotherapies for anxiety disorders (Mayo-Wilson et al, Lancet Psychiatry 2014, 1(5):368–376; Chen et al, Journal of psychiatric research 2019,

						control condition but the other is not, without comparing them directly (Makin and Orban de Xivry, 2019). We therefore ask for an amendment of these incorrect statistical applications to allow more confidence in the conclusions being drawn from the analyses. Quality of NMA evidence It is not clear whether the quality of and the confidence in the results of the NMA were taken into account when discussing results and making treatment recommendations (Salanti et al., 2014). In Appendix F only results for a few specific treatments are reported (e.g., CBT couple therapy, CBT vs. waiting list).Impact of risk of bias on outcome (see page 41 evidence review B)Risk of bias seems to have only been tested for the impact of publication bias (small study bias) on outcome. The impact of other forms of bias seems to have been not addressed. This is the more important since other researchers have found that most studies of those therapies recommended as first rank treatments are highly biased (Cuijpers et al., 2016).	118:73–83), panic disorder (Pompoli et al, The Cochrane database of systematic reviews 2016, 4(4):CD011004), and PTSD (Merz et al, JAMA Psychiatry 2019, 76(9):904–913; Mavranezouli et al, Psychological medicine 2020, 50(4): 542–555; Coventry et al, PLoS medicine 2020, 17(8):e1003262; Mavranezouli et al, J Child Psychol Psychiatry 2020, 61(1):18-29). The above suggest that NMA is recognised as an established method of evidence synthesis and not as an experimental technique. Consideration of cost-effectiveness is an essential element of NICE guidelines. The guideline economic analysis assessed concurrently the relative cost-effectiveness of all effective treatments with an adequate evidence base, both for less and more severe depression. Economic modelling would not be possible to carry out had the guideline utilised only pairwise MA and not NMA. This is because, in order to assess the relative cost-effectiveness across all treatments, the economic model must be informed with data on the relative effects (discontinuation, response, remission in this particular model) across all treatments, and this simultaneous reference to relative

							effects is only possible with NMA and not with pairwise MA. Consistency between direct and indirect evidence and transitivity are met when the distribution of the effect modifiers is the same across treatment comparisons. Effect modifiers are factors that interact with intervention effects and should be distinguished from prognostic factors that predict outcomes but do not interact with intervention effects. NMA is robust to differences between studies in prognostic factors. As you have mentioned, the assumptions behind NMA cannot be met when there is heterogeneity in populations and/or interventions in effect modifiers. Heterogeneity, can be a problem in both pairwise MA and NMA and should be considered prior to conducting the meta-analysis, and when interpreting the results. In the guideline NMA, a large part of heterogeneity was accounted for by splitting populations with less and more severe depression, using detailed treatment definitions [including treatment intensity and mode of delivery for psychological interventions] and categorising them using a class random effects model. Other

							parameters, such as sex, socio-economic factors, therapist factors, may contribute to heterogeneity, but only if they are effect modifiers. In such a large and complex dataset, these factors were inconsistently reported and thus the impact of them is difficult to explore. Of course, this would also be a problem had exclusively pairwise MA been conducted for all 142 RCTs for less severe depression and 534 RCTs for more severe depression that were included in the systematic review. Considering heterogeneity when assessing the hundreds of pairwise, independent comparisons of this dataset would make interpretation of the findings and conclusions as to which interventions are the best options highly problematic. A random class effects model was used for all NMAs to account for heterogeneity between treatments within class as well as between studies. In addition it was aimed to explain the heterogeneity by exploring the impact of a number of other potential effect modifiers and analytic decisions to assess their impact on model fit and heterogeneity for SMD, including: • the impact of small study bias (see bias-

							adjusted models) (pre-specified sensitivity analysis) • restricting analyses to non-pharmacological interventions only (pre-specified sensitivity analysis) • the impact of excluding studies that had less than 15 participants in any arm (post-hoc sensitivity analysis) • the impact of assuming additivity of control arms (e.g. assuming the relative effect of TAU vs TAU + CBT was equal to No treatment + CBT) (post-hoc sensitivity analysis) • the impact of excluding studies that had >5 points' contribution to the residual deviance (post-hoc sensitivity analysis) • the impact of restricting analyses to studies classified as "low risk of bias" for attrition (additional analysis performed post-consultation). Between-study heterogeneity in the NMA was formally assessed for each network and the results of this assessment and of potential impacts on transitivity and inconsistency were taken into account by the committee when interpreting the results of the NMA and making recommendations.

							It is correct that there is often low power to detect inconsistency, particularly when (as in several of the networks) there is high heterogeneity. This is essentially because heterogeneity and inconsistency are manifestations of the same problem – an imbalance of effect modifiers. Therefore, an exploration of the impact of potential effect modifiers on the results (e.g., using sensitivity analyses) and an understanding of their impact on both heterogeneity and inconsistency can help to determine whether they are indeed effect modifiers or not, and therefore whether assumptions of transitivity and consistency are likely to be reasonable. Note that whilst there may be baseline characteristics that differ between studies, the imbalance is only of concern if these are effect modifiers and is not of concern if these are only prognostic factors. Detailed results of inconsistency checks and comparison between mixed (NMA) and direct evidence as well as additional sensitivity analyses have been provided in Appendix M of Evidence review B, and supplements B5 and B6. The committee considered all these issues when making

							recommendations alongside the results of the pairwise MA, the economic modelling results and newly reviewed qualitative evidence. Recommendations take also into account individual patient needs and preferences, which might be argued to be an effect modifier the distribution of which could potentially differ across pharmacological, psychological and physical treatment trials. The committee agreed that treatment rankings in the NMA suggested uncertainty in the results. However, as explained above, the treatment rankings in the NMA were not the only criterion when assessing the evidence and making recommendations. The committee agreed that there is not very large difference in the effects sizes between individual CT/CBT and STPP, and this uncertainty in the NMA results is stated in several places in evidence review B, including the committee's discussion. It is noted that, for less severe depression, the effect on the SMD vs TAU was based on N=481 for individual CBT and N=49 for STPP. Also, the 95%CrI were much wider for STPP than for individual CBT. As stated in the

							evidence review B, the committee considered insufficient evidence on any treatment class that was derived from N<50 people across RCTs on each NMA outcome (after looking at the total size of the evidence base in this area and noticing that there were several treatment classes with larger volume of evidence), and did not consider those treatment classes for a practice recommendation, however, they made an exception for treatment classes already available on the NHS, such as STPP. For more severe depression, the effect on the SMD vs pill placebo was based on N=1044 for individual CBT and N=267 for STPP. There was evidence for effect vs pill placebo for individual CBT (as the 95%CrI did not cross the zero line) but not for the STPP class (however, effects for interventions within the STPP class did marginally show effect vs pill placebo). The recommendations and the ranking of treatments for a new episode of depression were also affected by the results of the guideline economic modelling, which was informed by additional outcomes, such as discontinuation, response in completers and remission in completers. The guideline economic analysis results, which were also

							characterised by uncertainty, suggested that individual CBT was more cost-effective than GP care but STPP was less cost-effective than GP care in both less and more severe depression. As repeated above, overall, when making recommendations, the committee considered the results of the NMA regarding the mean effects of each treatment class vs the reference treatment, the uncertainty around them (as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class. They also considered the results of the pairwise meta-analysis. The committee also considered the relative cost-effectiveness of interventions, as suggested by the guideline economic analysis. Other factors such as implementation issues (step 2 and current structure of IAPT services), treatment acceptability (expressed in discontinuation rates, which were incorporated into the economic analysis), side effects (drugs), and applicability of the evidence in the UK

							context (relating to problem solving, as well as tp acupuncture and antidepressant combination) were also taken into consideration. All this information on the evidence and committee's considerations are provided in Evidence review B. Judgements on 'good' evidence or 'some evidence' were made on the basis of 1) the magnitude of the effect and 2) the available evidence base regarding the number of people tested on each treatment, rather than the number of trials testing each treatment. The committee felt more confident to recommend treatments that had been tested on several hundreds of people and found to be effective (such as individual CT/CBT) rather than interventions tested on few people and found to be effective. For this reason, the committee decided not to consider interventions that had been tested on N<50 people, even though some of them (e.g., combined CT/CBT group + exercise group in less severe depression; mindfulness or meditation group in more severe depression) had shown very high effects in the NMA.

							In less severe depression, group CBT showed wide 95%CrI around its mean ranking in the economic analysis, however it is noted that these were very skewed and that in most iterations group CBT ranked in a high place among other treatments (since its mean ranking was 2.76 in an analysis involving 16 interventions). It is noted that group CBT was found to be dominant in its comparison with group BA (which ranked 2nd most cost-effective), i.e., it was less costly and more effective, and, in their in-between comparison, group CBT had an 85% probability of being more cost-effective than group BA (data not shown in the report). Similarly, it was shown to have an ICER of £1,466/QALY versus group exercise (3rd most cost-effective option), which is well below the NICE lower cost-effectiveness threshold of £20,000/QALY, and a probability of being cost-effective of 81% in their in-between comparison. Therefore, the uncertainty expressed in the rankings reflects uncertainty in the overall results across the 16 interventions included in the analysis, but not necessarily uncertainty in the relative cost-effectiveness of each intervention within the analysis.

							Comparisons were made between all treatment classes and all interventions, on every outcome examined in the NMA. However, it was not feasible to include all these results and/or comment on the differences in effect between all pairs of treatments examined in the main evidence report (this was also one of the reasons why NMA was employed, in order to synthesise available evidence and summarise results by ranking treatments and providing effects of each treatment versus a common reference treatment). Nevertheless, full results on the relative effects between all pairs of classes and interventions from the NMA are provided in Supplements B5 and B6, for less and more severe depression, respectively. Results from pairwise MA that have included all available head-to-head trial comparisons are reported in Supplements B2 and B3. The quality of the evidence underpinning the NMA was assessed by examining the factors considered in a GRADE profile (risk of bias, publication bias, inconsistency, indirectness and imprecision). The Cochrane risk of bias tool for RCTs was used to assess

							potential bias in each study included in the review. Risk of bias ratings for each RCT included in the NMA are provided in Supplement B1. The model goodness of fit and inconsistency were assessed for each NMA. Bias-adjusted models were run to explore and adjust for potential bias associated with small study size. Transitivity between populations participating in pharmacological and non-pharmacological studies was assessed in a sensitivity analysis which excluded pharmacological trials, as well as several other post-hoc sensitivity analyses that were run (see above). Finally, indirectness was considered by qualitatively assessing potential differences across the populations, interventions and outcomes of interest, and those included in the relevant studies that informed the NMA. Details of quality assessment, which were considered by the committee when interpreting the results of the NMAs, are provided under 'Quality assessment of studies included in the evidence review' separately for less and more severe depression, in Evidence review B. These factors were considered by the committee when making recommendations. A threshold analysis was also planned, as an alternative to GRADE for assessing

							confidence in guideline recommendations based on the NMA (Phillippo et al., Ann Intern Med 2019, 170(8):538-546). However, it was noted that, in addition to the results of the NMA, the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. For this reason, it was difficult to identify a clear decision rule to link the recommendations directly to the NMA results. Therefore, conducting a threshold analysis would not add value to decision making. This is reported under 'Quality assessment of studies included of studies included in the evidence review and the evidence' and also 'The committee's discussion of the evidence -> Interpreting the evidence -> The quality of the evidence'. In principle, adjusting for risk of bias in individual trials would be something that could be explored as a potential effect modifier. However, for these analyses to work, a good spread of "good" and "bad"

							studies across the network is needed, which is not the case, as it can be seen in the risk of bias assessments. To make this clear, a table of the number of studies with different risk of bias domains in both more and less severe depression for SMD has now been added in Appendix M of evidence review B. The committee were also presented with the risk of bias assessments for all the studies and took account of this when making their recommendations. The subgroup of studies rated as low risk of bias for attrition was investigated as a sensitivity analysis but found no evidence that this was an effect modifier. Although there are sufficient studies to analyse a low risk of bias subgroup for Blinding (participants), Blinding (care administrator) and Performance, these studies are almost exclusively pharmacological studies, and the analysis is equivalent to performing a subgroup analysis of pharmacological studies only. Given that a pre-specified sensitivity analysis of non-pharmacological studies only was conducted and found that results were not sensitive to this, it would be unlikely to detect any differences that might arise from a subgroup of

							pharmacological only (equivalent to low risk of bias for Blinding or Performance). Adjusting for small study effects captures a range of potential biases that are associated with smaller studies, including, but not restricted to, publication bias. Sensitivity analyses to risk of bias domains where it was possible / informative to do so have now been included (see above). However, in the absence of sufficient information to explore other risk of bias domains, the best proxy available was to explore the effect of study size which is often associated with risk of bias indicators. Boxplots of the risk of bias domains by the number of participants randomised per study arm have now been included in Appendix M of Evidence review B, which shows smaller studies to be at higher risk of bias across almost all domains in both more and less severe depression. The analysis of small study effects has the benefit that all studies can be included in the analyses simultaneously, thus increasing power to detect any effect. Cuijpers et al. (2016) assessed the quality of individual trials of psychotherapies for adults with depression and found that

							individual trials did not have enough power to identify small differences in effect. The authors concluded that 'Meta-analyses may be able to solve the problem of the low power of individual trials. However, many of these studies have considerable risk of bias, and if we only focused on trials with low risk of bias, there would no longer be enough studies to detect clinically relevant effects.' This is a limitation of the evidence base and not of the NMA per se and confirms the findings of the guideline risk assessment, according to which, most studies included in the review were at high risk of bias. This would also be a problem had a pairwise meta-analysis been conducted.

38	SH	Society for Psychotherapy Research	Evidence review B & Cost analysis	General	General	Economic analysis/modelling Overall, the experts who, on behalf of our stakeholder organisation, reviewed the two cost analyses of first episode depression reported these two ambitious analyses were well conducted and that what was done is transparent. They pointed out however that the resulting findings are heavily influenced by the NMA and that the developers have duly reported that the economic analysis results need to be viewed in light of these limitations (in particular some evidence of inconsistency). The authors of the economic analysis also themselves stated that the results overall were "characterised by considerable uncertainty, as reflected in the wide 95% credible intervals around their mean rankings" (evidence review B. p. 360).Overall comment: Acknowledging the comments of the authors of economic analysis about how the findings should be viewed, we (too) would like to point that the models overall show high levels of uncertainty related to the relative effectiveness and cost effectiveness of all the interventions, including a very high degree of uncertainty about estimates of cost. This is expressed in the relatively modest or limited difference in overall quality of life gains, cost per QALY gains, and net monetary benefits between most interventions, and wide 95% credible intervals (CIs)around their mean rankings. For example, group CBT was identified as having the highest net monetary benefit for less severe depression. However, the CIs imply that the net monetary benefit could be anywhere between the 1st most cost effective and the 12th most cost-effective. As such, as expressed above, we do not think the economic cost analysis	Thank you for your comment and for your positive feedback on the guideline economic modelling. It is true that the economic models of treatments for a new episode of depression were informed by the guideline NMAs on discontinuation, response in completers and remission in completers, and that any limitations and uncertainties of the NMAs are reflected in the methods and results of the economic models. Results were characterised by uncertainty, nevertheless, they did allow conclusions on cost-effectiveness to be made. For example, in less severe depression, group CBT did indeed show wide 95%CrI around its mean ranking, however it is noted that these were very skewed and that in most iterations group CBT ranked in a high place among other treatments (since its mean ranking was 2.76 in an analysis involving 16 interventions). It is noted that group CBT was found to be dominant in its comparison with group BA (which ranked 2nd most cost-effective), i.e., it was less costly and more effective, and, in their in-between comparison, group CBT had an 85% probability of being more cost-effective than group BA (data not shown in the report). Similarly, it was shown to have

						that was conducted warrants the suggested rankings of treatment recommendation. Given the lack of strong evidence of differences in the economic benefits of the different treatments we would strongly suggest that the hierarchy of treatment choices needs to be changed to provide a menu (non-ranked) of treatment choices. Some specific comments:(a) Overall, we feel that the models are very ambitious and, as with the NMA to assess clinical evidence, we are concerned that this developed model has not been tested before and consequently that its validity and reliability has not been made public for peer-reviewed scrutiny. This thus begs the question as to whether such an utmost important review of the evidence which is used to inform national treatment guidelines should utilise novel, and as such untested, models. The identified uncertainty in the results is a further and significant concern, which to our mind weakens the reliability of the treatment recommendations. (b) The analysis looks at a 2-year follow-up phase. It is unclear why only two years have been chosen; the economic evaluation for PTSD, for example, chose a 3-year time horizon (see National Institute for Health and Care Excellence. Post-traumatic stress disorder. NICE; 2018. https://www.nice.org.uk/guidance/ng116). We are, furthermore, concerned that the data utilised to model these effects are based on the 6-months follow-up data derived from the NMA. As emphasised above the lack of available long-term follow-up data is crucial here, and the assumption that the effects at 6-months follow-up are sustained is highly questionable. Although the short-term follow up of the	an ICER of £1,466/QALY versus group exercise (3rd most cost-effective option), which is well below the NICE lower cost-effectiveness threshold of £20,000/QALY, and a probability of being cost-effective of 81%. Therefore, the uncertainty expressed in the rankings reflects uncertainty in the overall results across the 16 interventions included in the analysis, but not necessarily uncertainty in the relative cost-effectiveness of each intervention within the analysis. Moreover, some interventions were found to be less cost-effective than GP care, which was the reference treatment and was considered as a benchmark. Overall, uncertainty in relative cost-effectiveness may be higher for interventions in close places in ranking, but is lower between interventions ranked further apart, e.g. at the top and at the bottom of the ranking. After reviewing the clinical and economic evidence (including uncertainties and limitations), the committee considered appropriate to rank recommended treatments taking into account clinical and cost-effectiveness as well as other issues such as the applicability of the evidence

						patient-level studies is a limitation that has not been acknowledged, this is important given that the impact of further-line treatment is likely to extend to the longer term, particularly cost savings.(c) The definition or criteria for 'more severe depression' is rather confusing and needs clarifying. Looking at the evidence review B: appendix j, p. 289ff. it states on the one hand: "multiple recurrent episodes have not been incorporated" and that a separate model for relapse prevention has been developed. Yet, further down when depression is defined it is stated: "People in the economic analysis were assumed to be experiencing their first depressive episode if they had less severe depression and their third depressive episode if they had more severe depression, to cover a range of presentations of adults with a new episode of depression in routine clinical practice. The number of previous episodes determined the study population's risk of relapse following remission of the current episode but had no impact on the effectiveness of interventions in treating their current episode." It is not clear how these decisions about definitions were made or indeed how they are scientifically justified. (d) A further concern of ours pertains to the additional scenario work that was carried out, which highlights that a stronger economic argument for all psychological interventions can be made when lower pay bands have been applied. We would urge NICE to consider the potential impact of this analysis and whether it might support further marginalisation of the psychological therapies professions with NHS services by providing an apparent rationale to reduce staff costs even more (with the	(e.g. for individual problem solving), but also taking account of patient clinical needs and preferences. Interventions are arranged in tables 1 and 2 of the guideline in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee did not consider it appropriate to present an entirely non-ranked menu, as this would not reflect the evidence base nor serve as a guide to choose for those who do not have pre-existing preferences. Regarding your specific comments:

						consequence that services would nearly entirely need to be staffed by trainees or newly qualified therapists/psychologists. Salary costs at band 7 can already be considered rather low and mean that professionals would struggle to make a living, which has significant potential workforce implications for a healthcare sector already struggling with workforce supply issues.(e) Lastly, we would like to point out that there are a number of limitations with the QALY metric and its application that should not be disregarded (Pettit et al., 2016). The empirical basis for the currently stipulated threshold range of £20,000 to £30,000 is limited and yet to be properly ascertained. Like for other newer and promising medical interventions that are more costly, the method for QALY calculation may need adjustment in particular for psychological therapies to realise the financial advantages.	(a) The models are built following Markov modelling principles. These are not novel or untested techniques. Actually, Markov modelling techniques are routinely used in the economic evaluation of healthcare interventions for over 20 years. The complexity of the guideline economic modelling lies in the number of interventions tested for each level of depression severity, rather than in the model's structure or underlying assumptions. (b) The 2-year follow-up phase (following treatment endpoint) was determined based on the committee's advice. The purpose of selecting a longer time horizon (rather than a short time horizon that would end right after treatment for the new episode was completed) was in order to allow the longer-term impact of treatment success or failure as well as of potential treatment discontinuation on costs and outcomes to be captured. Moreover, a 2-year follow-up allowed modelling events such as drug continuation and tapering and/or provision of relapse preventive interventions, where relevant. It is noted that the effects and course of depression beyond end of

							treatment were based on synthesis of data from long-term epidemiological studies that examined the course of depression, studies on relapse prevention (where this was relevant to model), as well as a UK cohort study that reported related resource use and costs incurred by people with depression, and not on extrapolation of short-term data from the RCTs included in the NMAs. The NMAs informed only the first 3 months of the models, i.e., from treatment initiation until treatment effect was measured (either after completion or early discontinuation of treatment). Results regarding relative cost-effectiveness of interventions are not expected to be substantially different between 2 and 3 years, given that the immediate effects of the interventions assessed were applied onto the first 3 months in the model. Beyond the initial treatment period, people in the model were assumed to follow the same course of depression (same risk of relapse and future recovery) across all treatments (but with different proportions of people in remission/at risk of relapse, as different proportions of people recovered, responded or remained depressed at treatment endpoint in each arm of the

							model, according to each treatment's relative effectiveness). (c) The text you cite around modelling recurrent episodes and the number of previous episodes are not related to the criteria for more severe depression. Definitions of less and more severe depression are provided in evidence review B, under 'Methods and Process - Summary of methods - Defining less and more severe depression' as well as in Appendix A. These definitions have been used throughout the report and across all analyses, including the economic analysis. The text you cite regarding multiple recurrent episodes describes the model structure and refers to future events, following treatment of a new episode. The text explains that the model included a two-year follow-up period, but (future) multiple recurrent episodes have not been incorporated in this model (which assesses 'acute' treatment) as they have been considered in a separate 'relapse prevention' model that was developed to support the respective review. The text has now been amended to clarify that the model has not incorporated multiple recurrent episodes that may happen in the

							future, following treatment of the new episode. Nevertheless, people in the model may have experienced depressive episodes before the treatment of their current episode. As stated, the number of previous episodes was needed in order to determine the risk of relapse following response/remission and had no impact on the effectiveness of the interventions in treating the current episode. In the base-case analysis, people with less severe depression were assumed to be experiencing their first depressive episode, while people with more severe depression were assumed to be experiencing their third depressive episode, based on the committee's advice. However, in deterministic sensitivity analysis, the number of previous episodes was increased from 0 to 2 in adults with less severe depression and was varied between 0 and 5 in adults with more severe depression (see 'Handling uncertainty' section). As seen in the results of sensitivity analysis, the impact of this change on the relative cost-effectiveness of treatments was negligible.

							(d) The committee agreed that the sensitivity analysis relating to delivery of high intensity psychological interventions by therapists in lower pay bands is not relevant and it has now been removed from the economic analysis appendix. This scenario was only tested in sensitivity analysis and it played no role in interpretation of the economic results or when formulating recommendations. (e) The analysis was based on NICE principles and according to the NICE guidelines manual. The QALY is the preferred NICE measure for health interventions, as the benefits from its use are considered to outweigh its limitations. In the guideline economic analyses, QALYs were estimated according to NICE recommendations (i.e., they were based on EQ-5D ratings, valued by UK population using the UK tariff). The NICE cost-effectiveness threshold was considered and used in decision-making in a consistent way with the NICE guidelines manual and other NICE guidance. Psychological interventions are not considered to be more or less innovative than other psychological interventions included in the economic

							analysis, and therefore there was no need to apply the NICE upper cost-effectiveness threshold.

39	SH	Tavistock and Portman NHS Foundation Trust	Evidence review D	025-367-368	Table 7 and Table 75	Miss-classifying of the Tavistock Adult Depression Study (Fonagy et al., 2015) We are very concerned that the inaccuracy that we have pointed out during the consultation of the second draft of this guideline has not been rectified and still appears in this draft. We therefore urge you to correct it this time.As stated in Table 7 and Table 75, the study is classified erroneously as augmenting any antidepressant with a psychological intervention versus continuing with the antidepressant only. As clearly indicated this study investigated the treatment of long-term psychoanalytic psychotherapy + TAU versus TAU. The study was designed as a pragmatic trial in order to reflect common NHS practice treatment guidelines. As such, TAU consists of a range of short-term treatments as recommended by NICE (2009), including CBT, counselling, IPT, CMHT, to which the primary care provider referred the patients to. The study did not follow an augmentation strategy. The study used a fundamentally different definition of TRD than proposed in this guideline that uses an exclusively pharmacological definition that requires operationalising of dose and duration monitoring. Furthermore, quality of life and functioning outcomes that are reported in the published paper are not included in Table 7 and we ask you to add them. The study used the GAF and the QlesQ.	Thank you for your comment. The interventions in the Fonagy 2015 study were classified as long-term psychodynamic psychotherapy + any antidepressant versus any antidepressant, as over 80% of participants were receiving antidepressants at baseline in both arms. The committee agreed that where this was the case categorising as 'any antidepressant' was more informative than the ill-defined treatment as usual which can be used to refer to a vast range of interventions or no treatment at all. This categorisation rule was consistently applied across studies that included a 'usual care' arm in order to more accurately reflect the treatment that participants were actually receiving. The further-line treatment review includes studies of both those with no or limited response and those with treatment resistance. The decision to use the same data sets for both questions to inform the development of recommendations for no or limited response was based on considerable similarities and overlaps between the two populations. The committee were also aware of problems in defining/categorising treatment resistant depression, particularly

							with regards to non-pharmacological interventions, as there does not appear to be a similarly accepted definition of failure to 2 adequate courses of psychological therapy. Data could not be extracted from the Fonagy 2015 study for quality of life or functioning outcomes as numbers were not reported by arm. Given the size of the evidence base it was not possible to contact all authors for missing data.

40	SH	Society for Psychotherapy Research	Evidence review D	99	33	We notice that the economic study by Town et al (2020) was not further considered when formulating recommendations, and question that decision and would like the committee to reconsider. The analyses were conducted with a most relevant "control" consisting of a robust medical and psychological treatment and not just a wait list control. Cost equivalence to community treatment is an important result, particularly when the effectiveness data on depression scores has been rated as "high quality" (see p. 365f). The study shows that the intervention is comparable in cost to treatment delivered in community mental health teams. Hence the probabilistic analysis revealed cost saving in only 2.5% of iterations. In our opinion, it is not a limitation that this intensive intervention is comparable in costs. Furthermore, costs were log-transformed so the PA reported are a conservative estimate of the value for money associated with ISTDP.Second, when evaluated at the group averages obtained from the study, Town et al., (2020) found that ISTDP was associated with lower cost and improved quality of life versus a community mental health team, as was reported by the study. We question the conclusion that ISTDP being associated with a 65% probability of being cost effective is irrelevant, particularly when you consider the comparison intervention arm.Though the field has moved to reporting probabilistic analysis only, the results of Town et al., (2020) none-the-less provide useful information for decision-makers. Finally, the guidelines fail to consider the CEA conducted using the depression measures. This demonstrates a clear finding of	Thank you for your comment. The economic study by Town et al. has been reconsidered and the judgment has now been changed to 'potentially serious limitations'. The study was based on a small study size (N=60), had highly skewed costs in the control arm (and this is why the intervention changed from dominant to having an ICER of £11,369/QALY once high volume service users were removed from analysis), and was conducted in Canada, therefore it is not directly applicable to the UK context. The CEA conducted using the depression measure was also considered, but it is less applicable to the NICE decision-making context, where QALY is the preferred measure of outcome.

						cost effectiveness and value for money in reducing depression symptoms.	
41	SH	Tavistock and Portman NHS Foundation Trust	Evidence review D	111 112	010-04000 6-013 01803 00320 33	Should say: ‘relative to continuing with antidepressants and community treatment ‘Should say: ‘relative to continuing with antidepressants and community treatment ‘Should say: ‘discontinuation of antidepressant medications ‘Should say ‘continuing with antidepressants and community treatment as usual ‘This is incorrect: The effect was in fact significant and spoke to less need for medication after ISTDP	Thank you for your comment. The interventions in the Fonagy 2015 study were classified as long-term psychodynamic psychotherapy + any antidepressant versus any antidepressant, as over 80% of participants were receiving antidepressants at baseline in both arms. The committee agreed that where this was the case categorising as 'any antidepressant' was more informative than the ill-defined treatment as usual which can be used to refer to a vast range of interventions or no treatment at all. Receipt of antidepressant medication after initiation of the intervention was not an

							outcome of interest and so evidence for this was not reviewed.
42	SH	Tavistock and Portman NHS Foundation Trust	Evidence review D	113	016-02101 6-032-028	The sample size reported here states N=92. If the study reported here is the Fonagy (2015) RCT, which we think it is, it should state N=129. The study used an intention-to-treat design. Furthermore, if GRADE rankings are corrected, the wording of "very low quality" should be changed accordingly.	Thank you for your comment. As reported in the Fonagy (2015) paper, in Table 3, the N for the 42 month timepoint (24 months post-intervention) is N=92. The committee have reviewed the GRADE rating and do not consider it appropriate to change it.
43	SH	Tavistock and Portman NHS Foundation Trust	Evidence review D	114-179	002-005	It states no evidence was identified for functioning and quality of life measures. This is incorrect and needs rectifying. Fonagy et al (2015) report: Functioning (GAF) at 24 months follow-up's= 0.69 (CI: 0.26-1.11). Both GAF (t=3.3, P<0.001) and QLESQ (t=3.1, P<0.001) at 24 month follow up show significant differences in favour of LTPP. Moderate-strong effect sizes can be inferred for QLESQ based on equivalent sample sizes for both measures. These promising findings need to be considered in this review. We request to add a clinical evidence statement in support of LTPP based on the reported effect size for the GAF at 24 months follow up; and that this informs further considerations and recommendations.	Thank you for your comment. Data could not be extracted from the Fonagy 2015 study for quality of life or functioning outcomes as numbers were not reported by arm. Given the size of the evidence base it was not possible to contact all authors for missing data.

44	SH	Tavistock and Portman NHS Foundation Trust	Evidence review D	367-368	Table 75	Inaccurate or unfair quality assessment of the Tavistock Adult Depression Study (Fonagy et al., 2015)Table 75 reports the GRADE assessment for the study as “very low”. We, however, noticed several inaccuracies that will have led to a wrong assessment, which we urge you to rectify. These include: Risk if bias: It is rated ‘serious’ on the grounds that there are “group differences at baseline”. As we had stated in both previous consultation responses, we consider this an unreasonable down-rating. As explained the difference were on education and receiving state benefits and not on any of the clinical characteristics or with respect to critical and additional outcomes. As previously pointed out, the study utilised a minimization protocol of those variables that are known to affect outcome, including gender, baseline severity and receiving/not receiving medication. Furthermore, as clearly stated in the paper, when the chance imbalance in education was moderated for by the statistical analysis, the effect remained and was robust. Imprecision: It is rated ‘serious’ for 24 months follow up on grounds that the “CI crosses thresholds for both clinically important benefit and no effect”. This is incorrect. (N.B. this is a SMD not an odds ratio so the line of no effect is zero). This criterion appears to have been applied inconsistently between studies. The 95% CI is 0.26 to 1.1. The SMD is 0.68. We are wondering what the threshold for clinically important benefit is? If it is 0.5, then this would need to be stated and justified (in particular for a group of patients with such complex and severe form of depression).Other consideration: reporting bias We are concerned, once again, that a mistake that we had already	Thank you for your comment. For the Fonagy et al. (2015) study, risk of bias was rated as serious due in part to the significant difference between groups at baseline. Almost regardless of what this difference is, it suggests that there is a problem with randomisation as randomisation is intended to balance out potentially confounding variables. The non-blinding of participants and intervention administrators also presents a risk of bias; however, the rating reflects the blinding of outcome assessors (otherwise the rating of the risk of bias would have been very serious). With regards to the imprecision rating highlighted in your comment. The thresholds for clinically important SMD effects are -0.5 and 0.5. The 95% CI of -1.1 to -0.26 crosses the threshold of no effect (although it does not cross the line of no effect), and so it has been downgraded once. This is consistent with the methods outlined in Supplement 1. In response to the additional information provided regarding the rating of ‘publication bias’ due to funding from the International

						pointed out in the first and second consultation of this draft guideline has not been addressed. As pointed out, the study was not partially funded by the International Psychoanalytic Association (IPA). The IPA had no input into the design, conduct, analysis, or interpretation of the findings of the study. The RCT was funded by the NHS. A qualitative arm was included into the study in 2009 (6 years after it was launched) and it was for this purpose that the study received two small grants from the IPA. Taking the above inaccuracies into account, the risk criteria for the study will need to be reviewed and adjusted accordingly. It should then also be amended in other part of the documents (e.g. p. 113) and recommendations need to be re-considered in light of this.	Psychoanalytic Association. This source of funding represents a potential interest. The committee agreed that it is important to rate equivalently across psychological and pharmacological trials, and as a pharmacological trial would be downgraded for publication bias if it was partially funded by a pharmaceutical company, then it is also consistent to do so here. It is important to note that the GRADE system 'quality' rating is not a value judgement on the quality of an individual study but rather an estimate of confidence that an estimate of the effect is correct and is unlikely to change with further research. Given that the evidence for long-term psychodynamic psychotherapy comes only from this single study, which has a moderate-to-small sample size, it is not possible to assert with a great degree of confidence that the addition of another study would not change the effect.

45	SH	Tavistock and Portman NHS Foundation Trust	Evidence review D	General	General	Exclusion of important bona-fine studies of long-term psychodynamic psychotherapy for further line treatment We have noticed that that two important RCTs investigating long-term treatments have been omitted in the further-line treatment review. We find this particular concerning, and thus ask for it to be amended, as they both have provided crucial evidence of the effectiveness of long-term psychodynamic psychotherapy, a treatment modality that is currently offered within NHS services and UK tertiary sector. It is further concerning as the findings from the Fonagy et al (2015) NHS study, as pointed out above, that found depression severity and functioning improved over the long-term, have been disregarded too. As such, we emphasise the importance to include the evidence from these three trials, not only to provide more patient choice, but moreover to provide psychological treatments that have actually been found to help in the long-term follow up. All three studies provide evidence that effects are sustained, even improved, over the long-term (2-3 year) follow-up. In many cases, depression manifests as a long-term condition rather than an acute one, which requires long term management using a variety of approaches to treatment and management. Individuals with enduring and complex forms of depression often report a background of developmental adversity and trauma. As this draft acknowledges, the problems experienced are multi-faceted and often severe and hugely debilitating. Research and clinical practice have shown that many individuals with chronic or complex forms of depression have tried the available and recommended first or second-line short-term	Thank you for your comment. The further-line treatment recommendation that cross-refers to psychological treatment options for more severe depression is for people whose depression has had no or a limited response to treatment with antidepressant medication alone. There was no evidence that specifically examined switching to a psychological intervention for those who have not responded to initial antidepressant treatment, however, the committee drew on the evidence for first-line treatments in more severe depression. The committee agreed that the psychological interventions that had been identified as effective and cost-effective for first-line treatment of more severe depression could be used for people who had not responded to antidepressants and wished to try a psychological therapy instead. Leuzinger-Bohleber et al 2019 was considered for the chronic depression review and was excluded. This study also did not meet eligibility criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line treatment, participants were not

						treatments without success (e.g., Leichsenring & Rabung 2011; Maj et al. 2020). Moreover, systematic reviews have repeatedly shown that in complex mental disorders, longer-term psychotherapy has been found to be superior to short-term psychotherapy (Leichsenring & Rabung, 2011, Leichsenring et al., 2013).Recommendation for psychological interventions for furtherline treatment (and chronic depression) defaults to the recommendations of the 'more severe' first episode list for no clear reasons. Considering the evidence at hand might will, however, provide different options of treatments are already available within our NHS. These omitted studies that need to be included under the further-line treatment review are:1.The Leuzinger-Bohleber et al 2019, which investigated long-term psychodynamic therapy and long-term CBT and found both to be effective. It was considered under the chronic depression review and excluded because >20% were not first-line treatment. However, we cannot see a valid reason for excluding it under further-line treatment as either chronic or treatment-resistant as the study population fulfil criteria for both.2. Knekt et al 2008/2013/2016), which investigated the effectiveness of long-term psychodynamic. It was for inexplicable reasons considered under first-line treatment only, excluded due to the population <80% first-line treatment. Again, it should have been included under further-line treatment as the study population fulfils the criteria.	randomised at the point of non-response, and it could not be regarded as an augmentation study following limited or no response to antidepressants as only 36% of participants were taking antidepressants at baseline. This study has now been added to the excluded studies list in supplement D. Knekt et al 2008/2013/2016 was considered under first-line treatment as detailed in your comment and did not meet criteria. It also did not meet criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line treatment (in fact those receiving psychotherapy within the previous 2 years were excluded), participants were not randomised at the point of non-response, and it could not be regarded as an augmentation study following limited or no response to antidepressants as only 22% of participants were receiving psychotropic medication at baseline. This study has now been added to the excluded studies list in supplement D. There was only single-study evidence (Fonagy et al. 2015) for augmenting antidepressant treatment with long-term

							psychodynamic psychotherapy, and the committee considered the evidence too limited to make a recommendation for long-term psychodynamic psychotherapy specifically. However, a treatment option in the recommendation for people whose depression has had no or a limited response to treatment with antidepressant medication alone, includes changing to a combination of psychological therapy and medication, which could include long-term psychodynamic psychotherapy although it is not listed as an example due to the limited evidence.

46	SH	Society for Psychotherapy Research	Evidence review D, E, F	General	General	We notice that economic studies for those populations with chronic depression have been excluded in the other three reviews within this draft guideline. However, treatment recommendations for this group are based on the economic evidence from populations with 'new depression episodes', which is highly concerning. As stressed above, it is wrong to assume that these study populations are similar. Even if these study populations were similar, other aspects of difference may play an important role, including (a) that health care pathways differ, (b) the model chosen for new episodes may not be appropriate in terms of number of remission states, (c) the two-year time horizon considered is not sufficiently long to capture relative differences in cost and effects between interventions for chronic pression.	Thank you for your comment. As with all other review questions, systematic reviews of economic evaluations for interventions for further line treatment of depression, chronic depression and depression with a co-existing personality disorder were also conducted. The systematic review of economic evaluations of interventions for further-line treatment included 17 studies that met inclusion criteria. These studies were considered alongside respective clinical evidence when formulating recommendations. No economic studies on chronic depression and depression with a co-existing personality disorder were identified. Regarding primary economic modelling, this was not possible to conduct across all areas due to the model complexity required and time restrictions. Thus, in accordance with NICE guideline methods, an economic plan was prepared in collaboration with the committee, which prioritised review questions for primary economic analysis, using as criteria the expected resource implications as well as the quality and the relevance of available clinical and economic evidence. Using these criteria, the area of treatments for a new episode of depression as well as the area of

							relapse prevention were identified as high priorities for de-novo economic modelling (as they were considered to have major resource implications and clinical and economic data were of adequate quality to allow robust modelling to be conducted). The area of chronic depression was not prioritised for de-novo economic modelling; however, the committee did consider it as an important area with potential resource implications. It is noted, though, that this area is expected to require complex economic modelling, that may not be possible to capture all relevant sub-groups, as this area includes a heterogeneous population that may follow very diverse treatment sequences and pathways. When formulating recommendations, the committee considered the existing clinical evidence on treatments for chronic depression. As there was no economic evidence in this area, the committee looked at the economic evidence on treatments for a new episode of depression only to check and confirm whether it supports recommendations for chronic depression (made based on the available clinical evidence). They noted that CBT, antidepressants and their combination were

							cost-effective in treating a new episode of depression. This observation gave them more confidence that antidepressants and CBT that has a focus on chronic depressive symptoms and associated maintaining processes are likely to be cost-effective in treating chronic depression.

47	SH	Tavistock and Portman NHS Foundation Trust	Evidence review I	General	General	Service user voice and choiceEmphasizing and integrating patient choice is an important part of NHS reform (DH, 2009). Coulter (2010) argues that the introduction of choice in to the healthcare market, particularly within the NHS, is a vital part of improving service user ratings of public health care services. In the King's Fund review of patient centred care, one of the five main themes to improve the post-reform NHS is engaging patients in decisions about their care. As an NHS Trust, we are as such very pleased about the overall tone within this guideline that stresses patient choice, shared decision making, and greater emphasis on individualised care and treatment plans. The qualitative evidence reviews I on patient choice has provided important and interesting insights that we notice have been integrated to guide the whole draft guideline. We applaud the committee for this great peace of work and its application. We are, however, disappointed that this review did not include research about service user experience of treatments, which, as previously advised, would provide direct first-person data to support the recommendations derived from the clinical and economic analysis. We believe that the results of that analysis would have provided the committee with the most relevant, evidence-based, arguments to support the task of offering interventions in a specific order where individuals have not expressed a preference over a particular one. As previously pointed out, there are numerous studies to that effect that could be synthesised. We therefore suggest for this review question to be refined in order to be more inclusive of studies of service-user experience of treatments.	Thank you for your comment. The experience of care section from the 2009 guideline was not included in this update (as specified in the scope). However, as your comment recognises, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment.

48	SH	Stakeholder coalition	Evidence Review I	General	General	The review evidence on service user experience We argued that creating sound policy requires that we draw on a diverse range of evidence, which includes qualitative research and service-user feedback. We were particularly concerned that the previous draft did not update the service-user experience section, thereby ignoring huge amounts of published studies providing the insights and knowledge of service-users. As such, we asked for a full systematic review of primary studies of service user experience of treatments, employing formal qualitative methodology to synthesise the findings and to incorporate these into the treatment recommendations. The guideline committee decided, however, instead to focus on a systematic review of 'patient choice'. We have questioned that decision and advised that despite its merits, it would not provide the appropriate evidence needed to inform treatment recommendation. Whilst the qualitative review carried out has highlighted the need for greater choice, which was indeed incorporated into the overall tenet of this draft guideline, it has not yielded an insight into the views and experience of the specific (pharmacological, psychological, psychosocial and physical) treatments. We have previously pointed to the numerous existing studies that would not only strengthen this treatment guideline by ensuring that the views and experiences of those who use the treatments recommended are properly taken account of, but would also adhere to what we believe to be the sine qua non of a publicly funded body tasked with devising clinical guidelines. We therefore recommend that this particular review is refined to focus more clearly on experiences of treatments.	Thank you for your comment. The experience of care section from the 2009 guideline was not included in this update (as specified in the scope). However, as your comment recognises, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment.

49	SH	Society for Psychotherapy Research	Evidence review I	General	General	Patient choice versus patient experience of treatmentA systematic review of qualitative studies informing questions around treatment choice is a welcome amendment. It has indeed provided important insight into service users' experience of 'patient choice' or the lack of it, and as such enriched the guideline in a meaningful way. However, as we have stressed before, this research question has not investigated the pivotal aspect of patient/service user experience of the psychological and medical treatments reviewed in this guideline. There is an important distinction to be made between making general decisions on which psychotherapeutic interventions are the most effective, and making contextually-sensitive decisions on which interventions will be effective (appropriate) for which patients/service users. We do not believe the present version, nor the suggested changes for the third revision of the guideline, adequately address these latter considerations, and thus will not provide sufficient guidance for clinicians about making contextually sensitive referrals. As such, we continue to stress our concern that the available evidence base is not being fully utilised. As emphasised previously, a full systematic review of primary studies examining experience of treatment is required, employing formal methodology for synthesis of study results, and incorporating these findings into a broader approach for the review. One of the reasons, why we stressed the importance to focus this evidence review on 'patient experience' of treatment rather than limiting it to 'patient choice' in this guideline, was for a synthesis of these available studies in order to strengthened this guideline in terms of a	Thank you for your comment. The experience of care section from the 2009 guideline was not included in this update (as specified in the scope). However, as your comment recognises, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment.

						focus on individualised care without discrimination. We would furthermore argue that that kind of evidence would provide much more valid reasons to support the tasks of offering interventions in a specific order to support joint decision-making where individuals have not expressed a preference over a particular one. We therefore suggest for this evidence review to be amended or refined in order to include relevant service-user experience of psychological, pharmacological and physical/psycho-social interventions.	

50	SH	UK Council for Psychotherapy	Evidence Review I, Guideline	General	General	Data on service user experience We argued that creating sound policy requires that we draw on a diverse range of evidence, which includes qualitative research and service-user feedback. We were particularly concerned that the previous draft did not update the service-user experience section, thereby ignoring huge amounts of published studies providing the insights and knowledge of service-users. As such, we asked for a full systematic review of primary studies of service user experience of treatments, employing formal qualitative methodology to synthesise the findings and to incorporate these into the treatment recommendations. The guideline committee decided, however, instead to focus on a systematic review of 'patient choice'. We have questioned that decision and advised that despite its merits, it would not provide the appropriate evidence needed to inform treatment recommendation. Whilst the qualitative review carried out has highlighted the need for greater choice, which was indeed incorporated into the overall tenet of this draft guideline, it has not yielded an insight into the views and experience of the specific (pharmacological, psychological, psychosocial and physical) treatments. We therefore have concerns about whether the guideline is as closely reflective of service user experience as it could be: The qualitative evidence used to draw conclusions about the nature of patients' choices overly focused on the experience of practitioners (15 of the included studies interview practitioners exclusively), of which eight were conducted outside of the UK. Given that many of the themes relating to professional perspectives are directly related to referral pathways and availability of treatment,	Thank you for your comment. As specified in the scope, the experience of care section from the 2009 guideline was not included in this update. However, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user and practitioner experience around choice of treatment. As outlined in the protocol, the committee agreed that it was important to include both service user and practitioner perspectives given the roles that both play in shared decision-making. The committee considered applicability of the studies to the UK service setting when interpreting the evidence. For example, as outlined in the other factors that the committee took into account section of Evidence review I, the committee discussed the relevance of studies which had been conducted in the US, as Primary Care Physicians do not undertake the same training as GPs and may have limited knowledge on depression. When making recommendations, the committee interpreted the evidence in light

						their relevance to a UK context is questionable. On page 67 from line 7 the committee call for 'identifying the mode of action of psychological interventions' for less severe depression as this would 'allow greater differentiation between the interventions and aid patient choice.' We welcome this call and recognise the need for greater differentiation between the interventions. Furthermore, we argue that a greater differentiation would be welcome for treatments for other, more severe forms of depression. What are described as modes of action in the draft Guideline, may be translated in psychotherapy research as 'mechanisms of action', or 'mechanisms of change' (Kazdin, 2007; 2009). We believe that qualitative evidence and evidence from case reports may be utilised to this end, in the form of a discrete evidence synthesis, such as performed for Evidence Review Section 6.2 of 'Developing NICE guidelines: the manual' identifies different approaches to qualitative evidence synthesis including the use of meta-ethnography and meta-synthesis which would be appropriate vehicles for incorporating qualitative evidence including case study to identify modes of action, and these approaches are already established in psychology and psychotherapy research (Timulak, 2009; Iwakabe and Gazzola, 2009; Levitt, 2018). The subsequent results could be distilled into talking points to be presented alongside the existing 'menu' of treatments set out in the Guideline, adding context to the dialogue between practitioner and patient in their arrival at a collaborative decision. This is a recommendation we make not only for the current Guideline but for future Guidelines which present	of their knowledge of the clinical context so that the 'reality' for people experiencing depression was taken into consideration and recommendations were made that were relevant to the populations that clinicians typically encounter. The committees' discussions on this are documented in 'The committee's discussion of the evidence' sections. The committee considered that the contextual features that you describe as requiring qualitative evidence to address, are taken into account by this interpretation of the clinical context by the committee. The predominance of antidepressants and primary care experiences in Evidence review I is driven by the eligible studies available. Only findings relevant to choose of treatment were extracted and included in this review. Thus, although studies may have included experiences of treatments, for instance, antidepressants, only retrospective experiences of how these treatments were offered, initially discussed, and initial preconceptions and preferences were relevant to this review. The McPherson et al. (2020) review was

						psychological therapies as treatments. While it is acknowledged that this part of the evidence review was focused on patient choice, a significant aspect of understanding service user preferences is their experience of receiving a treatment. Indeed, many of the included studies relating to antidepressant medication are focused on the experience of receiving this specific treatment rather its relation to any other in terms of choice. Given that such articles have been included, and the importance of understanding service user experiences in understanding treatment acceptability, it seems logical that broader search terms should have been used to include such data in relation to a broader range of treatments. By including mandatory search terms specifically relating to 'choice' (Appendix B, p71, line 10) many very relevant papers have not been included. For example: McPherson et al (2020) Patient experiences of psychological therapy for depression: a qualitative metasynthesis. This study includes qualitative data from over 600 patients, all with an active diagnosis of depression, and provides important insights into their experiences of receiving different talking therapies. Additionally, a service user driven consultation, specifically relating to choice of treatment for those with a diagnosis of depression in the UK can be found within the grey literature. Faulkner (2020) Informing a Decision Guide for Psychological Treatments for Depression. Finazzi & Macbeth (2021) Service users experience of psychological interventions in primary care settings: A qualitative meta-synthesis — also provide an up-to-date qualitative synthesis of the experience of patients	identified by the updated search and was checked for any relevant primary studies. Meta-synthesis results were not appropriate to extract due to differences in the review questions. This study is listed in the excluded studies in Supplement I. Faulkner (2020) was not identified by the searches or considered by the committee as it does not meet eligibility criteria, as grey literature was not considered. Finazzi & Macbeth (2021) does not meet eligibility criteria for this review as the focus is on service users experience of psychological treatments, which relates to the experience of care section of the 2009 guideline that (as specified in the scope) was not included in this update. In addition to the results of the network meta-analysis (NMA), the committee took other pragmatic factors into consideration when making recommendations about treatment of a new episode of depression, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account

						receiving therapy through IAPT services. While it is not exclusively focused on those with a depression diagnosis, the data are largely from this population. Once again, these authors conclude the importance of involving patients in choice in terms of more positive outcomes. Of the included studies focusing on patients, the majority pertain to the experiences of individuals taking antidepressant medications, as opposed to experiences in relation to different types of talking therapies. Eight qualitative investigations of patient experience focus exclusively on medication, with an additional study exploring experiences of antidepressant medication in comparison to CBT. Only two studies specifically assessed patient experience of non-pharmaceutical therapies: one of group therapy and one for guided self-help. This disparity appears at odds with the guideline itself which is largely focused on non-pharmaceutical therapies. No data have been included regarding patient experiences, or knowledge of, non-CBT focused talking therapies. Furthermore, there is a paucity of qualitative data pertaining to the experience of those receiving group or self-directed treatments. This appears at odds with the guideline itself, which is largely focused on talking therapies as first line treatment. While metanalyses have shown that improvements are seen for those who complete psychological therapies through IAPT, 60% of those who are referred never attend or do not complete more than one session (Moller et al 2019). Therefore, the majority of those who receive a treatment referral are being severely underserved and understanding of the reasons behind this high dropout rate is critical to improving patient care for those	individual needs and allow patient choice. The committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion. It was recognised by the committee that people who have had prior episodes of depression may also have preferences for their treatment based on prior experience or insight into their own depression patterns.

						experiencing depression in the UK. Given that such an understanding could most easily and meaningfully be derived from qualitative research, it seems important that such data should be included in the guidance where possible; particularly as it is likely to have implications for the patient experience and / /or acceptability of particular psychological treatments as recommended by NICE. As referenced throughout the guidance, patient choice is an important aspect of cost effectiveness. Given that high dropout rates are by no means cost effective nor efficacious in the patient's treatment, using qualitative data to better understand this seems crucial to these recommendations (see Windle et al, 2019 for a systematic review and meta-analysis re patient preferences and treatment adherence for depression). Given the lack of significant differences in efficacy between the treatments recommended in this guideline, much of the emphasis has fallen to health economic cost-effectiveness of different therapies. Nevertheless, when considering that only around 40% of referrals complete IAPT therapy (NHS digital 2021; Moller et al 2019) it seems sensible to weight the focus more in terms of individual patient preferences to ensure service users are receiving efficacious therapies that are acceptable to them. Dropout rates should also be considered in any analyses of cost effectiveness as: a) failed therapy and the cost of relapse is not cost effective and b) there is a significant body of research to show that when patients feel educated about, and involved with, their treatment options, adherence is higher (Windle et al 2019) The search criteria utilised for the evidence review did not employ stringent	

						criteria for those with a diagnosis, or active experience, of depression; nor were any studies included relating to additional diagnoses for which this guideline provides recommendations (e.g. borderline personality disorder). Despite these specific recommendations, there has been no exploration of patient experience or choice for those with dual diagnoses. Such data would be an important addition to the guidance as available evidence suggests that those with personality issues for example are likely to experience IAPT services in a different way to others. However, the specific needs of these individuals are not covered within the patient choice section, despite data being able to suggest that they may experience treatment in a different way and therefore have different preferences (Lamph et al,2020; Goddard, Wingrove & Moran, 2015). What is consistently highlighted across the qualitative data referenced by this guideline, as well as additional sources referenced in this response, is the importance of considering individual preferences and needs. While the guideline discusses patient choice throughout, and reinforces that GPs should work to establish this prior to referring, this is importantly not considered in the hierarchies of recommended treatments provided in the guideline. Given the differences in individual preferences for treatment, greater clarity should be provided to clinicians in terms of the differences between treatments so they are able to explain the options to provide patients with a choice. This should be more heavily emphasised within each section.	

51						We therefore recommend that this particular review is refined to focus more clearly on experiences of treatments.	Thank you for your comment. As specified in the scope, the experience of care section from the 2009 guideline was not included in this update. However, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment.

52	SH	Stakeholder coalition	Evidence reviews B, D, E, F, G	General	General	The categorisation of depressionWe noted during both previous consultations that the draft guideline is out of step with US and European guideline methodologies, leading to erroneous and unhelpful classification of research studies which do not match clinical or service user experiences. In particular we expressed our concerns to (a) the dichotomisation of depression into 'less severe' and 'more severe' in the evidence review of treatment of a new episode of depression, and (b) the separation of the more complex forms of depression into distinct groups. We remain very concerned that these two key methodological issues have not been changed as advised. Given that the treatment recommendations are based on these unvalidated distinctions of depression, their generalisability and applicability to clinical practice is highly questionable/disputable. We therefore urge for these categorisations to be reconsidered. We stress again that any treatment recommendations based on methodological choices that have not been validated will need to be viewed with caution. The distinction between less severe and more severe depressionWe uphold that there is neither methodological/statistical nor clinical validity of the categorisation of first episode depression into 'less severe' and 'more severe'. Most researchers and clinicians have a common understanding that depression severity levels fall into three broad categories of mild, moderate and severe (e.g., Wahl et al., 2014). Indeed, in the guideline itself these are referred to as the "traditional subcategories" (e.g., evidence review B, p.10, l.26). Having asked for it on numerous occasions, we are still short of a plausible	Thank you for your comment. The committee considered the current NICE classifications of mild to moderate and moderate to severe depression and agreed that although these classifications have been adopted quite widely there is potential uncertainty with regards to the management of moderate depression. The committee agreed that a dichotomy of less and more severe depression was clearer, and the guideline includes definitions (that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression includes the traditional categories of moderate and severe depression) in order to improve practical utility. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line

						explanation as to why the committee decided to diverge from traditional categorisations found in the majority of literature and, in so doing, adopt an unvalidated and unreliable methodology. We are particularly disappointed as in the last response that we received it stated: "these have been updated and are now based on published work". This, however, is inaccurate. None of the studies cited (Carmody, 2006; Rush, 2003; Uher, 2008; Wahl, 2014) provide evidence of a dichotomisation of depression severity. Moreover, Wahl et al (2014) clearly advocates the three traditional severity levels and provides clear threshold values for mild, moderate and severe depression (see their Table 3, p. 81). We further are concerned about the stringent inclusion/exclusion criteria for the two treatment reviews for new depression episodes. Many bona fide RCTs were excluded as their study populations reported > 20% of patients with chronic depression (> 2 years), > 20% of patients with a personality disorder, and > 20% receiving additional treatment (e.g., antidepressants or psychiatric care). Research has shown that 45% of patients diagnosed with depression are also suffering from a comorbid personality disorder (Friborg et al., 2014). In addition, usage of antidepressants is highly prevalent, with 17% of the adult population in the UK (7.3 million people) taking antidepressants between 2017-2018 (https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary). Not only is it rather uncommon for meta-analyses of psychotherapy trials for depression to exclude studies with more than 20% use of antidepressants (e.g., Cuijpers et al.,	presentations of depression are managed in primary care). The committee did not consider it problematic that the categorisations of depression used in this guideline were not in line with US and European guideline methodologies as there was no reason to believe that the different guidelines would be used in conjunction (thereby creating confusion), and the committee prioritised alignment with clinical practice in the UK. As highlighted in your comment, for the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then

						2021a, Cuijpers et al., 2020), exclusion of these and other criteria limits the representativeness and generalisability of the results. The distinction between more complex forms of depressionWe uphold that there is no evidence that warrants the distinctions between chronic depression, treatment-resistant depression, depression with personality disorder and psychotic depression. By doing so, this draft guideline provides erroneous and unhelpful classification of research studies with the consequence that treatment recommendations may also be erroneous. We notice that the review question for further-line treatment has been changed and now includes studies of psychotic depression, depression with personality disorders, chronic depression, and so-called treatment-resistant depression. However, in light of having kept the other reviews, we feel it has not really addressed the issue and may in fact lead to further confounding outcomes. In addition to being out of step with European and US guidelines, we are in particular concerned that it will be out of step with the clinical understanding of the groupings in the UK, especially with respect to chronic depression, and will thus lead to confusion instead of providing helpful guidance. Most individuals suffering from chronic depression (as defined here as lasting for at least two years) would have sought previous help; in particular when experiencing functional impairment and suicidality, as well as high rates of hospitalisation. It therefore seems contradictory and unhelpful to create such a sub-group of depressed patients. The configuration of the guideline could also lead to confusion among clinicians seeking treatment recommendations for	have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies

						chronic depression irrespective of whether an individual has sought previous help. As previously highlighted, the terms treatment-resistant and chronic depression are often used interchangeably and study populations often meet criteria for both (Abbass, 2006; Town & Abbass, 2017; Fonagy et al., 2015). This is also true for depression with a comorbid personality disorder (Abbass & Town, 2011; Friborg et al., 2014; Skodol et al., 2011).Taken together, we continue to be concerned that the categorisation and applied exclusion criteria for studies will have provided artefacts and led to treatment recommendations that cannot be easily applied to clinical practice. We therefore continue to stress the importance to address these concerns by (a) adopting the traditional classifications for the review of a new episode of depression, which may indeed include a fourth group of individuals whose depression is longer-lasting, (b) adjusting the exclusion criteria as advised above, and (c) combining the evidence review for all more complex forms of depression.	from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not.

							For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of psychotic depression, depression with coexisting personality disorder and chronic depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee reviewed the European Psychiatric Association classification but did not consider it appropriate to change the term to 'persistent depression' but considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered.

53	SH	Critical Psychiatry Network	Evidence Summary B	Section on less severe depression	General	Draft guidelines Page 23-30 Section 1.5.2 Whilst we welcome the committee's approach of recommending a variety of psychosocial interventions, and not prioritising drug treatment in less severe depression, we suggest that the committee should clearly suggest that antidepressants are not indicated in this situation, based on the committee's own review and other data on adverse effects that was not taken into consideration which is detailed below. In brief, antidepressants did not demonstrate statistically significant differences from treatment as usual (TAU) in any analysis presented for less severe depression. The analysis of cost effectiveness was conducted for antidepressants on the suspect premise that they showed a difference from TAU despite this difference not being statistically significant – that is, a treatment that was not shown to be effective was evaluated for cost-effectiveness. The study upon which this cost-effectiveness analysis was based did not show a clinically important difference for sertraline over placebo, amongst numerous methodological flaws. The adverse effects of medication in particular were not adequately evaluated in terms of balance of harms and benefits (which were assumed to be weighted towards benefit) and cost effectiveness due to relying on an unrepresentative single paper. Furthermore a neglect of the full costs of stopping antidepressants was neglected, in terms of personal loss of health and healthcare costs, using an inadequate four weeks of linear tapering as the model. The committee seems to have been inclined to prioritise existing clinical practice over the evidence produced by their own	Thank you for your comment, and for providing references by way of context for the points raised. The response has been structured around the main themes raised in your comment. <u>Effectiveness of antidepressants in less severe depression</u> It is true that SSRIs and TCAs did not show evidence of effect, but the same was found for the vast majority of psychological interventions. The committee noted that for the bias-adjusted NMA for less severe depression for the outcome of SMD the point estimate for the majority of intervention classes showed an improvement in depression symptoms, but most had very wide 95% credible intervals which crossed the line of no effect. It is noted that the mean SMD of TCAs and SSRIs versus TAU was -0.83 and -0.64, respectively. These effects were higher than the mean effects (versus TAU) of individual behavioural therapy, short-term psychodynamic psychotherapy, IPT and counselling, all of which were also considered in the economic modelling and

						review so that antidepressants, despite not demonstrating effectiveness in any analysis, were recommended. This present practice-bias also seems to have informed including treatments that patients would 'prefer' despite this preference being based not on sound evidence but on historical medical practice, not the usual basis for making evidence based recommendations. The inclusion of antidepressants as an alternative treatment to those who do not prefer other (evidence-based) treatment is likely to have ramifications to an outsized degree. As current clinical practice commonly includes giving antidepressants, the inclusion of antidepressants as an option is likely to mean that they are used more often than intended, with the perverse outcome that a treatment that did no demonstrate efficacy (or if relying on the short-term PANDA study, marginal efficacy beneath the considered clinically important) in an irrelevant time period, with a host of adverse effects, that have not been adequately accounted for, will end up being used in preference to other safe and effective treatments. These points are elaborated further below: Lack of effectiveness for antidepressants in less severe depression in any analysis conducted Specifically for effectiveness there was no effect when looking at SMD of depression scores (Table 3, page 21, Evidence Summary B), in terms of response (Table 6, page 28, Evidence Summary B), there was no data on remission (Table 8, page 30, Evidence Summary B), in bias-adjusted analysis of depression score change (Table 9, page 32, Evidence Summary B), there was no data on long term follow up for important outcomes examining antidepressant versus a control (Table	included in the treatment recommendations. Similarly, for the outcome of response, very few interventions (group CBT, group problem solving and group exercise) showed evidence of effect versus TAU, as indicated by their 95%CrI not crossing the line of no effect. Given the uncertainty and limitations around the clinical and cost-effectiveness data, the committee considered it important to provide a wide range of interventions to take into account individual needs and allow patient choice. Based on the clinical and cost-effectiveness evidence, the potential for side effects, and the knowledge and experience of the committee, it was agreed that antidepressants should not be routinely offered as a first-line treatment for less severe depression. However, the recommendation includes the exception that antidepressants can be offered if that is the person's preference. <u>Cost-effectiveness analysis</u>

						12, page 38, Evidence Summary B) or for 'critical' outcomes (Table 13, page 39, Evidence Summary B) and no evidence looking at pairwise effects (Table 14 and 15, page 40). Overall, therefore there was no analysis that found that antidepressants were more effective than TAU for less severe depression presented. Reliance on a methodologically flawed single study for evaluation of cost-effectiveness which did not demonstrate minimum clinically important differences for its primary outcome The committee evaluated the cost effectiveness of treatments that did not demonstrate clinical effectiveness in their own analysis or in the paper from which the cost effectiveness data was extracted. As above no analysis for less severe depression demonstrated a statistically significant or clinically important difference for antidepressants when compared to TAU. The committee seems to have used the PANDA study published as Lewis et al (2019) with economic analysis published as Hollingworth et al (2020) to derive cost-effectiveness for sertraline. However, this study suffers from more than the 'minor limitations' designated. This study found marginal differences of patients assigned to sertraline rather than placebo (13% reduction in PHQ-9 score, 95% CI 3% to 21%). The change in the primary outcome of depression score (PHQ-9) was 4.89 points in the sertraline group and 4.18 in the placebo group. The difference in change between the two groups was 0.8 points on the 27-point PHQ-9 scale. The minimum clinically important difference for PHQ-9 has been calculated as 3.0 (Lynch et al 2021) or 5.0 points (Lowe et al 2021). A change of 0.8 points does not meet the threshold for a minimally clinical important	Treatments selected for the cost-effectiveness analysis were those that had shown a higher effect than TAU and had been tested on more than 50 participants in the trials included in the NMA on the SMD outcome, as well as the NMAs on discontinuation and response in completers, which were the outcomes that informed the economic analysis in less severe depression. This was the minimum amount of evidence that a treatment class should have in order to be considered for a practice recommendation. The committee looked at the total size of the evidence base in this area (treatment of a new episode of depression) and the large volume of evidence for some treatment classes relative to others, and decided not to consider treatment classes with a small size of evidence base (tested on <50 participants) as there were several treatment classes with much larger volume of evidence. With the exception of group CBT, no other treatment tested on at least 50 people showed evidence of effect versus TAU on the SMD outcome of the guideline NMA.

						difference. This corresponds to an effect size of 0.18 (Hengartner et al 2020a), which is below the threshold NICE designated for minimum effect size of 0.5. Effects on anxiety were similarly small (effect size <0.25) (Hengartner et al 2020a). This was not evaluated by the committee because cost-effectiveness data was extracted from this study without first evaluating whether this was treatment produced a minimally clinically important difference. It is unclear why a single study was prioritised over the extensive analysis performed by NICE. Furthermore, unblinding was an issue in the PANDA study and may have exaggerated differences in the two groups due to expectation effects for those assigned to sertraline – 81% of patients correctly guessed they were assigned to placebo and 46% correctly guessed they were assigned to sertraline (Hengartner, 2020a). There was also a lack of power to detect adverse effects, such as suicidal behaviour, cardiovascular events or hepatotoxicity which are recognised for antidepressants, which was therefore not considered in cost-effectiveness data – and the difficulty and costs of stopping sertraline was not taken into account in this calculation (Hengartner, 2020a). Patients were also only excluded if they had used antidepressants in the previous 8 weeks so some participants may have had antidepressant withdrawal symptoms at baseline, artificially exaggerating the beneficial effect of commencing sertraline which would resolve these symptoms, likely to register on symptom scales for anxiety and depression. Prioritisation of short symptom changes over long term quality of life and functioning outcomes Furthermore, less useful data was prioritised by the	The cost-effectiveness of treatments was evaluated based on the guideline economic analysis. The PANDA study was included in the systematic review of economic evidence as it met inclusion criteria, but, like other studies included in the economic review, it was only marginally considered when assessing the relative cost-effectiveness between interventions of interest and when making recommendations. As it is stated under The committee's discussion of the evidence -> Cost effectiveness and resource use: "Existing economic evaluations assessed a limited range of pharmacological, psychological and physical interventions in, mostly, pairwise comparisons, so it was difficult for the committee to draw any robust conclusions on the relative cost effectiveness of the full range of interventions that are available for the treatment of adults with a new episode of less severe depression." Hence, the committee relied heavily on the results of the guideline economic analysis, which was informed by the guideline NMAs, in order to make recommendations. No cost-effectiveness data were extracted from the PANDA study to inform the guideline economic analysis, nor was the PANDA

						committee – although the committee recognised that long-term studies and quality of life and functioning were more important than short term or symptom score reductions, because there was more information for the latter evaluation of effectiveness was made on short term symptom scores; long-term outcomes, including quality of life and functioning scores (which found large effects for a number of treatments) were neglected. It does not seem reasonable to prioritise less relevant data simply because it exists in greater quantities. This risks extrapolating recommendations for long-term treatment based on short term studies with outcomes that may be irrelevant to long-term benefits to patients. We recommend that if the committee does nothing else that it at least include in its research recommendations that studies evaluating treatment for depression should be conducted over relevant time periods (e.g. 1-2 years or longer) and evaluating the most relevant outcomes for patients of quality of life and functional status. Derivation of long-term treatment recommendations from short term studies Short term studies of antidepressants are particularly ill suited to extrapolate to long-term recommendations because long term studies find much less promising results than short term studies – for example 3.7% of patients in the STAR-D trial at one year were free of relapse and did not drop out of the study (Pigott et al, 2010). Some authors have suggested poorer long term outcomes may result from tolerance (Kinrys et al, 2019). Use of unsuitable data for evaluating harms If despite the lack of demonstrated effectiveness of antidepressants in less severe depression, the committee still	study used to draw conclusions on the relative cost-effectiveness of sertraline versus other treatments, simply because the PANDA study compared sertraline to placebo and not to any other active intervention of interest. <u>Quality of life and functioning outcomes, and longer-term follow-up</u> The committee agree that quality of life and functioning outcomes, and long-term follow-up, are important. The committee noted the limited evidence for quality of life and functioning outcomes and for longer-term follow-up which made it difficult to compare these outcomes across interventions and inform new recommendations. These outcomes and follow-up time points were included for the research recommendations in the guideline. <u>Recommendations based on short-term studies</u> The guideline does not recommend long-term antidepressant treatment (except in the case of those at higher risk of relapse who have remitted with antidepressant

						chooses to consider their cost-effectiveness, there remains an alarming lack of consideration for the full extent of the harms (and therefore the cost of the harms) of this medication class. A single study looking at just 5 adverse effects (Anderson et al 2012) was used to estimate adverse effects for antidepressants to estimate their costs. This study retrospectively evaluated a commercially available national database used for making claims for payments. In other words, this database relied on clinicians to enter side effects using an ICD-9-CM diagnostic code into the medical records of patients during antidepressant use to make a claim from a healthcare provider in the USA. This is a very high threshold to determine that an adverse effect is having a significant effect on a person. As the authors of the study says "data from medical claims are subject to a considerable degree of under-detection because fewer patients may actually go to a doctor for these particular symptoms" (p.119, Anderson et al 2012). The authors go on to say "More general estimates of the occurrence of side effects associated with SSRIs are higher: increased agitation in up to 20% of users, nausea in up to 20%, sedation in up to20%, and sexual dysfunction in up to 20% (Whooley and Simon, 2000)" The authors further emphasise the "relatively low sensitivity of medical claims data for detecting these side effects at their true rates in treatment settings" (p.122, Anderson et al 2012).Marked under-estimation is clearly evident when examining the results derived as in Table 80 on page 316 of Evidence Summary B. An estimation that 0.07% of people on SSRI, 0.09% of people on SNRIs and 0.06% of people on mirtazapine will develop more	treatment), and includes a recommendation (in the preventing relapse section of the guideline) that the potential risks of continuing with antidepressants long term, and how these balance against the risks of depression relapse, should be discussed with people with depression. The committee noted that relapse still occurs in people continuing to take antidepressants (referred to as tolerance in your comment). The committee agreed that it is not clear if this is a true loss of effect of the antidepressant, or could be due to other factors including a loss of the placebo effect or non-adherence. The relapse prevention review for this guideline (Evidence review C) shows good evidence that SSRIs, SNRIs and TCAs were effective relapse prevention treatments, compared to pill placebo or no treatment, with follow-up of up to 2 years. Although the committee did discuss that there may be some limitations with the data for continued antidepressants compared to pill placebo, as abrupt antidepressant discontinuation and immediate switch to pill placebo increases risk of relapse and may induce withdrawal symptoms that register as increased depression scores, and so over-

						than one side effect is implausible. For instance, on the SPC for citalopram, https://www.medicines.org.uk/emc/product/5737/smpc#gref the most commonly used antidepressant in England there are 8 adverse effects that are 'very common' (occur in more than 10% of patients), including sleep disorder, somnolence, insomnia, headache, increased sweating and asthenia, 33 adverse effects which are 'common' (occur in 1% -10% of patients), with many more rarer adverse effects. Studies find rates of treatment-emergent sexual dysfunction of 30-60% in patients on SSRIs (Gregorian et al 2002). These values do not seem at all consistent with the reported estimate of 0.07% of SSRI users will experience a side effect. It has also been found that adverse effects are more common in longer term users of antidepressants than in the short term RCTs from which the SPC data is partially derived (Bet et al. 2013), with further details of incidence rates from this study in the response to Evidence Summary B below (which are often more than two orders of magnitude greater than that derived from Anderson et al. 2012). Additional costs of withdrawal or not being able to stop antidepressants not take into account While there is no cost associated with stopping many of the non-pharmacological treatments outlined in this guidance, there is considerable costs to stopping antidepressants as outline in this guidance, which is not included in the cost-analysis. There are costs to people's wellbeing and there are costs to the health care system. In the first category there are the costs of time off work, inability to perform social roles such as caring for children or elderly dependents, and in some people long-	inflate the comparison of relapse rates achieved with continued antidepressants. For preventing relapse, the committee noted that, in both psychological and pharmacological trials, there appeared to be diminishing returns in terms of efficacy over the longer-term. The committee also discussed the issue of people remaining on antidepressant medication in the long-term, potentially with debilitating adverse effects. For these reasons they recommended regular follow-up for people continuing with antidepressant medication with no more than 6 months between reviews. <u>The suitability of data for evaluating harms</u> In order to estimate the rate of side effects for use in the economic analysis a review of studies was conducted. This has now been updated to include further studies reporting side effects of antidepressants. The committee reviewed the evidence and agreed that the rate of side effects used in the model should reflect side effects that resulted in a measurable reduction in health-related quality of life and led to additional healthcare resource use (e.g. additional GP visits and possibly medication

						standing inability and suicide (Guy et al, 2020; Hengartner et al 2020b). Additionally there are the costs to the health care system – which include increased visits to the doctor, the requirement to prescribe liquid versions of medication and increased monitoring throughout the process which can take months and in some patients years. For example the prescription of liquid mirtazapine for 2 years to help someone stop their medication (a common time period) can cost 24*80 = 1920 pounds. Other medications are cheaper than this but extra costs should be taken into account in the cost-effectiveness analysis. The overview of this process was given in Evidence Summary B, page 324 that: "Acute pharmacological treatment was administered over 12 weeks. At the end of this period, adults with less severe depression who achieved remission had their drug gradually discontinued (tapered); this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over the period of one month (according to routine clinical practice, as advised by the committee)."This is not an accurate summary of the process of stopping – the committee's own recommendation is that patients stay on antidepressant for several months for an episode so 12 weeks is an under-estimation of the costs. Consequently the time required for stopping drugs is also under-estimated as it might take several months for a patient to stop a drug tolerable and linear reduction over 4 weeks has never been demonstrated to be effective for patients on anything but extremely short term treatment. This section therefore under-estimates the time and resources required for stopping these medications. Furthermore, there will also	for their management). The study by Anderson et al., which was used to inform the rate of side effects in the guideline economic analysis, reported prevalence data on 5 common side effects from a large USA managed care claims form that included 36,400 adults who were newly diagnosed with depression and were initiated on antidepressant monotherapy. Antidepressants assessed in the study included all classes of interest for the economic model. It is noted that the prevalence of side effects in the study, which was used in the guideline economic analysis, ranged from 4.7% (trazodone) to 9.2% (SNRIs). The figures of 0.07%, 0.09% etc. cited in the evidence review B as the prevalence of side effects of antidepressants were typos and have been corrected in the report (however, the economic analysis has used the correct figures reported in the Anderson et al. study). The committee reviewed evidence according to which, although side effects from antidepressants are often reported by patients, only a small proportion is considered 'bothersome' or is mentioned to the prescribing physician. The committee also expressed the view that studies

						be a group of people for whom coming off their antidepressant will be too aversive because of the withdrawal effects and who will then continue to use this medication for several years or the rest of their lives, leading to unnecessary medication costs, as conservatively estimated in Davies et al, 2021. A study looking at stopping unnecessary antidepressants found that 93% of patients were unable to stop (Eveleigh et al., 2017). The REDUCE study in England is aiming to help 20% of patients stop unnecessary antidepressants, meaning that 80% of patients on unnecessary antidepressants will stay on their medication for years or perhaps life long. This will lead to considerable unnecessary costs to the health system and exposure to adverse effects to patients. The near certainty that a large proportion of people will continue their medication beyond what guidelines recommend should be taken into account. Given the potential for extensive harms from antidepressants we do not think that the conclusion of the committee on page 60, line 42-44 of Evidence Summary B "However, the committee agreed that the potential benefits of treating depression were likely to outweigh the potential harms" is warranted. As this section of the evaluation is concerned with mild depression, unlikely to have severe consequences for sufferers, and for which antidepressants have not been shown to have a clinically important difference, whilst the adverse effects of antidepressants, much more extensive than acknowledged by the committee will be the same for people with mild or severe conditions, we do not share the confidence of the committee that benefits will 'likely'	specifically asking participants to self-report the presence of side effects, or to choose from a list of potential side effects, tend to overestimate the prevalence of side effects in the study population, particularly as these studies use uncontrolled study designs and the causality between the antidepressant use and the reported side effects is not established; therefore, using data from such studies would likely overestimate the impact of side effects on the relative cost-effectiveness between pharmacological and non-pharmacological treatments, especially as psychological treatments are assumed to have zero risks of side effects. In contrast, the committee expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, such as those reported in the study used to inform the guideline economic model, are more representative of the risk of side effects that have an impact on health-related quality of life and healthcare costs. The committee were also aware that apart from common side effects, there may be serious side effects from antidepressants, which are costly to treat and are likely to reduce the health-related quality of life of people who

						outweigh harms, and implore the committee to more carefully evaluate harms, weighting and costing them appropriately. Inclinations to support existing clinical practice over evidenceA bias to cultural inertia, whereby treatments currently given, would tend to be favoured seems to be evident in the deliberations of the committee. This seems to explain why antidepressants which did not demonstrate efficacy in any analysis for less severe depression were recommended. It also underpins the notion of the committee that treatments should be offered because patients 'prefer' them, discussed further below. An inclination of the committee to support currently existing practice seemed to play an unusually strong role in making decisions about what to include in the recommendations to the point that the NICE Technical Support Unit were unable "to identify a clear decision rule to link the recommendations directly to the NMA results" (lines 15-16, page 58, Evidence summary B) so that they were unable to conduct a threshold analysis to account for uncertainty. This indicates the degree to which the NICE committee introduced subjective judgements to make decisions about what to include. The evidence review is explicit that the judgement relied on the members 'clinical experience' and 'need for inclusivity' (line18-19, page 58, Evidence summary B). Given that NICE is supposed to present objective data it is concerning that objective data was over-ruled by a potential over-reliance on particular clinicians' experiences. It is also unclear how 'inclusivity' was utilised as a criterion in the provision of options for medical treatment when it seems to have been used primarily to include	experience them more significantly. However, these side effects do not occur frequently, and their impact on the relative cost-effectiveness of antidepressants is expected to be very low. Discussion of the above points has now been added in Evidence review B, in Appendix J (Economic modelling methods -> Other clinical input parameters -> Probability of development of side effects from antidepressant treatment). In addition, the economic analysis has now included a sensitivity analysis that uses a 40% risk of side effects (assumed to cause a reduction in health-related quality of life and to trigger extra healthcare resource use), to explore the impact of a higher rate of side effects on the relative cost-effectiveness of antidepressants alone or combined with CBT. As expected, the position of these interventions in ranking fell, but their cost-effectiveness relative to psychological interventions did not materially change. Results (reduction in the relative cost-effectiveness of antidepressants) were more substantial for less severe depression, where, however, the recommendation was to not routinely offer

						antidepressants despite a lack of evidence for their inclusion. In Lines 24 -34 on page 62 of Evidence B, it says: "The committee also discussed the role of pharmacological therapy in the treatment of less severe depression – the clinical results for depression symptoms had been similar to those seen for the psychological therapies, and the cost-effectiveness results had shown that both SSRIs and TCAs were likely to be cost-effective (they were placed 3rd and 4th in the cost-effectiveness ranking respectively). In addition, there may be people who do not wish or are not able to participate in a psychological or physical therapy, may prefer a pharmacological treatment, or would like to commence pharmacological treatment if there is a wait before they can commence another treatment. Based on these discussions, the committee recommended SSRIs as an alternative treatment, as these were generally better tolerated and safer than TCAs (italics added)."This rationale for recommendations does not seem reasonable. SSRIs had not shown significant differences from TAU on depression scales (SMD), response rate and no remission data was found. For QoL and functioning there was no data. Yet it was considered by the committee that there was similarity in effectiveness to other treatments. Furthermore, the committee decided that people who would not be motivated to use effective and cost-effective treatments like CBT or BA should be offered an alternative. It does not seem possible that a treatment which is not effective can be a suitable alternative treatment to treatments which are. Additionally, the idea of patients preferring a pharmacological treatment as a rationale for	antidepressants unless there was a preference for this type of therapy. For more severe depression, changes in the results were less substantial, and, again, they were consistent with the recommendations and the hierarchy for this population, according to which combined CBT+antidepressants was placed first, followed by individual CBT and BA, and then antidepressants alone. The impact of withdrawal symptoms has been taken into account by the committee. For this reason there are specific recommendations on how to stop antidepressant medication, and a key research recommendation on the incidence and severity of withdrawal symptoms for antidepressant medication. Although the term side effects is used for the outcome 'discontinuation due to side effects', in terms of data extraction, drop-outs due to any adverse events were captured provided they were reported. Although the committee acknowledge that this outcome in the context of short-term RCTs provides limited evidence for the potential of harms in the longer term, there

						offering this as an alternative is not a convincing reason for including this recommendation. Any preference that a patient might have for an antidepressant is based on existing cultural practice (not to mention the cultural saturation with messages that antidepressants are effective from multiple sources). To include antidepressants as an alternative treatment based on the sentiment of the public seems contrary to the purpose of NICE's evidence reviews to provide treatments that are objectively effective. Whilst many patients may prefer opioids for pain the committee making recommendations on the management of primary pain did not recommend opioids just to satisfy public wishes, but objectively evaluated their benefits and harms. The same analogy might apply to the wish for patients to have upper respiratory symptoms treated with antibiotics. Furthermore, the consideration that people might want to take an antidepressant while they wait for therapy does not seem the purview of this committee whose stated purpose is recommend clinically effective and cost effective treatments for less severe depression. It does not seem reasonable to recommend an ineffective treatment simply because the waitlist for an effective treatment is too long. The inclusion of antidepressants as an alternative treatment is likely to have ramifications to an outsized degree. As practice commonly includes giving antidepressants, the inclusion of antidepressants as an option is likely to mean it is used more often than intended, with the perverse outcome that a treatment that did no demonstrate efficacy (or if relying on the short-term PANDA study, marginal efficacy beneath the considered clinically important) in an irrelevant time period,	is a recommendation about starting antidepressants that recommends discussing harms and includes as examples some of the harms you mention (the recommendation includes weight gain, sedation, and effects on sexual function, as examples). The guideline also includes a specific recommendation for prescribing antidepressant medication for older people. The list of potential harms is not exhaustive, but the committee agreed that, in their experience, the examples given were the side-effects that people were concerned about. <u>Costs of stopping antidepressants</u> Costs of time off work and inability to perform social roles were outside the scope of the economic analysis, which adopted a NHS and personal social services perspective, based on the NICE Guidelines Manual for interventions funded by the NHS. Additional visits to healthcare professionals over the period of tapering were considered in the analysis. Liquid preparations are not routinely required during tapering, and therefore they were not considered in the economic modelling.

						with a host of adverse effects that have not been adequately accounted for, will end up being used in preference to other safe and effective treatments. Bet PM, Hugtenburg JG, Penninx BWJH, Hoogendijk WJG. Side effects of antidepressants during long-term use in a naturalistic setting. Eur Neuropsychopharmacol. 2013 Nov;23(11):1443–51.Davies J, Cooper RE, Moncrieff J, Montagu L, Rae T, Parhi M. The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications. Addict Behav. 2021;107143.Fornaro M, Anastasia A, Novello S, Fusco A, Pariano R, De Berardis D, et al. The emergence of loss of efficacy during antidepressant drug treatment for major depressive disorder: An integrative review of evidence, mechanisms, and clinical implications. Pharmacol Res. 2019 Jan;139:494–502.Gregorian RS, Golden KA, Bahce A, Goodman C, Kwong WJ, Khan ZM. Antidepressant-induced sexual dysfunction. Ann Pharmacother. 2002 Oct;36(10):1577–89.Guy A, Brown M, Lewis S, Horowitz MA. The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition. Therapeutic Advances in Psychopharmacology. 2020 Jan 9;10:204512532096718.Hengartner MP, Plöderl M, Braillon A, Jakobsen JC, Gluud C. Sertraline in primary care: comments on the PANDA trial. Lancet Psychiatry. 2020 Jan;7(1):17.Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic	The related recommendation has been amended to say that these be considered once very small doses have been reached and slow tapering cannot be achieved using tablets or capsules. The recommendation involves a small sub-group of people who need to take very small doses of liquid preparations during last stages of tapering, over a short time period. The economic analysis has now been amended, in line with relevant recommendations: antidepressants are assumed to be received for at least 1 year following successful treatment (or 2 years if relapse prevention with antidepressants is required), and linear tapering is assumed to happen over 3 months, based on the committee's expert opinion. During tapering, additional GP visits have been modelled. In response to your comment, the committee discussion of the evidence section in Evidence review B has been amended to make more explicit the committee's consideration of the potential for side effects and withdrawal effects and to clarify how recommendations were made

						Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573.Kinrys, Gustavo, Alexandra K. Gold, Vincent D. Pisano, Marlene P. Freeman, George I. Papakostas, David Mischoulon, Andrew A. Nierenberg, and Maurizio Fava. 2019. "Tachyphylaxis in Major Depressive Disorder: A Review of the Current State of Research." Journal of Affective Disorders 245 (October 2018): 488–97.Lerner, Alicja, and Michael Klein. 2019. "Dependence, Withdrawal and Rebound of CNS Drugs: An Update and Regulatory Considerations for New Drugs Development." Brain Communications, no. 2019 (October). https://doi.org/10.1093/braincomms/fcz025.Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care. 2004 Dec;42(12):1194–201.Lynch CP, Cha EDK, Jenkins NW, Parrish JM, Mohan S, Jadczak CN, et al. The Minimum Clinically Important Difference for Patient Health Questionnaire-9 in Minimally Invasive Transforaminal Interbody Fusion. Spine. 2021 May 1;46(9):603–9.Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: Current status of research. Psychother Psychosom. 2010;79(5):267–79.Solomon, David A., Andrew C. Leon, Timothy I. Mueller, William Coryell, Jedediah J. Teres, Michael A. Posternak, Lewis L. Judd, Jean Endicott, and Martin B. Keller. 2005. "Tachyphylaxis in Unipolar Major Depressive Disorder." The Journal of Clinical Psychiatry 66 (3): 283–90.NICE evidence B summaryWe suggest there are seven major issues with the way that the committee decided on treatments to include in the treatment of less severe depression1)inadequate assessment of harms of use,	based on the committee's interpretation of the clinical and cost effectiveness evidence, the potential for harms, and the need for patient's to be able to receive treatment in line with their preferences and individual needs. <u>Interpreting the evidence, and existing clinical practice</u> The committee do not agree that they prioritised current clinical practice over evidence. Assessment and interpretation of the evidence to inform guideline recommendations is at the heart of the work of the committee. The committee's interpretation, judgement, and clinical experience is particularly important here given the considerable uncertainty associated with the evidence. The clinical results for the effect of antidepressants on depression symptoms were similar to those seen for the psychological therapies, showing an improvement in depression symptoms but considerable uncertainty, and the cost-effectiveness results showed both SSRIs and TCAs were likely to be cost-effective (they

						including in cost-effectiveness analysis2)use of short time points to extrapolate to long term treatment3) neglect to include costs of stopping interventions in cost effectiveness analysis4) neglect of more important outcomes for less important outcomes for which there was more data5) neglect of methodological flaws that exaggerate the effect particularly of antidepressants in trials6) evaluation of the cost-effectiveness of treatments that were not effective7) Inclination by the committee to support existing clinical practice over evidenceIn more detail:Inadequate assessment of harms in determining balance of risk and harms, including in cost effectiveness assessmentsThe review question for this section of the analysis was " For adults with a new episode of less severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?" (lines 3-5, page 16, Evidence B)While there was extensive analysis of the efficacy of treatments according to many possible outcomes only a single measure of tolerability assessed by drop outs due to 'side effects' (this term is itself misleading because it artificially prioritises the effect for which drug manufacturers sought marketing authorisation although some 'side effects' may be more common than the intended effect – adverse effects is a more objective way to refer to these effects). Discontinuation dues to side effects as an indicator for tolerability places a very high threshold for adverse effects occurring in a 8 week trial. For example, antidepressants cause 30% of people to become overweight in years of use (Gafoor et al., 2018), a hugely impactful effect not present in	were placed 4th and 7th in the base-case cost-effectiveness ranking respectively, although they dropped to 10th and 14th place, respectively, in sensitivity analysis that considered a higher risk of side effects). Given the uncertainty and limitations around the clinical and cost-effectiveness data, the committee considered it important to provide a wide range of interventions including psychological, physical and pharmacological options, to take into account individual needs and allow patient choice. The committee considered the fact that there may be people who do not wish or are not able to participate in a psychological or physical therapy, or may prefer a pharmacological treatment. It was also recognised by the committee that people who have had prior episodes of depression may have preferences for their treatment based on prior experience or insight into their own depression patterns. On this basis, antidepressants (specifically SSRIs as these are generally better tolerated and safer than TCAs) were included as a treatment option for people with less severe depression. However, based on the evidence that some psychological interventions may be more effective, and

						an 8 week study, with similar reasoning applicable to sexual problems, emotionally numbing, etc. These adverse effects may not cause a person to drop out of a trial, especially one in which they are paid to participate, but this effect over years or decades may have significant effects on social relationships, self-image and confidence, not to mention the physical health effects outlined below. Consequently the modelling does not adequately balance long term harms with benefits, given extraordinary attention to assessing benefits and vanishingly little assessment of harms. The effects of antidepressants are marginal or non-existent for this group but their adverse effects are myriad, as listed below. These adverse (or side) effects are clearly more significant than for CBT or problem solving. In lines 39-44 of page 60 in Evidence B summary, the committee said this:"The potential harms identified were attrition, with people not completing courses of treatment, issues with acceptability and the possibility of people deteriorating despite treatment (as data in clinical trials of all treatments estimated this could happen in 7-10% of people). However, the committee agreed that the potential benefits of treating depression were likely to outweigh the potential harms."We do not understand this statement. It is not consistent with the findings of the efficacy review, which show no statistically significant effects on depression, and it is based on an inadequate assessment of adverse effects. It does not address the damage that medications can produce to the brain and the body, some of which are listed below. It also makes a blanket conclusion that "the potential benefits of treating depression were likely to outweigh the potential	considering safety and tolerability, the committee agreed that SSRIs should only be considered for use after taking into account the other treatment options offered. Although the committee did not want to prohibit the use of antidepressants where these were the patient's preference, given the potential for side effects and/or withdrawal effects and the availability of psychological and physical treatments that were similarly effective, the committee made a strong recommendation that medication should not be the default treatment for people with less severe depression, unless it was the person's preference to take antidepressants rather than engage in a psychological or physical intervention. The potential for side effects is included in Table 1 in the guideline under 'Other things to think about'. Furthermore, in response to your comment, it has been made more explicit in the committee discussion of the evidence section of Evidence review B, that one of the reasons the committee agreed that antidepressants should not be routinely offered as a first-line treatment

						harms." That may be a perfectly reasonable assumption when it comes to an innocuous treatment like problem solving or CBT but it is completely unwarranted when discussing medications potentially used for years that affect the brain and body in myriad recognised adverse ways, as below. There is already recognition that half of patients will have trouble stopping their drugs because of withdrawal effects, and some may not be able to do so and for others the difficulties of stopping will be so great that they are disabled by the process (Guy et al 2020) and for others the consequences include suicide (Hengartner et al., 2020). Given that this analysis concerns the treatment of 'less severe depression' it does not appear that the committee has provided a balanced assessment of harm and benefit, given the effects of mild depression are not so devastating that they justify any 'potential harms.'This lack of attention to the harms produced by treatment extends to the cost effective analysis which fails to take into effect the costs of obesity, sexual dysfunction, gastrointestinal, endocrine, haematological, etc adverse effects caused by antidepressants that manifest in increased medical visits, increased diagnostic investigations and treatment and a loss of quality of life.Cost effectiveness analysis including costs of harmsIn the cost-effectiveness analysis, the results from a single study looking at just five adverse effects in people over the age of 13 (Anderson et al., 2012), which finds incidence rates of adverse effects far lower than other studies (and even that the package inserts of drugs report). This study retrospectively evaluated a commercially available national database used for making claims for	for less severe depression was based on the potential for side effects and/or withdrawal effects. The reference to inclusivity refers to the need to support patient choice, and the emphasis on choice extends beyond antidepressants to other interventions as well. For instance, counselling is included in the treatment options for less severe depression although it appeared to be less cost-effective than GP care, based on the informal consensus of the committee that there may be some sub-groups of people in whom supportive empathetic counselling may help, particularly those with psychosocial, relationship or employment problems contributing to their depression, and that in these groups counselling may be more cost-effective than in the wider population of people with depression. The committee agreed that antidepressants should not be offered on the basis of waiting times for psychological interventions. There is a recommendation that for people on waiting lists providing self-help material could be considered in the interim. In response to your comment,

						payments. In other words, this database relied on clinicians to enter side effects using an ICD-9-CM diagnostic code into the medical records of patients during antidepressant use to make a claim from a healthcare provider in the USA. This is a very high threshold to determine that an adverse effect is having a significant effect on a person. As the authors of the study says "data from medical claims are subject to a considerable degree of underdetection because fewer patients may actually go to a doctor for these particular symptoms" (p.119, Anderson et al 2012). The authors go on to say "More general estimates of the occurrence of side effects associated with SSRIs are higher: increased agitation in up to 20% of users, nausea in up to 20%, sedation in up to20%, and sexual dysfunction in up to 20% (Whooley and Simon, 2000)" The authors further emphasise the "relatively low sensitivity of medial claims data for detecting these side effects at their true rates in treatment settings" (p.122, Anderson et al 2012). Furthermore the patients in this study had an average exposure to antidepressants of 198 days which is likely to be considerably shorter than many people on antidepressants in England and so may not be representative, given that about half of patients on antidepressants in the UK have been on them for more than 2 years (Johnson et al. 2012). Overall, this is a wholly inadequate study to use to estimate the risk of adverse effects in people on antidepressants. Therefore it is likely to be a very pronounced underestimate to conclude that SSRIs will cause side effects in 0.07% of people, or 0.09% for SNRIs or 0.06% for mirtazapine as done in Table 80 on page 316 of Evidence Summary B. In contrast, in a naturalistic study	the reference to waiting lists in terms of antidepressants has been removed from Evidence review B. <u>Methodological flaws in the studies included in the clinical evidence review</u> In the absence of published or accepted minimally important differences (MIDs) for all depression scales included in the review, the committee agreed to use the GRADE default MIDs. For dichotomous outcomes minimally important thresholds for a RR of 0.8 and 1.25 respectively were used as default MIDs in the guideline. For continuous outcomes minimally important thresholds for a SMD of -0.5 and 0.5 respectively were used as default MIDs in the guideline. This is outlined in the review protocols and Supplement 1 (Methods). The committee prioritised standardised mean difference (SMD) of depression symptom change scores at treatment endpoint as the primary critical outcome, as they recognised that continuous changes in scores on depression scales will show changes for people who have both fully and partially recovered and this was agreed by

						of several hundred patients on antidepressants the risk of reporting one or more side effect was 33% for SSRIs, 33% for TCAs, 37% for venlafaxine and 40% for mirtazapine (Bet et al. 2013). The proportion of patients who reported three or more side effects were 31% for SSRIs, 39% for TCAs, 36% for venlafaxine, and 24% for mirtazapine. The conclusion of this paper was that "side effects are common and persistent." These incidences are consistent with what is reported in the SPCs of antidepressants, for example for citalopram for which 8 symptoms occur in more than 10% of patients and 33 occur in 1-10% of patients (https://www.medicines.org.uk/emc/product/5737/smpc#gref). The incidence rates in Table 80 are more than two orders of magnitude lower than these rates and do not appear to be reasonable estimates. A greater variety of adverse effects should be evaluated using data representative of adverse effects in people on long term medication who are explicitly asked whether they are experiencing specific adverse effects. A selection of some adverse effects from other studies:Adverse effectsThe adverse (or side) effects of antidepressants include numerous physical and psychological symptoms. Generally, adverse effects reported by surveys of long-term antidepressant users are greater than those reported by the manufacturers, which are derived from studies that are mostly of 6 to 12 weeks in duration.(Bet et al. 2013; Read	the committee to be the best measure of clinical effectiveness. However, dichotomous data was also extracted and analysed to examine consistency of effects, to use in the economic modelling, and to maximise the data available through transforming response data to change from baseline where continuous data was not available (see Appendix M of Evidence report B). Regarding economic modelling, use of dichotomous outcomes allowed defining model health states and linking to appropriate health state utility values and estimation of QALYs, which is the NICE preferred outcome measure and allows judgements on cost-effectiveness within the NICE decision-making context. Estimation of QALYs would not be possible had exclusively continuous outcomes, without any transformation, been used in modelling. The committee were aware of the risk of non-blinding of participants due to adverse effects, and also considered the blinding of outcome assessors when making risk of bias judgements. The potential for bias introduced by short placebo run-ins and abrupt discontinuation

Muscle spasms, twitching	9	12
Dry mouth	22	49
Profuse sweating	20	20
Sexual dysfunction	23	20
Nausea	10	4
Constipation	8	20
Diarrhoea	7	4
Weight gain	19	22
Dizziness	12	11

Table 1 Proportion of patients in primary and secondary care taking commonly used antidepressants reporting adverse effects.

Emotional effects

Some adverse effects are subtle, are not often addressed in routine studies and may not be recognised by all users. In surveys of a convenience sample of people who were on antidepressants for longer (most on for more than three years) rates of adverse effects were even higher:

- emotional numbness (71%),
- 'feeling foggy or detached' (70%),
- feeling not like myself (66%),

of prior antidepressant treatment is not relevant to Evidence review B as the focus is on first-line treatment of a new episode of depression. For the relapse prevention review, the speed of tapering was considered in the risk of bias assessments, and in the committee's interpretation of the evidence.

Publication bias was considered in the bias adjusted NMA models. Small sample size studies are associated with publication bias as small studies with positive results are more likely to be published compared with small studies with negative results, and may also be associated with lower study quality. As the NMAs included a significant number of small studies, sensitivity analyses were carried out on selected outcomes, which adjusted for bias associated with small study size effects. The analyses, which were based on the assumption that the smaller the study the greater the bias, attempted to estimate the "true" treatment effect that would be obtained in a study of infinite size.

Data from unpublished studies were also included where they could be extracted from the previous 2009 NICE Depression

						• drowsiness (63%), • reduction in positive feelings (60%).(Read and Williams 2018) Although this self-selected sample may not be a representative sample of all antidepressant users, 50% of this group reported suicidality that they attributed to the antidepressant.(Read and Williams 2018) One survey found about 46% of patients reported emotional blunting.(Goodwin et al. 2017) This emotional numbing is described as "feeling emotionally detached" and "reduced sympathy and empathy".(Price, Cole, and Goodwin 2009). Some authors suggesting that emotional numbing may be the principal effect of antidepressants, experienced as helpful by some people.(Goldsmith and Moncrieff 2011; Goodwin et al. 2017) Other experts have suggested that use of antidepressants might undermine a person's autonomy and resilience, increasing their dependence on medical help.(Kendrick 2021) ***Weight gain*** Long-term use of antidepressants may cause a greater degree of weight gain than established in short-term trials. In one case-control observational study with almost 2 million patient years of follow up, in England, with patients taking SSRIs, SNRIs, and other commonly used antidepressants such as mirtazapine and tricyclics there was a 30% increased chance of people of normal weight becoming overweight or obese in 10 years of follow up, compared to people not taking	guideline or from a systematic review (including the Cipriani 2018 NMA), and a considerable number of unpublished antidepressant trials were included in the NMAs.

						antidepressants.(Gafoor, Booth, and Gulliford 2018) There was also a 30% increased chance of overweight people taking antidepressants becoming obese in 10 years compared to overweight people not taking antidepressants.(Gafoor, Booth, and Gulliford 2018) It is possible that residual confounding might contribute to these associations. The effects were most marked for mirtazapine (50% increased chance of greater than 5% weight gain) and, notably, citalopram had greater effects than other SSRIs.(Gafoor, Booth, and Gulliford 2018) ***Cognitive effects*** Meta-analysis has also found that antidepressants produce cognitive impairment in healthy controls, on tests of information processing, memory, hand-eye co-ordination, concentration, as well as higher order functions.(Hindmarch 2009) There was variation between different antidepressants with SSRIs producing between 1 and 16% impairments (where proportions referred to the number of test points where impairment was found), while venlafaxine produced 9% impairment, mirtazapine produced 35% impairment, and older tricyclics producing between 19% and 47% impairment (highest for amitriptyline).(Hindmarch 2009) These studies are useful in that they exclude confounding by an underlying disorder by studying the effects of antidepressants in healthy controls. Small studies find that MMSE scores (a crude measure of cognition that detects coarse changes in cognitive ability) decreased over consecutive weeks of follow-up in people with OCD given antidepressants.(Sayyah et al. 2016)	

						The long-term consequences of these cognitive impairments have not been investigated. ***Risks in older people*** For older people adverse effects can be more overt. A retrospective cohort study of over 61,000 patients found that the absolute risks over 1 year of exposure to SSRIs (adjusted for comorbidities and a range of potential confounding variables) of: • 5.7% for falls, • 2.6% for stoke/TIA, • 0.5% for upper gastrointestinal bleeding, • 0.38% for seizures and • 0.44% for hyponatraemia.(C. Coupland et al. 2011) Absolute risks over 1 year for all-cause mortality were 7.04% for patients not taking antidepressants, 8.12% for those taking TCAs, 10.61% for SSRIs, and 11.43% for other antidepressants.(C. Coupland et al. 2011) This observational research is susceptible to confounding by indication, and residual confounding, so differences in characteristics between patients prescribed different antidepressants could account for some of the associations between them and the adverse outcomes.(C. Coupland et al. 2011). Nevertheless, they raise concerns about the effects of antidepressant use in this age group.	

						Potential increase in risk of dementia There is also evidence that antidepressants may increase risk of dementia. A large nested case-control study of 225 000 people found a dose-response relationship between total exposure to antidepressants and risk of diagnosis with dementia.(C. A. C. Coupland et al. 2019) Those patients with the highest exposure to antidepressants – more than 3 years of daily use of standard doses - had a 34% increased chance of dementia over those patients not exposed at all to antidepressants. Another nested case-control study of 40,000 people found similar results, with antidepressants with the strongest cholinergic properties (amitriptyline, dosulepin and paroxetine) producing a 10% increased risk of dementia.(Richardson et al. 2018) Other antidepressants (largely SSRIs), with lesser anticholinergic effects were also associated with dementia but associations were greater for prescriptions closer to dementia incidence suggesting reverse causation as a possible association.(Richardson et al. 2018) Although efforts were taken in both of these studies to control for symptom score, diagnoses, there is the possibility that residual confounding may explain some of the associations. ***Withdrawal effects*** Withdrawal effects from antidepressants occur commonly and can be severe in some people (Davies and Read 2019). The	

						likelihood and severity seem to increase with longer term use. Some patients will not be able to stop their antidepressants because of aversive withdrawal symptoms. A study looking at stopping unnecessary antidepressants found that 93% of patients were unable to stop (Eveleigh et al., 2017). The REDUCE study in England is aiming to help 20% of patients stop unnecessary antidepressants, meaning that 80% of patients on unnecessary antidepressants will stay on their medication for years or perhaps life long. This will lead to considerable unnecessary costs to the health system and exposure to adverse effects to patients. ***Sexual effects*** Sexual adverse effects can include a lack of desire as well as reduced sexual sensation, and can include failure to orgasm in both genders.(Rothmore 2020) It is now recognised that these sexual effects can persist even after cessation of antidepressants in a minority of patients, named post-SSRI sexual dysfunction (PSSD), and was recently recognised by the European Medicines Agency.(Reisman 2020; Bala, Nguyen, and Hellstrom 2018) Sexual side effects can negatively affect a person's self-esteem, quality of life and relationships. ***Tardive dysphoria*** Although not widely accepted there has been concern for some time that long-term use of antidepressants can itself induce dysphoria.(Fava 2020; El-Mallakh, Gao, and Jeannie	

						Roberts 2011) This has been thought related to the process of tolerance to these medications, involving serotonin receptor desensitisation, which can 'overshoot' leading to opposite effects to those originally produced by the medications.(Fava 2020) This has been seen as analogous to opioid-induced hyperalgesia(Lee et al. 2011) and the increase in anxiety seen in long-term use of benzodiazepines.(Ashton 1987) For example, one observation study found that depressed people who used antidepressants long-term had poorer long-term outcomes compared to with non-users or those who used them short-term, even after controlling for baseline depressive severity.(Hengartner, Angst, and Rössler 2018) This is consistent with other prospective observational studies with 1-9 year follow-ups which also found poorer outcome in antidepressant users compared to non-users.(Vittengl 2017; Goldberg et al. 1998; Bockting et al. 2007) Ashton, Heather. 1987. "Benzodiazepine Withdrawal: Outcome in 50 Patients." British Journal of Addiction 82 (6): 665–71. Bala, Areeg, Hoang Minh Tue Nguyen, and Wayne J. G. Hellstrom. 2018. "Post-SSRI Sexual Dysfunction: A Literature Review." Sexual Medicine Reviews 6 (1): 29–34. Bet, Pierre M., Jacqueline G. Hugtenburg, Brenda W. J. H. Penninx, and Witte J. G. Hoogendijk. 2013. "Side Effects of Antidepressants during Long-Term Use in a Naturalistic Setting." European Neuropsychopharmacology: The Journal of the	

						European College of Neuropsychopharmacology 23 (11): 1443–51. Bockting, Claudi L. H., Mascha C. Ten Doesschate, Jan Spijker, Philip Spinhoven, Maarten W. J. Koeter, and Aart H. Schene. 2007. "Continuation and Maintenance Use of Antidepressants in Recurrent Depression." Psychotherapy and Psychosomatics 77 (1): 17–26. Coupland, Carol A. C., Trevor Hill, Tom Dening, Richard Morriss, Michael Moore, and Julia Hippisley-Cox. 2019. "Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study." JAMA Internal Medicine 179 (8): 1084–93. Coupland, Carol, Paula Dhiman, Richard Morriss, Antony Arthur, Garry Barton, and Julia Hippisley-Cox. 2011. "Antidepressant Use and Risk of Adverse Outcomes in Older People: Population Based Cohort Study." BMJ (Clinical Research Ed.) 343 (aug02 1): d4551. Davies, James, and John Read. 2019. "A Systematic Review into the Incidence, Severity and Duration of Antidepressant Withdrawal Effects: Are Guidelines Evidence-Based?" Addictive Behaviors 97 (August): 111–21. El-Mallakh, Rif S., Yonglin Gao, and R. Jeannie Roberts. 2011. "Tardive Dysphoria: The Role of Long Term Antidepressant Use in-Inducing Chronic Depression." Medical Hypotheses 76 (6): 769–73. Fava, Giovanni A. 2020. "May Antidepressant Drugs Worsen the Conditions They Are Supposed to Treat? The Clinical Foundations of the Oppositional Model of	

						Tolerance." Therapeutic Advances in Psychopharmacology 10 (January): 2045125320970325. Gafoor, Rafael, Helen P. Booth, and Martin C. Gulliford. 2018. "Antidepressant Utilisation and Incidence of Weight Gain during 10 Years' Follow-up: Population Based Cohort Study." BMJ (Clinical Research Ed.) 361 (May): k1951. Goldberg, David, Martin Privett, Bedirhan Ustun, Greg Simon, and Michael Linden. 1998. "The Effects of Detection and Treatment on the Outcome of Major Depression in Primary Care: A Naturalistic Study in 15 Cities." The British Journal of General Practice: The Journal of the Royal College of General Practitioners 48 (437): 1840–44. Goldsmith, Lucy, and Joanna Moncrieff. 2011. "The Psychoactive Effects of Antidepressants and Their Association with Suicidality." Current Drug Safety 6 (2): 115–21. Goodwin, G. M., J. Price, C. De Bodinat, and J. Laredo. 2017. "Emotional Blunting with Antidepressant Treatments: A Survey among Depressed Patients." Journal of Affective Disorders 221 (October): 31–35. Guy A, Brown M, Lewis S. The "patient voice": patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. Therapeutic Advances in [Internet]. 2020; Available	

						from: https://journals.sagepub.com/doi/abs/10.1177/2045125320967183 Hengartner, Michael P., Jules Angst, and Wulf Rössler. 2018. "Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30 Years." Psychotherapy and Psychosomatics 87 (3): 181–83. Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573. Hindmarch, I. 2009. "Cognitive Toxicity of Pharmacotherapeutic Agents Used in Social Anxiety Disorder." International Journal of Clinical Practice 63 (7): 1085–94. Kendrick, Tony. 2021. "Strategies to Reduce Use of Antidepressants." British Journal of Clinical Pharmacology 87 (1): 23–33. Lee, Marion, Sanford M. Silverman, Hans Hansen, Vikram B. Patel, and Laxmaiah Manchikanti. 2011. "A Comprehensive Review of Opioid-Induced Hyperalgesia." Pain Physician 14 (2): 145–61.	

						Price, Jonathan, Victoria Cole, and Guy M. Goodwin. 2009. "Emotional Side-Effects of Selective Serotonin Reuptake Inhibitors: Qualitative Study." The British Journal of Psychiatry: The Journal of Mental Science 195 (3): 211–17. Read, John, and James Williams. 2018. "Adverse Effects of Antidepressants Reported by a Large International Cohort: Emotional Blunting, Suicidality, and Withdrawal Effects." Current Drug Safety 13 (3): 176–86. Reisman, Yacov. 2020. "Post-SSRI Sexual Dysfunction." BMJ 368. https://doi.org/10.1136/bmj.m754. Richardson, Kathryn, Chris Fox, Ian Maidment, Nicholas Steel, Yoon K. Loke, Antony Arthur, Phyo K. Myint, et al. 2018. "Anticholinergic Drugs and Risk of Dementia: Case-Control Study." BMJ 361 (April): k1315. Rothmore, Jody. 2020. "Antidepressant-Induced Sexual Dysfunction." The Medical Journal of Australia 212 (7): 329–34. Sayyah, Mehdi, Kaveh Eslami, Shabnam AlaiShehni, and Leila Kouti. 2016. "Cognitive Function before and during Treatment with Selective Serotonin Reuptake Inhibitors in Patients with Depression or Obsessive-Compulsive Disorder." Psychiatry Journal 2016 (August): 5480391. Vittengl, Jeffrey R. 2017. "Poorer Long-Term Outcomes among Persons with Major Depressive Disorder Treated with Medication." Psychotherapy and Psychosomatics 86 (5): 302–4.	

						1) <u>use of short time points to extrapolate to long term treatment</u> The NMA used studies of short duration to extrapolate to longer term treatment. While this may be reasonable for treatments like CBT which have been shown to have increasing effects over time (Cuijpers et al, 2013) it is fraught for dealing with pharmacological interventions that can have changing effects over time, particularly as regards tolerance. Most studies of antidepressants go for 6-12 weeks. As found in the NMA, the effects are marginal or absent compared with placebo. However, most patients are treated with antidepressants for months or years – indeed the present guidelines recommend months of treatment for one episode and 2 years for higher risk people. In the long term antidepressants have been shown to have poor results – e.g in the STAR-D 3.7% of people remitted or did not drop out (Pigott et al 2010) or in long-term follow up (Hengartner et al., 2018). A specific concern for antidepressants is tolerance so that short term effects are likely to diminish in the longer term. Like all psychoactive substances tolerance is an issue with antidepressants, although it has been down played by manufacturers. There is evidence of tolerance in animals administered long-term antidepressants.(Popa et al., 2010) It	

						is also evident in clinical studies: in one longitudinal study it was observed that 25% of patients required increased dosages of antidepressant over time(Solomon et al., 2005) consistent with the development of tolerance. A systematic review found that rates of tachyphylaxis (the clinical consequence of tolerance) occurred in 9% to 57% of patients with depression treated with antidepressants (Kinrys et al., 2019). Given the common experience of withdrawal symptoms, which indicate a parallel physiological adaptation, development of tolerance to antidepressants should be unsurprising (Reidenberg, 2011; Lerner and Klein, 2019). A recent systematic review outlines all the possible causes of tolerance to antidepressants, highlighting pharmacokinetic and pharmacodynamic mechanisms (amongst others) that are the common mechanisms for all psychoactive medications (Fornaro et al., 2019). The existence of tolerance means that any effects that occur at 8 weeks are likely to diminish over time. The extrapolation from short term studies – or even longer studies that go for over 6 months – is not suitable for drug treatments that are taken for years because of this phenomenon. The issues for extrapolation from short term studies to long terms studies is clear for other medications that cause tolerance like benzodiazepines and opioids – which appear effective in the short term but lose their effect in the long term. This point should give the committee pause about	

						making recommendations for long-term treatment based on short term treatment for drugs for which tolerance is an issue. It is probable that over the long term that the different treatments recommended for less severe depression will have quite different trajectories in terms of effectiveness over time. This was emphasised recently in a meta-analysis of long-term outcomes for depression which found that psychotherapy was more effective than antidepressants at 12 months (Furukawa et al., 2021). Although this time point is also fairly short compared with the time period that a large proportion of people are on antidepressants for it speaks to the differences that occur at longer time periods. It is consistent with the notion that interventions like therapy become more useful over the long term because of learning skills (managing emotions, analysing thoughts) but that medications become less effective (tolerance to their beneficial effects and accumulation of their adverse effects). The committee should take into account these indications that the long-term effects of treatment, particularly medication, are not well represented by short term studies. Cuijpers P, Hollon SD, Van Straten A, Bockting C, Berking M, Andersson G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open. 2013;3(4):1–8.	

						Fornaro M, Anastasia A, Novello S, Fusco A, Pariano R, De Berardis D, et al. The emergence of loss of efficacy during antidepressant drug treatment for major depressive disorder: An integrative review of evidence, mechanisms, and clinical implications. Pharmacol Res. 2019 Jan;139:494–502. Furukawa TA, Shinohara K, Sahker E, Karyotaki E, Miguel C, Ciharova M, et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. World Psychiatry. 2021 Oct;20(3):387–96. Hengartner MP, Angst J, Rössler W. Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30 Years. Psychother Psychosom. 2018 Apr 20;87(3):181–3. Kinrys, Gustavo, Alexandra K. Gold, Vincent D. Pisano, Marlene P. Freeman, George I. Papakostas, David Mischoulon, Andrew A. Nierenberg, and Maurizio Fava. 2019. “Tachyphylaxis in Major Depressive Disorder: A Review of the Current State of Research.” Journal of Affective Disorders 245 (October 2018): 488–97. Lerner, Alicja, and Michael Klein. 2019. “Dependence, Withdrawal and Rebound of CNS Drugs: An Update and Regulatory Considerations for New Drugs	

						Development." Brain Communications, no. 2019 (October). https://doi.org/10.1093/braincomms/fcz025. Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: Current status of research. Psychother Psychosom. 2010;79(5):267–79. Popa, Daniela, Julie Cerdan, Christelle Repérant, Bruno P. Guiard, Jean-Philippe Guilloux, Denis J. David, and Alain M. Gardier. 2010. "A Longitudinal Study of 5-HT Outflow during Chronic Fluoxetine Treatment Using a New Technique of Chronic Microdialysis in a Highly Emotional Mouse Strain." European Journal of Pharmacology 628 (1–3): 83–90. Reidenberg, Marcus M. 2011. "Drug Discontinuation Effects Are Part of the Pharmacology of a Drug." The Journal of Pharmacology and Experimental Therapeutics 339 (2): 324–28. Solomon, David A., Andrew C. Leon, Timothy I. Mueller, William Coryell, Jedediah J. Teres, Michael A. Posternak, Lewis L. Judd, Jean Endicott, and Martin B. Keller. 2005. "Tachyphylaxis in Unipolar Major Depressive Disorder." The Journal of Clinical Psychiatry 66 (3): 283–90.	

						1) <u>Neglect of costs of stopping interventions in cost effectiveness evaluations</u> While there is no cost associated with stopping many of the non-pharmacological treatments outlined in this guidance, there is considerable costs to stopping antidepressants as outline in this guidance, which is not included in the cost-analysis. There are costs to people's wellbeing and there are costs to the health care system. In the first category there are the costs of time off work, inability to perform social roles such as caring for children or elderly dependents, and in some people long-standing inability and suicide (Guy et al, 2020; Hengartner et al 2020). Additionally there are the costs to the health care system – which include increased visits to the doctor, the requirement to prescribe liquid versions of medication and increased monitoring throughout the process which can take months and in some patients years. For example the prescription of liquid mirtazapine for 2 years to help someone stop their medication (a common time period) can cost 24*80 = 1920 pounds. Other medications are cheaper than this but extra costs should be taken into account in the cost-effectiveness analysis. The overview of this process was given in Evidence Summary B, page 324 that: "Acute pharmacological treatment was administered over 12 weeks. At the end of this period, adults with less severe depression who achieved remission had their	

						drug gradually discontinued (tapered); this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over the period of one month (according to routine clinical practice, as advised by the committee)." This is not an accurate summary of the process of stopping – the committee's own recommendation is that patients stay on antidepressant for several months for an episode so 12 weeks is an under-estimation of the costs. Consequently the time required for stopping drugs is also under-estimated as it might take several months for a patient to stop a drug tolerable and linear reduction over 4 weeks has never been demonstrated to be effective for patients on anything but extremely short term treatment. This section therefore under-estimates the time and resources required for stopping these medications. Furthermore, there will also be a group of people for whom coming off their antidepressant will be too aversive because of the withdrawal effects and who will then continue to use this medication for several years or the rest of their lives, leading to unnecessary medication costs, as conservatively estimated in Davies et al, 2021. Davies J, Cooper RE, Moncrieff J, Montagu L, Rae T, Parhi M. The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications. Addict Behav. 2021;107143.	

						Guy A, Brown M, Lewis S. The “patient voice”: patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. Therapeutic Advances in [Internet]. 2020; Available from: https://journals.sagepub.com/doi/abs/10.1177/2045125320967183 Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573. 4) neglect of more important outcomes for less important outcomes for which there was more data The committee recognised that quality of life and functioning were more important than change on symptoms score but chose to de-prioritise these valued outcomes because there was more data for symptom score change. The same choice was made with respect to long term outcomes – although these were recognised as more relevant they were de-prioritised with respect to short term outcomes because there was more data available for short term outcomes. If there is not relevant evidence for the outcome of primary importance	

						then there should be uncertainty expressed and the committee should be transparent and indicate this, following the principle of first do no harm, rather than drawing conclusions on potentially irrelevant short term treatment looking at symptoms scores that possibly have no great relevance to long term outcomes. This is particularly pertinent given the conceptualisation of depression given by NICE in these guidelines – that it is caused by adversities in people's lives. It follows then that solving these problems or finding ways to navigate or live with them are what produces a more satisfying life with meaningful pursuits (as well captured by QoL and functional measures). Many drugs might produce a short term reduction in depression scores (e.g. alcohol, cocaine, heroin) but this is not the same thing as being an effective treatment for depression. Using quality of life and functional outcomes and long-term outcomes finds a number of treatments that are useful and so should provide recommendations enough for the committee without resorting to extrapolation from short term and potentially irrelevant outcome measures. <u>5)Neglect of methodological flaws which exaggerate the beneficial effects of antidepressants in trials, many of which are outlined in Munkholm et al. 2019</u>	

						-failure to take into account evidence based ways of determining clinically important differences in evaluating the effects of treatments. The committee arbitrarily chose an effect size of 0.5 as a cut off for determining a clinically important difference. However other analyses based on clinician assessment of thousands of participants have found that a change of 8 points on the HAM-D or an effect size of 0.875 is required for a clinician to observe even minimal improvement (Leucht et al, 2013). It is therefore possible that the committee has used too low a threshold to decide on clinically important differences. - The efficacy of antidepressants is often exaggerated by dichotomisation of continuous data, a practice disapproved of by statisticians because of the loss of power. The use if the category of 'response', of a 50% reduction in depression scale score from baseline is arbitrary and has not been demonstrated to have clinical relevance. The use of this cut-off for dichotomisation has the effect of inflating the apparent differences between placebo and antidepressant (Kirsch and Moncrieff, 2007). As noted by the committee this tends to increase the benefits attributed to antidepressants. This is because the baseline depression score in most studies is about 13-24 points on the HAM-D (13 in this analysis for less severe and 24 for more severe depression) meaning a 50% reduction is about an 7-12 point reduction on the HAM-D scale. As placebo tends to reduce HAM-D by 10 points and antidepressants by 12 points, dividing them in the middle tends to exaggerate the benefits.	

						-unblinding of patients in the antidepressant arm (by adverse or 'side' effects) are likely to induce expectation effects improving depression scores. In studies designed to remove expectation effects – for example, giving all patients an antidepressant but telling half they received an active placebo the effect on depression scores is three times the size in the group told the drug was an antidepressant versus those told it was an active placebo (Faria et al 2017) -the practice of abruptly taking patients off antidepressants before the start of the trial to re-allocate them to placebo or antidepressant (called 'placebo run-in') would exaggerate differences in depression scores because patients allocated to placebo would experience withdrawal effects while those allocated to antidepressant would have those withdrawal effects resolved. If analysis of Cipriani et al. (2019) is restricted to just those studies that do not include placebo run in the SMD between placebo and AD is 0.22 (1.4 HAM-D points) -publication bias. It has been estimated that more than 1000 AD trials have been conducted. In the Cipriani et al (2019) meta-analysis, 522 studies were included of which only 86 were unpublished. Looking at only the unpublished studies finds an SMD between placebo and antidepressant of 0.15 (HAM-D change of 1 point) -if only those studies which were unpublished and for which there was no placebo run-in the effect size between	

						antidepressant and placebo was 0.08 SMD (equivalent to 0.5 HAM-D points). Some of these limitations will also be relevant to other treatment modalities but many are specific to antidepressants – for example, the placebo run-in which could be tested in the existing data set using a sensitivity analysis. Faria V, Gingnell M, Hoppe JM, Hjorth O, Alaie I, Frick A, et al. Do You Believe It? Verbal Suggestions Influence the Clinical and Neural Effects of Escitalopram in Social Anxiety Disorder: A Randomized Trial. EBioMedicine. 2017 Oct;24:179–88. Furukawa TA, Maruo K, Noma H, Tanaka S, Imai H, Shinohara K, et al. Initial severity of major depression and efficacy of new generation antidepressants: individual participant data meta-analysis. Acta Psychiatr Scand. 2018 Jun 1;137(6):450–8. Horowitz M, Taylor D. How do we determine whether antidepressants are useful or not? Lancet Psychiatry. Elsevier BV; 2019 Nov;6(11):888. Horowitz M, Wilcock M. Newer generation antidepressants and withdrawal effects: reconsidering the role of antidepressants and helping patients to stop. Drug Ther Bull. 2022 Jan;60(1):7–12.	

						Kirsch I, Moncrieff J. Clinical trials and the response rate illusion. Contemp Clin Trials. 2007;28(4):348–51. Leucht, Stefan, Hein Fennema, Rolf Engel, Marion Kaspers-Janssen, Peter Lepping, and Armin Szegedi. 2013. "What Does the HAMD Mean?" Journal of Affective Disorders 148 (2–3): 243–48. Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. BMJ Open. 2019;9(6):e024886. Volkmann C, Volkmann A, Müller CA. On the treatment effect heterogeneity of antidepressants in major depression: A Bayesian meta-analysis and simulation study. PLoS One. 2020 Nov 11;15(11):e0241497. 6) <u>evaluation the cost-effectiveness of treatments that were not effective</u> It was difficult to understand why the cost-effectiveness of SSRIs and TCAs were evaluated when they were not found to be effective – if a treatment is not effective, it does not seem possible for it to be cost-effective.	

						The NMA showed no effect for SSRIs or SMA in terms of change in depression score (as indicated by SMD). The same was true when an NMA for response rate was performed. Nevertheless the committee noted " that for the outcome of response, antidepressants (TCAs and SSRIs) appeared to be more effective than seen for the outcome of SMD." See below for a discussion of why response rates are misleading and not recommended by statisticians. However even despite the exaggeration of benefit produced by dichotomisation into response rates SSRIs and TCAs failed to differentiate from TAU and indeed did less well than pill placebo (See Figure 4 on page 27) and Table 6 on p.28. of Evidence Summary B. There was no evidence of remission presented for SSRIs or TCAs. In further analyses, SSRIs and TCAs did not separate from TAU for bias-adjusted SMDs of depression symptom change scores. There was no evidence presented for ADs alone compared with a control group for QoL of functional outcomes, although several other treatments did show significant differences compared with control conditions. For the long term follow up (more than 6 months) there was no evidence presented for antidepressants along versus a control group, but much evidence of robust effects for other treatments. Given this lack of effectiveness for antidepressants in any of the analyses it is difficult to understand why they were included in a cost effectiveness analysis.	

						If the reasoning was that studies outside of the NMA were used such as the PANDA study evaluating sertraline versus placebo published as Lewis et al, 2019, then this study suffers from the limitation that it presented 12 week data (of small effect size, and marginal significance). This study suffers from the limitations outlined above – the time period observed has little relevance to the time period over which antidepressants are used (many months, often years, sometimes decades) during which effects are likely to diminish due to tolerance (Fornaro et al 2019) and indeed long-term outcomes from antidepressants are poor (Pigott, 2010; Furukawa, 2021). It seems difficult to follow how a single short-term study focusing on a single medication which produced marginal results could be used to over-rule the entire process of the NMAs conducted by the committee which did not find this class of medications to be effective. 7) <u>Inclinations to support existing clinical practice over evidence</u> A bias to cultural inertia, whereby treatments currently given, would tend to be favoured seems to be evident in the deliberations of the committee. An inclination of the committee to support currently existing practice seemed to play an unusually strong role in making decisions about what to include in the recommendations to the point that the NICE Technical Support Unit were unable "to identify a clear	

						decision rule to link the recommendations directly to the NMA results" (lines 15-16, page 58, Evidence summary B) so that they were unable to conduct a threshold analysis to account for uncertainty. This indicates the degree to which the NICE committee introduced subjective judgements to make decisions about what to include. The evidence review is explicit that the judgement relied on the members 'clinical experience' and 'need for inclusivity' (line18-19, page 58, Evidence summary B). Given that NICE is supposed to present objective data it is concerning that objective data was over-ruled by a potential over-reliance on particular clinicians' experiences. It is also unclear why 'inclusivity' is a criterion used in the provision of options for medical treatment when it seems to have been used primarily to include antidepressants despite a lack of evidence for their inclusion. Lines 24 -34 on page 62 of Evidence B "The committee also discussed the role of pharmacological therapy in the treatment of less severe depression – the clinical results for depression symptoms had been similar to those seen for the psychological therapies, and the cost-effectiveness results had shown that both SSRIs and TCAs were likely to be cost-effective (they were placed 3rd and 4th in the cost-effectiveness ranking respectively). In addition, there may be people who do not wish or are not able to participate in a psychological or physical therapy, may prefer a	

						pharmacological treatment, or would like to commence pharmacological treatment if there is a wait before they can commence another treatment. Based on these discussions, the committee recommended SSRIs as an alternative treatment, as these were generally better tolerated and safer than TCAs." This degree of subjectivity is troubling, especially given SSRIs had not shown significant differences from TAU on depression scales (SMD), response rate and no remission data was found. QoL and functioning there was no data. Yet it was considered by the committee that there was similarity in effectiveness to other treatments. Furthermore, the committee thought that people who would not be motivated to use effective and cost-effective treatments like CBT or BA should be offered an alternative. It does not seem possible that a treatment which is not effective be a suitable alternative treatment to treatments which are. Additionally, the idea of patients preferring a pharmacological treatment as a rationale for offering this as an alternative does not make sense either. Any preference that a patient might have for an antidepressant is based on the cultural saturation with messages that antidepressants are effective from multiple sources. To include antidepressants as an alternative treatment based on the sentiment of the public seems contrary to the purpose of NICE's evidence reviews to provide treatments that are objectively effective. Whilst many	

						patients may prefer opioids for pain the committee making recommendations on the management of primary pain did not recommend opioids just to satisfy public wishes, but objectively evaluated their benefits and harms. The inclusion of antidepressants as an alternative treatment is likely to have ramifications to an outsized degree. As practice commonly includes giving antidepressants, the inclusion of antidepressants as an option is likely to mean it is used more often than intended, with the perverse outcome that a treatment that did no demonstrate efficacy (or if relying on the short-term PANDA study, marginal efficacy) in an irrelevant time period, with a host of adverse effects that are not accounted for, will end up being used in preference to other safe and effective treatments.	

54						Table 1 Proportion of patients in primary and secondary care taking commonly used antidepressants reporting adverse effects. Emotional effectsSome adverse effects are subtle, are not often addressed in routine studies and may not be recognised by all users. In surveys of a convenience sample of people who were on antidepressants for longer (most on for more than three years) rates of adverse effects were even higher: emotional numbness (71%), 'feeling foggy or detached' (70%), feeling not like myself (66%), drowsiness (63%), reduction in positive feelings (60%).(Read and Williams 2018) Although this self-selected sample may not be a representative sample of all antidepressant users, 50% of this group reported suicidality that they attributed to the antidepressant.(Read and Williams 2018) One survey found about 46% of patients reported emotional blunting.(Goodwin et al. 2017) This emotional numbing is described as "feeling emotionally detached" and "reduced sympathy and empathy".(Price, Cole, and Goodwin 2009). Some authors suggesting that emotional numbing may be the principal effect of antidepressants, experienced as helpful by some people.(Goldsmith and Moncrieff 2011; Goodwin et al. 2017) Other experts have suggested that use of antidepressants might undermine a person's autonomy and resilience, increasing their dependence on medical help.(Kendrick 2021) Weight gain Long-term use of antidepressants may cause a greater degree of weight gain than established in short-term trials. In one case-control observational study with almost 2 million patient years of follow up, in England, with patients taking SSRIs, SNRIs, and other commonly used antidepressants	

						such as mirtazapine and tricyclics there was a 30% increased chance of people of normal weight becoming overweight or obese in 10 years of follow up, compared to people not taking antidepressants.(Gafoor, Booth, and Gulliford 2018) There was also a 30% increased chance of overweight people taking antidepressants becoming obese in 10 years compared to overweight people not taking antidepressants.(Gafoor, Booth, and Gulliford 2018) It is possible that residual confounding might contribute to these associations. The effects were most marked for mirtazapine (50% increased chance of greater than 5% weight gain) and, notably, citalopram had greater effects than other SSRIs.(Gafoor, Booth, and Gulliford 2018) Cognitive effectsMeta-analysis has also found that antidepressants produce cognitive impairment in healthy controls, on tests of information processing, memory, hand-eye co-ordination, concentration, as well as higher order functions.(Hindmarch 2009) There was variation between different antidepressants with SSRIs producing between 1 and 16% impairments (where proportions referred to the number of test points where impairment was found), while venlafaxine produced 9% impairment, mirtazapine produced 35% impairment, and older tricyclics producing between 19% and 47% impairment (highest for amitriptyline).(Hindmarch 2009) These studies are useful in that they exclude confounding by an underlying disorder by studying the effects of antidepressants in healthy controls. Small studies find that MMSE scores (a crude measure of cognition that detects coarse changes in cognitive ability) decreased over consecutive weeks of follow-up in people with OCD given antidepressants.(Sayyah et al. 2016)	

						The long-term consequences of these cognitive impairments have not been investigated. Risks in older peopleFor older people adverse effects can be more overt. A retrospective cohort study of over 61,000 patients found that the absolute risks over 1 year of exposure to SSRIs (adjusted for comorbidities and a range of potential confounding variables) of:5.7% for falls, 2.6% for stoke/TIA, 0.5% for upper gastrointestinal bleeding, 0.38% for seizures and 0.44% for hyponatraemia.(C. Coupland et al. 2011)Absolute risks over 1 year for all-cause mortality were 7.04% for patients not taking antidepressants, 8.12% for those taking TCAs, 10.61% for SSRIs, and 11.43% for other antidepressants.(C. Coupland et al. 2011) This observational research is susceptible to confounding by indication, and residual confounding, so differences in characteristics between patients prescribed different antidepressants could account for some of the associations between them and the adverse outcomes.(C. Coupland et al. 2011). Nevertheless, they raise concerns about the effects of antidepressant use in this age group.Potential increase in risk of dementiaThere is also evidence that antidepressants may increase risk of dementia. A large nested case-control study of 225 000 people found a dose-response relationship between total exposure to antidepressants and risk of diagnosis with dementia.(C. A. C. Coupland et al. 2019) Those patients with the highest exposure to antidepressants – more than 3 years of daily use of standard doses - had a 34% increased chance of dementia over those patients not exposed at all to antidepressants. Another nested case-control study of 40,000 people found similar results, with	

						antidepressants with the strongest cholinergic properties (amitriptyline, dosulepin and paroxetine) producing a 10% increased risk of dementia.(Richardson et al. 2018) Other antidepressants (largely SSRIs), with lesser anticholinergic effects were also associated with dementia but associations were greater for prescriptions closer to dementia incidence suggesting reverse causation as a possible association.(Richardson et al. 2018) Although efforts were taken in both of these studies to control for symptom score, diagnoses, there is the possibility that residual confounding may explain some of the associations. Withdrawal effectsWithdrawal effects from antidepressants occur commonly and can be severe in some people (Davies and Read 2019). The likelihood and severity seem to increase with longer term use. Some patients will not be able to stop their antidepressants because of aversive withdrawal symptoms. A study looking at stopping unnecessary antidepressants found that 93% of patients were unable to stop (Eveleigh et al., 2017). The REDUCE study in England is aiming to help 20% of patients stop unnecessary antidepressants, meaning that 80% of patients on unnecessary antidepressants will stay on their medication for years or perhaps life long. This will lead to considerable unnecessary costs to the health system and exposure to adverse effects to patients. Sexual effectsSexual adverse effects can include a lack of desire as well as reduced sexual sensation, and can include failure to orgasm in both genders.(Rothmore 2020) It is now recognised that these sexual effects can persist even after cessation of antidepressants in a minority of patients, named post-SSRI	

						sexual dysfunction (PSSD), and was recently recognised by the European Medicines Agency.(Reisman 2020; Bala, Nguyen, and Hellstrom 2018) Sexual side effects can negatively affect a person's self-esteem, quality of life and relationships. Tardive dysphoriaAlthough not widely accepted there has been concern for some time that long-term use of antidepressants can itself induce dysphoria.(Fava 2020; El-Mallakh, Gao, and Jeannie Roberts 2011) This has been thought related to the process of tolerance to these medications, involving serotonin receptor desensitisation, which can 'overshoot' leading to opposite effects to those originally produced by the medications.(Fava 2020) This has been seen as analogous to opioid-induced hyperalgesia(Lee et al. 2011) and the increase in anxiety seen in long-term use of benzodiazepines.(Ashton 1987) For example, one observation study found that depressed people who used antidepressants long-term had poorer long-term outcomes compared to with non-users or those who used them short-term, even after controlling for baseline depressive severity.(Hengartner, Angst, and Rössler 2018) This is consistent with other prospective observational studies with 1-9 year follow-ups which also found poorer outcome in antidepressant users compared to non-users.(Vittengl 2017; Goldberg et al. 1998; Bockting et al. 2007)Ashton, Heather. 1987. "Benzodiazepine Withdrawal: Outcome in 50 Patients." British Journal of Addiction 82 (6): 665–71.Bala, Areeg, Hoang Minh Tue Nguyen, and Wayne J. G. Hellstrom. 2018. "Post-SSRI Sexual Dysfunction: A Literature Review." Sexual Medicine Reviews 6 (1): 29–34.Bet, Pierre M., Jacqueline G. Hugtenburg, Brenda W. J. H. Penninx, and Witte	

						J. G. Hoogendijk. 2013. “Side Effects of Antidepressants during Long-Term Use in a Naturalistic Setting.” European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 23 (11): 1443–51.Bockting, Claudi L. H., Mascha C. Ten Doesschate, Jan Spijker, Philip Spinhoven, Maarten W. J. Koeter, and Aart H. Schene. 2007. “Continuation and Maintenance Use of Antidepressants in Recurrent Depression.” Psychotherapy and Psychosomatics 77 (1): 17–26.Coupland, Carol A. C., Trevor Hill, Tom Dening, Richard Morriss, Michael Moore, and Julia Hippisley-Cox. 2019. “Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study.” JAMA Internal Medicine 179 (8): 1084–93.Coupland, Carol, Paula Dhiman, Richard Morriss, Antony Arthur, Garry Barton, and Julia Hippisley-Cox. 2011. “Antidepressant Use and Risk of Adverse Outcomes in Older People: Population Based Cohort Study.” BMJ (Clinical Research Ed.) 343 (aug02 1): d4551.Davies, James, and John Read. 2019. “A Systematic Review into the Incidence, Severity and Duration of Antidepressant Withdrawal Effects: Are Guidelines Evidence-Based?” Addictive Behaviors 97 (August): 111–21.El-Mallakh, Rif S., Yonglin Gao, and R. Jeannie Roberts. 2011. “Tardive Dysphoria: The Role of Long Term Antidepressant Use in-Inducing Chronic Depression.” Medical Hypotheses 76 (6): 769–73.Fava, Giovanni A. 2020. “May Antidepressant Drugs Worsen the Conditions They Are Supposed to Treat? The Clinical Foundations of the Oppositional Model of Tolerance.” Therapeutic Advances in Psychopharmacology 10 (January): 2045125320970325.Gafoor, Rafael, Helen P. Booth, and	

						Martin C. Gulliford. 2018. “Antidepressant Utilisation and Incidence of Weight Gain during 10 Years’ Follow-up: Population Based Cohort Study.” BMJ (Clinical Research Ed.) 361 (May): k1951.Goldberg, David, Martin Privett, Bedirhan Ustun, Greg Simon, and Michael Linden. 1998. “The Effects of Detection and Treatment on the Outcome of Major Depression in Primary Care: A Naturalistic Study in 15 Cities.” The British Journal of General Practice: The Journal of the Royal College of General Practitioners 48 (437): 1840–44.Goldsmith, Lucy, and Joanna Moncrieff. 2011. “The Psychoactive Effects of Antidepressants and Their Association with Suicidality.” Current Drug Safety 6 (2): 115–21.Goodwin, G. M., J. Price, C. De Bodinat, and J. Laredo. 2017. “Emotional Blunting with Antidepressant Treatments: A Survey among Depressed Patients.” Journal of Affective Disorders 221 (October): 31–35.Guy A, Brown M, Lewis S. The “patient voice”: patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. Therapeutic Advances in [Internet]. 2020; Available from: https://journals.sagepub.com/doi/abs/10.1177/2045125320967183Hengartner, Michael P., Jules Angst, and Wulf Rössler. 2018. “Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30 Years.” Psychotherapy and Psychosomatics 87 (3): 181–83.Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from	

						a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573.Hindmarch, I. 2009. “Cognitive Toxicity of Pharmacotherapeutic Agents Used in Social Anxiety Disorder.” International Journal of Clinical Practice 63 (7): 1085–94.Kendrick, Tony. 2021. “Strategies to Reduce Use of Antidepressants.” British Journal of Clinical Pharmacology 87 (1): 23–33.Lee, Marion, Sanford M. Silverman, Hans Hansen, Vikram B. Patel, and Laxmaiah Manchikanti. 2011. “A Comprehensive Review of Opioid-Induced Hyperalgesia.” Pain Physician 14 (2): 145–61.Price, Jonathan, Victoria Cole, and Guy M. Goodwin. 2009. “Emotional Side-Effects of Selective Serotonin Reuptake Inhibitors: Qualitative Study.” The British Journal of Psychiatry: The Journal of Mental Science 195 (3): 211–17.Read, John, and James Williams. 2018. “Adverse Effects of Antidepressants Reported by a Large International Cohort: Emotional Blunting, Suicidality, and Withdrawal Effects.” Current Drug Safety 13 (3): 176–86.Reisman, Yacov. 2020. “Post-SSRI Sexual Dysfunction.” BMJ 368. https://doi.org/10.1136/bmj.m754.Richardson, Kathryn, Chris Fox, Ian Maidment, Nicholas Steel, Yoon K. Loke, Antony Arthur, Phyo K. Myint, et al. 2018. “Anticholinergic Drugs and Risk of Dementia: Case-Control Study.” BMJ 361 (April): k1315.Rothmore, Jody. 2020. “Antidepressant-Induced Sexual Dysfunction.” The Medical Journal of Australia 212 (7): 329–34.Sayyah, Mehdi, Kaveh Eslami, Shabnam AlaiShehni, and Leila Kouti. 2016. “Cognitive Function before and during Treatment with Selective Serotonin Reuptake Inhibitors in Patients with Depression or Obsessive-Compulsive Disorder.”	

						Psychiatry Journal 2016 (August): 5480391.Vittengl, Jeffrey R. 2017. "Poorer Long-Term Outcomes among Persons with Major Depressive Disorder Treated with Medication." Psychotherapy and Psychosomatics 86 (5): 302–4.use of short time points to extrapolate to long term treatmentThe NMA used studies of short duration to extrapolate to longer term treatment. While this may be reasonable for treatments like CBT which have been shown to have increasing effects over time (Cuijpers et al, 2013) it is fraught for dealing with pharmacological interventions that can have changing effects over time, particularly as regards tolerance. Most studies of antidepressants go for 6-12 weeks. As found in the NMA, the effects are marginal or absent compared with placebo. However, most patients are treated with antidepressants for months or years – indeed the present guidelines recommend months of treatment for one episode and 2 years for higher risk people. In the long term antidepressants have been shown to have poor results – e.g in the STAR-D 3.7% of people remitted or did not drop out (Pigott et al 2010) or in long-term follow up (Hengartner et al., 2018). A specific concern for antidepressants is tolerance so that short term effects are likely to diminish in the longer term. Like all psychoactive substances tolerance is an issue with antidepressants, although it has been down played by manufacturers. There is evidence of tolerance in animals administered long-term antidepressants.(Popa et al., 2010) It is also evident in clinical studies: in one longitudinal study it was observed that 25% of patients required increased dosages of antidepressant over time(Solomon et al., 2005) consistent with the development	

						of tolerance. A systematic review found that rates of tachyphylaxis (the clinical consequence of tolerance) occurred in 9% to 57% of patients with depression treated with antidepressants (Kinrys et al., 2019). Given the common experience of withdrawal symptoms, which indicate a parallel physiological adaptation, development of tolerance to antidepressants should be unsurprising (Reidenberg, 2011; Lerner and Klein, 2019).A recent systematic review outlines all the possible causes of tolerance to antidepressants, highlighting pharmacokinetic and pharmacodynamic mechanisms (amongst others) that are the common mechanisms for all psychoactive medications (Fornaro et al., 2019). The existence of tolerance means that any effects that occur at 8 weeks are likely to diminish over time. The extrapolation from short term studies – or even longer studies that go for over 6 months – is not suitable for drug treatments that are taken for years because of this phenomenon. The issues for extrapolation from short term studies to long terms studies is clear for other medications that cause tolerance like benzodiazepines and opioids – which appear effective in the short term but lose their effect in the long term. This point should give the committee pause about making recommendations for long-term treatment based on short term treatment for drugs for which tolerance is an issue. It is probable that over the long term that the different treatments recommended for less severe depression will have quite different trajectories in terms of effectiveness over time. This was emphasised recently in a meta-analysis of long-term outcomes for depression which found that psychotherapy was	

						more effective than antidepressants at 12 months (Furukawa et al., 2021). Although this time point is also fairly short compared with the time period that a large proportion of people are on antidepressants for it speaks to the differences that occur at longer time periods. It is consistent with the notion that interventions like therapy become more useful over the long term because of learning skills (managing emotions, analysing thoughts) but that medications become less effective (tolerance to their beneficial effects and accumulation of their adverse effects). The committee should take into account these indications that the long-term effects of treatment, particularly medication, are not well represented by short term studies. Cuijpers P, Hollon SD, Van Straten A, Bockting C, Berking M, Andersson G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open. 2013;3(4):1–8.Fornaro M, Anastasia A, Novello S, Fusco A, Pariano R, De Berardis D, et al. The emergence of loss of efficacy during antidepressant drug treatment for major depressive disorder: An integrative review of evidence, mechanisms, and clinical implications. Pharmacol Res. 2019 Jan;139:494–502.Furukawa TA, Shinohara K, Sahker E, Karyotaki E, Miguel C, Ciharova M, et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. World Psychiatry. 2021 Oct;20(3):387–96.Hengartner MP, Angst J, Rössler W. Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30	

						Years. Psychother Psychosom. 2018 Apr 20;87(3):181–3.Kinrys, Gustavo, Alexandra K. Gold, Vincent D. Pisano, Marlene P. Freeman, George I. Papakostas, David Mischoulon, Andrew A. Nierenberg, and Maurizio Fava. 2019. "Tachyphylaxis in Major Depressive Disorder: A Review of the Current State of Research." Journal of Affective Disorders 245 (October 2018): 488–97.Lerner, Alicja, and Michael Klein. 2019. "Dependence, Withdrawal and Rebound of CNS Drugs: An Update and Regulatory Considerations for New Drugs Development." Brain Communications, no. 2019 (October). https://doi.org/10.1093/braincomms/fcz025.Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: Current status of research. Psychother Psychosom. 2010;79(5):267–79.Popa, Daniela, Julie Cerdan, Christelle Repérant, Bruno P. Guiard, Jean-Philippe Guilloux, Denis J. David, and Alain M. Gardier. 2010. "A Longitudinal Study of 5-HT Outflow during Chronic Fluoxetine Treatment Using a New Technique of Chronic Microdialysis in a Highly Emotional Mouse Strain." European Journal of Pharmacology 628 (1–3): 83–90.Reidenberg, Marcus M. 2011. "Drug Discontinuation Effects Are Part of the Pharmacology of a Drug." The Journal of Pharmacology and Experimental Therapeutics 339 (2): 324–28.Solomon, David A., Andrew C. Leon, Timothy I. Mueller, William Coryell, Jedediah J. Teres, Michael A. Posternak, Lewis L. Judd, Jean Endicott, and Martin B. Keller. 2005. "Tachyphylaxis in Unipolar Major Depressive Disorder." The Journal of Clinical Psychiatry 66 (3): 283–90.Neglect of costs of stopping interventions in cost effectiveness evaluationsWhile there is no cost associated	

						with stopping many of the non-pharmacological treatments outlined in this guidance, there is considerable costs to stopping antidepressants as outline in this guidance, which is not included in the cost-analysis. There are costs to people's wellbeing and there are costs to the health care system. In the first category there are the costs of time off work, inability to perform social roles such as caring for children or elderly dependents, and in some people long-standing inability and suicide (Guy et al, 2020; Hengartner et al 2020). Additionally there are the costs to the health care system – which include increased visits to the doctor, the requirement to prescribe liquid versions of medication and increased monitoring throughout the process which can take months and in some patients years. For example the prescription of liquid mirtazapine for 2 years to help someone stop their medication (a common time period) can cost 24*80 = 1920 pounds. Other medications are cheaper than this but extra costs should be taken into account in the cost-effectiveness analysis. The overview of this process was given in Evidence Summary B, page 324 that: "Acute pharmacological treatment was administered over 12 weeks. At the end of this period, adults with less severe depression who achieved remission had their drug gradually discontinued (tapered); this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over the period of one month (according to routine clinical practice, as advised by the committee)."This is not an accurate summary of the process of stopping – the committee's own recommendation is that patients stay on antidepressant for several months for an episode so 12 weeks	

						is an under-estimation of the costs. Consequently the time required for stopping drugs is also under-estimated as it might take several months for a patient to stop a drug tolerable and linear reduction over 4 weeks has never been demonstrated to be effective for patients on anything but extremely short term treatment. This section therefore under-estimates the time and resources required for stopping these medications. Furthermore, there will also be a group of people for whom coming off their antidepressant will be too aversive because of the withdrawal effects and who will then continue to use this medication for several years or the rest of their lives, leading to unnecessary medication costs, as conservatively estimated in Davies et al, 2021. Davies J, Cooper RE, Moncrieff J, Montagu L, Rae T, Parhi M. The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications. Addict Behav. 2021;107143.Guy A, Brown M, Lewis S. The “patient voice”: patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. Therapeutic Advances in [Internet]. 2020; Available from: https://journals.sagepub.com/doi/abs/10.1177/2045125320967183Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573.4) neglect of more important outcomes for less important outcomes for which there was	

						more data The committee recognised that quality of life and functioning were more important than change on symptoms score but chose to de-prioritise these valued outcomes because there was more data for symptom score change. The same choice was made with respect to long term outcomes – although these were recognised as more relevant they were de-prioritised with respect to short term outcomes because there was more data available for short term outcomes. If there is not relevant evidence for the outcome of primary importance then there should be uncertainty expressed and the committee should be transparent and indicate this, following the principle of first do no harm, rather than drawing conclusions on potentially irrelevant short term treatment looking at symptoms scores that possibly have no great relevance to long term outcomes. This is particularly pertinent given the conceptualisation of depression given by NICE in these guidelines – that it is caused by adversities in people's lives. It follows then that solving these problems or finding ways to navigate or live with them are what produces a more satisfying life with meaningful pursuits (as well captured by QoL and functional measures). Many drugs might produce a short term reduction in depression scores (e.g. alcohol, cocaine, heroin) but this is not the same thing as being an effective treatment for depression. Using quality of life and functional outcomes and long-term outcomes finds a number of treatments that are useful and so should provide recommendations enough for the committee without resorting to extrapolation from short term and potentially irrelevant outcome measures. 5)Neglect of methodological	

						flaws which exaggerate the beneficial effects of antidepressants in trials, many of which are outlined in Munkholm et al. 2019-failure to take into account evidence based ways of determining clinically important differences in evaluating the effects of treatments. The committee arbitrarily chose an effect size of 0.5 as a cut off for determining a clinically important difference. However other analyses based on clinician assessment of thousands of participants have found that a change of 8 points on the HAM-D or an effect size of 0.875 is required for a clinician to observe even minimal improvement (Leucht et al, 2013). It is therefore possible that the committee has used too low a threshold to decide on clinically important differences. - The efficacy of antidepressants is often exaggerated by dichotomisation of continuous data, a practice disapproved of by statisticians because of the loss of power. The use if the category of 'response', of a 50% reduction in depression scale score from baseline is arbitrary and has not been demonstrated to have clinical relevance. The use of this cut-off for dichotomisation has the effect of inflating the apparent differences between placebo and antidepressant (Kirsch and Moncrieff, 2007). As noted by the committee this tends to increase the benefits attributed to antidepressants. This is because the baseline depression score in most studies is about 13-24 points on the HAM-D (13 in this analysis for less severe and 24 for more severe depression) meaning a 50% reduction is about an 7-12 point reduction on the HAM-D scale. As placebo tends to reduce HAM-D by 10 points and antidepressants by 12 points, dividing them in the middle	

						tends to exaggerate the benefits. -unblinding of patients in the antidepressant arm (by adverse or 'side' effects) are likely to induce expectation effects improving depression scores. In studies designed to remove expectation effects – for example, giving all patients an antidepressant but telling half they received an active placebo the effect on depression scores is three times the size in the group told the drug was an antidepressant versus those told it was an active placebo (Faria et al 2017)-the practice of abruptly taking patients off antidepressants before the start of the trial to re-allocate them to placebo or antidepressant (called 'placebo run-in') would exaggerate differences in depression scores because patients allocated to placebo would experience withdrawal effects while those allocated to antidepressant would have those withdrawal effects resolved. If analysis of Cipriani et al. (2019) is restricted to just those studies that do not include placebo run in the SMD between placebo and AD is 0.22 (1.4 HAM-D points)-publication bias. It has been estimated that more than 1000 AD trials have been conducted. In the Cipriani et al (2019) meta-analysis, 522 studies were included of which only 86 were unpublished. Looking at only the unpublished studies finds an SMD between placebo and antidepressant of 0.15 (HAM-D change of 1 point)-if only those studies which were unpublished and for which there was no placebo run-in the effect size between antidepressant and placebo was 0.08 SMD (equivalent to 0.5 HAM-D points).Some of these limitations will also be relevant to other treatment modalities but many are specific to antidepressants – for example, the placebo run-in which could be tested in the existing data set	

						using a sensitivity analysis. Faria V, Gingnell M, Hoppe JM, Hjorth O, Alaie I, Frick A, et al. Do You Believe It? Verbal Suggestions Influence the Clinical and Neural Effects of Escitalopram in Social Anxiety Disorder: A Randomized Trial. EBioMedicine. 2017 Oct;24:179–88.Furukawa TA, Maruo K, Noma H, Tanaka S, Imai H, Shinohara K, et al. Initial severity of major depression and efficacy of new generation antidepressants: individual participant data meta-analysis. Acta Psychiatr Scand. 2018 Jun 1;137(6):450–8.Horowitz M, Taylor D. How do we determine whether antidepressants are useful or not? Lancet Psychiatry. Elsevier BV; 2019 Nov;6(11):888.Horowitz M, Wilcock M. Newer generation antidepressants and withdrawal effects: reconsidering the role of antidepressants and helping patients to stop. Drug Ther Bull. 2022 Jan;60(1):7–12. Kirsch I, Moncrieff J. Clinical trials and the response rate illusion. Contemp Clin Trials. 2007;28(4):348–51.Leucht, Stefan, Hein Fennema, Rolf Engel, Marion Kaspers-Janssen, Peter Lepping, and Armin Szegedi. 2013. “What Does the HAMD Mean?” Journal of Affective Disorders 148 (2–3): 243–48.Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. BMJ Open. 2019;9(6):e024886.Volkmann C, Volkmann A, Müller CA. On the treatment effect heterogeneity of antidepressants in major depression: A Bayesian meta-analysis and simulation study. PLoS One. 2020 Nov 11;15(11):e0241497.evaluation the cost-effectiveness of treatments that were not effectiveIt was difficult to understand why the cost-effectiveness of SSRIs	

						and TCAs were evaluated when they were not found to be effective – if a treatment is not effective, it does not seem possible for it to be cost-effective. The NMA showed no effect for SSRIs or SMA in terms of change in depression score (as indicated by SMD). The same was true when an NMA for response rate was performed. Nevertheless the committee noted " that for the outcome of response, antidepressants (TCAs and SSRIs) appeared to be more effective than seen for the outcome of SMD." See below for a discussion of why response rates are misleading and not recommended by statisticians. However even despite the exaggeration of benefit produced by dichotomisation into response rates SSRIs and TCAs failed to differentiate from TAU and indeed did less well than pill placebo (See Figure 4 on page 27) and Table 6 on p.28. of Evidence Summary B. There was no evidence of remission presented for SSRIs or TCAs. In further analyses, SSRIs and TCAs did not separate from TAU for bias-adjusted SMDs of depression symptom change scores. There was no evidence presented for ADs alone compared with a control group for QoL of functional outcomes, although several other treatments did show significant differences compared with control conditions. For the long term follow up (more than 6 months) there was no evidence presented for antidepressants along versus a control group, but much evidence of robust effects for other treatments. Given this lack of effectiveness for antidepressants in any of the analyses it is difficult to understand why they were included in a cost effectiveness analysis.	

						If the reasoning was that studies outside of the NMA were used such as the PANDA study evaluating sertraline versus placebo published as Lewis et al, 2019, then this study suffers from the limitation that it presented 12 week data (of small effect size, and marginal significance). This study suffers from the limitations outlined above – the time period observed has little relevance to the time period over which antidepressants are used (many months, often years, sometimes decades) during which effects are likely to diminish due to tolerance (Fornaro et al 2019) and indeed long-term outcomes from antidepressants are poor (Pigott, 2010; Furukawa, 2021). It seems difficult to follow how a single short-term study focusing on a single medication which produced marginal results could be used to over-rule the entire process of the NMAs conducted by the committee which did not find this class of medications to be effective. 6) <u>Inclinations to support existing clinical practice over evidence</u> A bias to cultural inertia, whereby treatments currently given, would tend to be favoured seems to be evident in the deliberations of the committee. An inclination of the committee to support currently existing practice seemed to play an unusually strong role in making decisions about what to include in the recommendations to the point that the NICE Technical Support Unit were unable "to identify a clear decision rule to link the recommendations directly to the NMA	

						results" (lines 15-16, page 58, Evidence summary B) so that they were unable to conduct a threshold analysis to account for uncertainty. This indicates the degree to which the NICE committee introduced subjective judgements to make decisions about what to include. The evidence review is explicit that the judgement relied on the members 'clinical experience' and 'need for inclusivity' (line18-19, page 58, Evidence summary B). Given that NICE is supposed to present objective data it is concerning that objective data was over-ruled by a potential over-reliance on particular clinicians' experiences. It is also unclear why 'inclusivity' is a criterion used in the provision of options for medical treatment when it seems to have been used primarily to include antidepressants despite a lack of evidence for their inclusion. Lines 24 -34 on page 62 of Evidence B "The committee also discussed the role of pharmacological therapy in the treatment of less severe depression – the clinical results for depression symptoms had been similar to those seen for the psychological therapies, and the cost-effectiveness results had shown that both SSRIs and TCAs were likely to be cost-effective (they were placed 3rd and 4th in the cost-effectiveness ranking respectively). In addition, there may be people who do not wish or are not able to participate in a psychological or physical therapy, may prefer a pharmacological treatment, or would like to commence	

						pharmacological treatment if there is a wait before they can commence another treatment. Based on these discussions, the committee recommended SSRIs as an alternative treatment, as these were generally better tolerated and safer than TCAs." This degree of subjectivity is troubling, especially given SSRIs had not shown significant differences from TAU on depression scales (SMD), response rate and no remission data was found. QoL and functioning there was no data. Yet it was considered by the committee that there was similarity in effectiveness to other treatments. Furthermore, the committee thought that people who would not be motivated to use effective and cost-effective treatments like CBT or BA should be offered an alternative. It does not seem possible that a treatment which is not effective be a suitable alternative treatment to treatments which are. Additionally, the idea of patients preferring a pharmacological treatment as a rationale for offering this as an alternative does not make sense either. Any preference that a patient might have for an antidepressant is based on the cultural saturation with messages that antidepressants are effective from multiple sources. To include antidepressants as an alternative treatment based on the sentiment of the public seems contrary to the purpose of NICE's evidence reviews to provide treatments that are objectively effective. Whilst many patients may prefer opioids for pain the committee making	

						recommendations on the management of primary pain did not recommend opioids just to satisfy public wishes, but objectively evaluated their benefits and harms. The inclusion of antidepressants as an alternative treatment is likely to have ramifications to an outsized degree. As practice commonly includes giving antidepressants, the inclusion of antidepressants as an option is likely to mean it is used more often than intended, with the perverse outcome that a treatment that did no demonstrate efficacy (or if relying on the short-term PANDA study, marginal efficacy) in an irrelevant time period, with a host of adverse effects that are not accounted for, will end up being used in preference to other safe and effective treatments.	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

55	SH	Care To Listen	General	31	Table 2	Although we are also pleased that counselling is quite rightly recognised as a suitable treatment for more severe depression we are also mindful that so many clients in the NHS are not offered the longer-term counselling referred to here. It is acknowledged that the IAPT programme is not limited to clients with less severe depression but that in fact many clients with severe, recurrent and complex presentations are seen for short periods of time (not always 8 plus sessions but often 6). The reason for this is often that there are not the longer term counselling options in existence for NHS patients. Care To Listen provides a Not For Profit, Social Enterprise service to try and plug this gap by offering lower cost counselling but we are aware of many clients who would benefit from longer term counselling who are unable to afford even low cost counselling. Their only option is to re-refer themselves to short term, free at the point of use counselling on multiple occasions and it feels important that the guidelines acknowledge this reality.	Thank you for your comment. The recommended intervention intensities were based on relevant information reported in the RCTs that were considered in the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience of optimal delivery of interventions within the NHS. Provision of counselling, in line with what is recommended in the guideline will be a matter for local implementation.

56	SH	Society for Psychotherapy Research	General	55	19	Nature of depression In both previous consultations, we have raised concerns with respect to how depression has been conceptualised in the guideline, which we would like to reiterate.The definition of depression in the guideline is descriptive and symptom based, rather than explanatory. In this, it is disorder focussed. It uses a practical severity classification which determines the step on which the person is placed at entry into the healthcare system.However, since depression is often an extension of or inextricably linked to the person's personality, assessment should take account of that aspect of a person's being.Symptom based definitions of depression are a practical way of categorising disorder with benefits in communication, research and service provision. However, symptoms may have meaning and can be signposts to what is wrong in a person's life and might be open to change. Depression is not just an imposed disorder but frequently is part of that person's life narrative: the relationship with genetic and cultural inheritance, the interaction with their growing up and life, the quality and supportiveness of personal relationships, their ability to work and love and the opportunities open to them to have either or both, and the meaning they take and impose on their world. While welcome reference is made to multiple complicating problems (guideline, p. 55, l.19), little reference is made across the draft as a whole to assessing the person in the context of their life, personality and situation. Where is reference to the need for formulation, ideally following a psycho-social-biological approach? (see e.g., Aveline 1999). The fine details of a patient's depression can point the way to	Thank you for your comment. The committee recognise the limits of the current nosolgy of depression and acknowledge that the problems of depression need to be addressed in a wider personal and social context. Throughout the guideline, and particularly in the sections on initial assessment and choice of treatments, there is a strong theme of collaborative decision making about care. Personal narratives, psychological formulation and the importance of the social context are not referred to explicitly in the recommendations but they form part of assessment. As specified in the scope, the recognition, assessment and initial management section from the 2009 guideline was not included in this update. In line with NICE processes, the 2009 content has been carried across to this updated guideline. However, the evidence on recognition, assessment and initial management has not been reviewed.

						which therapy or combination or sequence of therapy are likely to be most apt. Thus, as stressed previously, that the service user experience evidence section was not updated with respect to including a synthesis of the available studies on how patients experience and would define their depression is very regrettable.	

57	SH	Tavistock and Portman NHS Foundation Trust	General	General	General	Conceptual framework of depression Was previously pointed out, we believe that the conceptual framework for depression within the draft guideline, has serious consequences relating to clinical management and for research. In relation to the distinction between chronic depression and TRD, earlier versions of the Guidance decided not to use the TRD category. This was based on evidence for the existence of a more loosely defined heterogeneous group of long-term, difficult to treated depressive conditions, frequently associated with dysthymia and co-morbid common mental disorders, various personality disorders/traits and serious psycho-social disability. Furthermore, this draft guideline still refers to many studies noting the frequent comorbidity in depression with physical illnesses and other mental health disorders, nonetheless the definition of complex depression is only focussed on co-morbidity with personality disorder and psychosis. It does not include other co-morbidities nor does it include other aspects of complexity, such as childhood and/or adult trauma, poor functioning and severe relationship difficulties. We are thus concerned that the draft guidelines exclude RCTs that include dual diagnoses or co-morbidity with other mental health disorders apart from personality disorder. Furthermore, many patients with depression and personality disorder also fulfil criteria for chronic and/or TRD, again highlighting the overlap between these categories.• The clinical setting: In the case of TRD, this is often defined as being akin to a medical condition, and a language is used which relates to pharmacology, dose and response. Within a clinical setting, a rather different	Thank you for your comment. For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of psychotic depression, depression with coexisting personality disorder and chronic depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee reviewed the European Psychiatric Association classification but did not consider it appropriate to change the term to 'persistent depression' but considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered.

						conception is used and the entire psychosocial functioning of the patient is considered. The draft guideline therefore do not correspond to the reality of the clinical setting.• The research setting: This has an impact on definitions used within research. The guidance implicit to the NICE guidelines for depression will not be consistent with the APA (DSM-5) and the European Psychiatric Association (EPA) guidance (Jobst et al. 2016) if the current conceptualisation are adopted.Furthermore, the guidance will complicate outcome research, as many participants in trials included in the TRD meta-analysis meet the guideline's definition of chronic depression and/or complex depression.In order to address these concerns, we suggest for a combination of these categories, and add the review for first line treatment for chronic depression (which appears here to refer more to dysthymia or non-debilitating persistent depression) under the evidence review B questions. We fear that the current categorisation system will be rather confusion for referrers.Refences cited:APA. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association.Jobst A et al. (2016) European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. European Psychiatry, 33, 18 – 36.	The committee recognised that factors such as other mental health comorbidities, drug and alcohol misuse, social and environmental factors and a history of poor response to treatment can contribute to the complexity of depression. However, the committee noted that comorbidity with a range of other mental disorders also occurred in participants in studies for first line treatment. The committee agreed to include a separate review question for the first-line treatment or relapse prevention for people with depression and coexisting personality disorder. This decision was based on the committee's knowledge and experience that personality disorders can complicate the treatment of depression (see for example the meta-analysis by Newton-Howes et al (2006) Personality disorder and the outcome of depression: meta-analysis of published studies. British Journal of Psychiatry, 188, 13-20)).

58	SH	Tavistock and Portman NHS Foundation Trust	General	General	General	Partial remission We are concerned that partial remission rates have still not been included as critical outcomes, and strongly suggest for this to be changed.As previously highlighted, full remission or recovery from a severe depression baseline might be difficult to achieve and as such creates unrealistic hopes which may as a consequence lead to further disappointments. As previously pointed out, treatments which help some service users move from severe depression to mild or moderate depression (i.e., 'partial recovery'), are still clinically meaningful and as such worth recommending.In line with this, we noticed that partial remission was also not included as an outcome for the economic analysis.	Thank you for your comment. The guideline includes continuous changes in scores on depression scales as a critical outcome for every treatment question, which will show changes for people who have both fully and partially recovered. This was agreed by the committee to be a better way to capture this data than the use of a dichotomous outcome for partial recovery. The economic analysis does not focus primarily on full remission. The economic analysis of treatments for a new episode of less severe depression has modelled only response (defined as at least 50% improvement in depressive symptoms) which may reflect full remission or not (depending on the starting point of depressive symptoms). Full remission was not considered in this population, due to lack of sufficient data in the respective NMA. The economic analysis of treatments for a new episode of more severe depression has considered full remission (i.e., a score on a depressive symptom scale that was below the cut-off point for a depression diagnosis) and also response that did not reach full remission (i.e. 50% improvement in depressive symptoms that

							was however not adequate to reach the scale cut-off point characterising full remission). The utility data attached to the model health states also reflected, as relevant, symptom improvement not reaching remission and/or symptom improvement reaching remission. Therefore, partial remission has been considered in the economic analysis for both populations.

59	SH	Active Partnerships National Team	General	General	General	The barriers to being active for those diagnosed with a mental health conditions should be addressed in any exercise treatment pathway created. This will support patient attrition rates.Britain thinks (2016) identified the top barriers for people living with a long-term condition (including mental health conditions):Physical pain before, during or after exerciseFeeling tired before, during or after exerciseLack of motivationOur latest IAPT investment has demonstrated behaviour change workshops have been successful in supporting people with depression to be more active and manage symptoms. These practical workshops identify the barriers people experience and incorporate behaviour change support tools. We would welcome the opportunity to share this insight to support the development of the guidelines.	Thank you for your comment. The table of treatment options states that any barriers to undertaking physical activity should be considered and addressed, and adaptations to the exercise regimen should be implemented if necessary. The committee were interested to hear about the behaviour change workshops and agreed this would be useful so have passed this to the NICE shared learning team. In addition, to encourage people to move more the committee added, based on their knowledge and experience, advice that any level of exercise may be beneficial and added a recommendation stating this.

60	SH	Active Partnerships National Team	General	General	General	Which areas will have the biggest impact on practice and be challenging to implement? - Clinicians are a trusted source of patient information, therefore offering exercise as a treatment option will help patients become more aware of the important role of exercise in the management of mental health and bring about benefits for physical health too.Given the symptoms associated with depression i.e. low motivation and fatigue, recruitment and attrition rates could be challenging if the expectation of patients is to complete 60 minutes x 3 times a week within the exercise treatment pathway.If delivered effectively, the exercise treatment pathway and broader 'move more' support (in adjunct to all treatment pathways) has potential to improve longer term self-care and relapse prevention. - Would implementation of any of the draft recommendations have significant cost implications? An exercise on referral, structured exercise treatment programme will require venue and facilitator costs. The high frequency suggested (3 times a week for 60 minutes) could be financially challenging for commissioners. We suggest reducing the frequency and duration required for this type of provision to reduce the cost and the inclusion of broader, less structured activity that is widely accessible and affordable such as universal community provision and self-led physical activity. - What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)There are a number of existing programme and activities that the guidelines could refer to that Sport England have funded or co-developed:Resources	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this, including financial. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. Implementation issues will be considered by NICE where relevant support activity is being planned. However, the committee also supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this. Thank you for telling us about the existing physical activity programmes and campaigns. These will be passed onto the NICE shared learning team. Thank you for telling us about the impact of Covid-19 on exercise activities and how some of these have been overcome using online or other alternatives.

						for clinicians to support patients to be more active:Moving Medicine - a free initiative developed by The Faculty of Sport and Exercise Medicine, Sport England, Office for Health Improvement and Disparities and British Association of Sport and Exercise Medicine which supports healthcare professionals integrate physical activity conversations into routine clinical care. It includes evidence-based resources specifically for the treatment of depression. We Are Undefeatable – an inspiring, inclusive, and empathetic 'We are Undefeatable' campaign (https://weareundefeatable.co.uk/about-us) developed alongside 16 leading health and social care charities. This supports and encourages people with health conditions to find ways to be active that works with each person's conditions. This campaign runs several times a year nationally and can be activated in any healthcare care setting. Resources are free and are available via the Supporters' Hub.We welcome the opportunity to discuss further linking to these wider resources.Resources patients can access to help them become more active:Self-led activity - We Are Undefeatable, Join the Movement, Active 10, 10 Today and Couch to 5k, Couch to fitnessCommunity based provision - OurParks and Parkrun.We welcome the opportunity to discuss further linking to these wider resources.Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.The Covid-19 pandemic has caused disruption to the delivery of sport and physical activity. Whilst much provision has recovered and returned to face-to-face delivery, some is still	

						delivering via alternative methods i.e. online/home workouts. Many people (particularly those with long term conditions and who are more likely to be classed as clinically vulnerable) have found it difficult to return to their typical pre pandemic physical activity habits. Some have found alternative online alternatives, others have de-conditioned and their activity levels have decreased. This needs to be factored into delivery. Our recent IAPT physical activity investments have adapted well and have included online physical activity provision or self-led time within treatment pathways if patients feel concerned about socialising out in the community	

61	SH	Care To Listen	General	General	General	We are disappointed to understand that data from the IAPT programme is not being used as a core evidence base for the decisions around treatment guidelines for the treatment of depression. As the largest evidence base of real-life treatment of depression in the UK we cannot understand why this data is not being used. With easy ways to sift data relating to which interventions were used at which point as well as weekly logging of the prescribed medication status of patients, it is perfectly possible to examine this data through a wide variety of lenses and gain a more accurate picture of what works best. As a provider of counselling for an IAPT service we are proud of the way in which the thousands of clients hours have conducted over the past 5 years+ have contributed to an evidence base that only used to exist for CBT-related interventions. To not use this data to inform decision-making in this important area seems incomprehensible to us.	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

62	SH	NHS England and Improvement	General	General	General	Dosulepin is mentioned 3 times in the guidance, but as far as we can see the “do not use” recommendation from previous guidance does not appear. We suggest that there is a sound basis for continuing with the Do not use (initiate for new patients) dosulepin and this should be included as part of this update.	Thank you for your comment. The warning relating to the use of tricyclics has been strengthened to advise about their potential danger in overdose and no longer refers to amitriptyline or dosulepin, so they no longer appear as named treatment options.

63	SH	Stakeholder coalition [APPG for Prescribed Drug Dependence; Association for Dance Movement Psychotherapy UK (ADMP UK); Association for Family Therapy and Systemic Practice (AFT); Association for Psychoanalytic Psychotherapy in the NHS (APP); Association of Child	General	General	General	Summary of acknowledgments and remaining concernsHaving raised several serious concerns with the first and second version of this draft guideline as a stakeholder coalition, we are responding to this iteration as a group with respect to these concerns.We would like to begin by acknowledging the significant efforts made to engage with the concerns we have raised with the previous drafts of this guideline – we are grateful for the meaningful stakeholder engagement process. We welcome the substantial additional work that has been carried out to address our shared concerns. We notice that as a result this third draft is much improved. We are particularly pleased about the stronger focus on individualised care and the significant emphasis on the importance of service user choice and shared decision-making throughout this third iteration of the treatment guideline. We also would like to acknowledge the greater overall transparency and clarity provided in this draft. As summarised in our position statement, and outlined and discussed during previous consultations, we have identified six key concerns regarding the methodology adopted to inform the selection, grouping and analysis of supporting evidence. We have emphasised that, if all of these are not adequately addressed, the resulting treatment recommendations cannot be relied on and may therefore impede the care of millions of people in the UK experiencing depression. While we strongly welcome that some of the methodological flaws we raised have been addressed in this iteration, we need to point out that not all of them have been adequately resolved. We therefore maintain that this draft version, although much improved, continues to	Thank you for your comment. The committee considered the current NICE classifications of mild to moderate and moderate to severe depression and agreed that although these classifications have been adopted quite widely there is potential uncertainty with regards to the management of moderate depression. The committee agreed that a dichotomy of less and more severe depression was clearer, and the guideline includes definitions (that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression includes the traditional categories of moderate and severe depression) in order to improve practical utility. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line presentations of depression are managed in primary care).

		Psychotherapists (ACP); Brighton Therapy Centre British Acupuncture Council; British Association of Art Therapists (BAAT); British Association for Counselling and Psychotherapy (BACP); British Association for Music Therapy (BAMT); British Association of Social				be of concern. While these methodological concerns remain unaddressed, we continue to question the trustworthiness of the resulting treatment recommendations in the guideline.As such, we believe that a significant proportion of individuals suffering from depression could be impeded from accessing the right treatment for them. We are particularly concerned about the care of individuals who experience more complex and persistent forms of depression. Already disadvantaged in many respects, we have serious doubts that this group will receive the most appropriate treatment following the treatment recommendation in this draft. In summary we recommend the following amendments before the guideline is published:Inconsistencies regarding the utilisation of outcomes derived from long-term follow-up needs addressing.Adopting the traditional classifications for the review of a new episode of depression – mild, moderate, severe and adjust the exclusion criteria to allow for higher ecological validity.Trials where the majority of the population is clinically complex (i.e., has a comorbid psychosis or personality disorder), chronic or treatment resistant need to be combined and partial recovery needs to be included as critical outcome.Findings from indirect or mixed comparisons using Network Meta-Analysis (NMA) should only be used to supplement evidence derived from direct comparison (using the standard meta-analyses carried out)The review evidence on service user experience needs to be refined to focus more clearly on experiences of treatments.The hierarchy of treatment options for individuals with a new depression episode must be replaced with a menu (non-ranked) to	For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of psychotic depression, depression with coexisting personality disorder and chronic depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered. The guideline includes continuous changes in scores on depression scales as a critical outcome for every treatment question,

		Workers British Psychoanalytic Association (BPA); British Psychoanalytic Council (BPC); British Psychoanalytic Society (and Institute of Psychoanalysis); British Psychological Society (BPS); British Psychotherapy Foundation (BPF); Camden Psychotherapy Unit (CPU);				accurately reflect the findings that all included interventions were clinically and cost effective.The evidence from important and well-known UK pragmatic trials needs to be considered fully, not partially.	which will show changes for people who have both fully and partially recovered. This was agreed by the committee to be a better way to capture this data than the use of a dichotomous outcome for partial recovery. NICE do not accept that the use of NMA was inappropriate and using NMAs both to assess clinical effectiveness and to inform the economic model was in accordance with the NICE guidelines manual. However, pairwise data were also presented separately in the new version of the guideline to enable an easier comparison between direct and NMA results. There was also a peer review of all NMAs by a NICE Technical Support Unit contractor and the code for the NMAs was published. NICE recognises that no statistical technique will ever lead to an indisputably 'correct' answer, since they all involve assumptions and extrapolations of the available data. Both the committee and quality assurance team considered any limitations of the analysis and the confidence they had in it when making recommendations. The data from the NMA was also considered alongside the other sources of data, including the pairwise data, economic

		College of Mental Health Pharmacy (CMHP); Community Housing and Therapy (CHT); Council for Evidence-based Psychiatry (CEP); Dochealth; European Association for Psychotherapy (EAP); European Association for Gestalt Therapy (EAGT); Institute of Health Visiting					model results and newly reviewed qualitative evidence. As specified in the scope, the experience of care section from the 2009 guideline was not included in this update. However, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment. Based on their overall review of the clinical evidence the committee agreed that some treatment classes and interventions appeared to be more effective than others, but there was otherwise little to choose between treatments. The committee therefore reviewed the results of the health economic modelling which determined which treatments were cost-effective and used this to develop a suggested prioritisation of which treatments should be offered to people with depression, or considered for use. In response to stakeholder comments some changes have been made to the tables guided by the principles of offering the least intrusive

		(IHV); Interpersonal Psychotherapy UK (IPT-UK); Metanoia Institute; Mind; Motion to Mind™; National Survivor User Network (NSUN); OPENspace Research Centre; Psychotherapy and Counselling Union (PCU); Psychotherapy Foundation; Society for Psychother					intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice. Interventions are arranged in the tables in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee did not consider it appropriate to present an entirely non-ranked list based on the evidence reviewed. The committee were aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were

		apy Research UK (SPR UK); South London and Maudsley NHS Foundation Trust (SLAM); Tavistock and Portman NHS Foundation Trust; Tavistock Relationships; The Association of Clinical Psychologists UK (ACP-UK); The Association for Cognitive Analytic Therapy					stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

		(ACAT); The British Association of Dramatherapists (BADth); The Mindfulness Initiative; The National Association for People Abused in Childhood; The Survivors Trust; Universities Psychotherapy and Counselling Association (UPCA); UK Association for Gestalt Practitioners (UKAGP);					

		UK Association for Humanistic Psychology Practitioners (UKAHPP); UK Council for Psychotherapy (UKCP); UK Person-Centred Experiential (UKPCE)					

64	SH	Society for Psychotherapy Research	General	General	General	Lack of evidence does not mean “no evidence”We are still concerned about the underlying tone in this draft guideline that continues to convey two wrong assumptions: firstly, that the existence of more evidence equals stronger evidence and secondly that the lack of evidence (or in the case of these reviews, the omission of evidence due to their failure to make the inclusion criteria) equals no evidence. It needs to be borne in mind that absence of evidence is not evidence of ineffectiveness (Roth and Fonagy 2004). Furthermore, more studies do not imply higher efficacy.Following, for example, Chambless and Hollon (1998), two RCTs are sufficient for a treatment to be classified as efficacious. Yet there is a lot of wording throughout the various documents that would need to be re-phrased to make it clear that the results stated and discussed in the guideline are very much dependent on the methodology of these particular reviews.	Thank you for your comment. The committee agrees that absence of evidence is not absence of effectiveness. However in developing the guideline, recommendations can only be made for those interventions where there is evidence of their effectiveness.

65	SH	Society for Psychotherapy Research	General	General	General	The inclusion of long-term follow-up dataWe welcome and applaud the inclusion of some data on longer-term outcomes in the analyses, yet we notice an inconsistent approach in utilising the findings to inform treatment recommendation. (This inconsistency further appears to favour some treatment approaches over others without justification which is highly problematic). We welcome NICE's recognition that long-term effectiveness is an important outcome. As we have stressed repeatedly during the consultations and meetings, to report and integrate evidence that demonstrates whether treatment effects can be sustained over time or appear, or indeed disappear, after treatment has ended over the long-term follow-up, is paramount in particular with respect to a long-term condition such as depression. We therefore welcome the amendment to include long-term follow-up data in all the treatment reviews.However, we also note – and regret - that very few of the included studies actually report long-term follow-up data; as such we acknowledge that these outcomes cannot be easily prioritised. Despite the low numbers of studies that have reported long-term follow-up data, we welcome NICE's decision to analyse the available data nonetheless and take the findings into consideration for treatment recommendation. We, however, noticed inconsistencies in doing so that need to be rectified. For example, as highlighted in Table 13 on p.39, for less severe depression, 4 studies showed a statistically significant effect at their respective follow-up point. Yet only the 2 studies on group CBT and the one study on group problem-solving was considered whereas the study in STPP was not! Another	Thank you for your comment. The committee agree that long-term follow-up is important and share your disappointment that this is not more routinely measured and reported. Long-term follow-up is included in the research recommendations in the guideline. As highlighted in table 13 of Evidence report B and the corresponding 'committee discussion of the evidence' section, group CBT and group problem-solving showed benefits on depression symptoms at follow-up compared to treatment as usual, and CBT with antidepressants showed benefits compared to antidepressants alone. The committee agreed that this provided a useful indication that the results seen from the NMA for group CBT and group problem-solving may be maintained over a longer period. A 6-month follow-up of short-term psychodynamic psychotherapy (STPP) compared to non-directive counselling found a benefit for STPP for the outcomes of depression symptoms and remission at 6 months, but the committee noted that this small amount of evidence did not change their view, based on the NMA results, that these treatments had similar levels of

						example pertains to the further-line treatment recommendations, where the statistically significant findings of LTPP at follow-up was not considered whilst for other treatments it was (p. 113).Moreover, it appears that only studies that yielded a statistically significant effect at the relevant follow-up point were considered, whilst those that did not find an effect were not, especially in the reviews for new episodes. Again, the findings of all of these studies would need to be taken into account as they provide important information as to whether a treatment has been found to lose its effect after treatment ended. For example, for less severe depression 55 out of 127 studies included in the NMA had follow-up data (43%). Of those 4 were found to show statistically significant effects at their respective follow-up point (Table 13 on p.39). This means that 51 studies did not show a statistically significant effect. Similarly, for those with more severe depression, 27 studies were identified with follow-up data, and out of those 7 were found to have a statistically significant effect (Table 27, p.109). Again, this means that 19 studies showed no sustained effect. We cannot find where these important findings (of lack of treatment efficacy in longer-term follow ups) were both emphasised and considered in terms of the treatment recommendations.Given its importance, we suggest that NICE comments on this important aspect of the data treatment in the guideline. Additionally, we would suggest that NICE adds to their research recommendations for all future studies to include a meaningful long-term follow-up in order to provide evidence of sustained treatment effects for depression, especially given	effectiveness. In the further-line treatment evidence report (D), under the 'committee discussion of the evidence' section the committee highlight the sparsity of follow-up data from further-line treatment studies. The committee noted that a small number of studies could be combined in meta-analyses for outcomes up to 6 months after endpoint, however, beyond this point it was predominantly single-study analyses. The committee considered this limited evidence and noted that a small number of studies showed evidence for sustained benefits on depression outcomes associated with augmenting antidepressants with CBT (up to 40 months), IPT (up to 12 months), short-term psychodynamic psychotherapy (up to 12 months), and long-term psychodynamic psychotherapy (up to 2 years). The committee agreed that the effects on depression outcomes at follow-up were generally in line with the effects observed at endpoint, and this strengthened their confidence in the recommendations.

						that research and clinical practice has shown that two thirds of patients relapse and appear thus not to have benefitted from their first-line treatment (p.7 of evidence review D). Two-thirds of the UK population with depression equates to more than 2 million individuals (from ONS and NICE data, 2021), who are estimated to be likely not to benefit from first-line treatments recommended. As such, it is critical that studies are designed to provide the evidence of treatments that help in the long-term/show sustained effects after treatment has ended.	

66	SH	Society for Psychotherapy Research	General	General	General	The inclusion of functioning and quality of life measures We welcome and applaud the inclusion of functioning and quality of life measures. We regret that of those studies included in the reviews, only a few had reported on these crucial outcomes.Consequently, the committee decided to disregard these findings, however, we notice inconsistency in doing so. Results showing an effect on these measures were highlighted and indeed taken into consideration when interpreting results and formulating treatment recommendations for some treatment modalities (especially in favour of CBT), and not for others (for example psychodynamic psychotherapy). In addition to addressing these inconsistencies and hence taking a consistent approach to the evaluation of all treatment approaches, we would like to suggest that a sentence be added in the relevant sections in all documents referring to functioning and quality of life measures, in particular the importance of (a) future studies that report on such outcomes, and (b) for existing studies to publish these findings where the data was collected. As Paludan-Muller et al. (2021) have stressed, that many pharmacological trials collect such data but do not report it. The same can probably said about psychological treatments.	Thank you for your comment. The committee agree that quality of life and functioning outcomes are important. The committee noted the limited evidence for these outcomes and included quality of life and functioning outcomes for the research recommendations in the guideline. The committee does not agree that the limited findings available were disregarded or considered inconsistently. The committee considered all clinically important and statistically significant effects on quality of life and functioning outcomes. However, given the sparsity of this evidence, and that it was broadly consistent with the findings observed for critical depression outcomes, the committee did not consider it necessary to make any changes to recommendations based on effects observed for quality of life and functioning outcomes.

67	SH	Society for Psychotherapy Research	General	General	General	All psychological treatments recommended are short-term. There is a need to include longer-term treatments as an optionThis point further elaborates an important issue delineated above. This is that in the current guideline, all psychological treatments recommended are short-term, ranging between 6 – 16 sessions. As has been stressed in this guideline response at various points, non-response to treatment has usually been found to be high amongst individuals with depression, with one in three individuals estimated or found not to respond to offered treatments. Very recently, Cuijpers et al (2021a) have found that response and remission rates across different approaches of short-term psychotherapy are not satisfactory, with rates of response of 41% and remission of about 30%. This draft guideline fails to discuss this important aspect of patient response to treatment (specifically the high levels of depression remission and treatment non-response in depression), and we ask for this absence to be addressed. As stressed by many, more studies on the outcome of long-term treatments are needed. And as such, we ask that in the section about research recommendations is included a call for studies that investigate the effectiveness of longer-term psychotherapies along with the recommendation that all research studies ought to include a long-term follow-up. An additional important research recommendation, alongside the one included on mechanism of change, would be the investigation of differential effects, i.e., which individuals with depression would benefit more from short-term and which from longer-term psychotherapies. Research and clinical practice have shown	Thank you for your comment. The committee agree that long-term follow-up is important and included long-term follow-up in the research recommendations in the guideline. The number of research recommendations that the committee can develop is limited and long-term treatments or the investigation of differential effects for short-term relative to long-term treatments were not prioritised for separate and additional research recommendations. However, the research recommendation on mechansisms of action of effective psychological interventions recognises the room for improvement in terms of treatment recovery rates and recommends further research in order to isolate the most effective components in order to develop more potent, cost-effective and acceptable treatments. This research recommendation also recommends that psychological interventions are analysed in terms of therapy structure (for example session duration, frequency), in addition to generic therapeutic components (for example therapeutic relationship, rationale; remoralization), and specific ingredients.

						that many individuals with chronic or complex forms of depression have tried the available and recommended first or second-line short-term treatments without success (e.g., Leichsenring & Rabung 2011; Maj et al. 2020). However, in the guideline the recommendation for those classified as having treatment-resistant depression, chronic depression, and depression with PD defaults back to first or further-line treatment recommendation - i.e. once again to a short-term treatment, instead of recommending a longer-term treatment. In complex mental disorders, longer-term psychotherapy proved to be superior to short-term psychotherapy (Leichsenring & Rabung, 2011, Leichsenring et al., 2013).This is particularly perplexing as there is evidence of the effectiveness of longer-term treatments, both for long-term CBT (e.g., Leuzinger-Bohleber et al., 2019) and long-term psychodynamic psychotherapy (e.g. Fonagy et al., 2015; Leuzinger-Bohleber et al., 2019) for individuals diagnosed with treatment-resistant/chronic depression. For individuals suffering from depression and comorbid personality disorder in particular, dose- effect relationships suggest that long-term treatments are required to improve response and remission rates (Kopta et al., 1994). The Leuzinger-Bohlehber et al (2019) study was excluded from the chronic depression review as >20% had previous treatments, and for unexplained and inexplicable reasons it was not included under the further-line treatment review. Although the Fonagy et al., 2015 study was included, their important findings that both depression severity and functioning improved over the long-term have been ignored. Moreover, there exist numerous	The further-line treatment recommendation that cross-refers to psychological treatment options for more severe depression is for people whose depression has had no or a limited response to treatment with antidepressant medication alone. There was no evidence that specifically examined switching to a psychological intervention for those who have not responded to initial antidepressant treatment, however, the committee drew on the evidence for first-line treatments in more severe depression. The committee agreed that the psychological interventions that had been identified as effective and cost-effective for first-line treatment of more severe depression could be used for people who had not responded to antidepressants and wished to try a psychological therapy instead. Leuzinger-Bohleber et al 2019 was considered for the chronic depression review and was excluded. This study also did not meet eligibility criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line

						qualitative studies and reviews of patient experience that highlight that GPs, service providers and service-users stress that the currently available short-term treatments are inadequate, including studies that were reviewed in the 2009 update of this guideline and two studies that were reviewed in the evidence review I on patient choice (Johnston 2007; Mercier 2011, p. 52).One of the reasons why we stressed the importance of focusing the evidence review on 'patient experience' of treatment rather than limiting it to 'patient choice' in this guideline, was to allow a synthesis of all these available studies. Such a synthesis may have highlighted crucial insights that could have been incorporated into and strengthened this guideline that in its current form discriminates against those who want and need longer-term treatments.	treatment, participants were not randomised at the point of non-response, and it could not be regarded as an augmentation study following limited or no response to antidepressants as only 36% of participants were taking antidepressants at baseline. This study has now been added to the excluded studies list in supplement D. There was only single-study evidence (Fonagy et al. 2015) for augmenting antidepressant treatment with long-term psychodynamic psychotherapy, and the committee considered the evidence too limited to make a recommendation for long-term psychodynamic psychotherapy specifically. However, a treatment option in the recommendation for people whose depression has had no or a limited response to treatment with antidepressant medication alone, includes changing to a combination of psychological therapy and medication, which could include long-term psychodynamic psychotherapy although it is not listed as an example due to the limited evidence. As specified in the scope, the experience of care section from the 2009 guideline was

							not included in this update. However, a new review question on patient choice was added to this update that includes a systematic review of primary qualitative studies that focus specifically on service user experience around choice of treatment.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

68	SH	Society for Psychotherapy Research	General	General	General	The usage of the term counselling We would like to point out that how the word 'Counselling' as used in this draft is misleading and prejudicial to a particular employment group. In the UK, Counselling is a level of training, it is not a modality of treatment. As such, counsellors can be from a variety of modalities. Looking at the trials included under counselling and they are almost entirely in the Humanistic camp. It appears that 'counselling' is being used as a label for humanistic therapies (including person-centred and experiential therapies) but that this is not at all clear in this draft guideline. This is an important issue of language thus that needs to be clarified. The guideline should specify the modality of counselling (i.e., humanistic, dynamic, couple, family etc.) in the same way that they refer to different families or waves of cognitive and behavioural therapy approaches.Similarly confusing is that psychodynamic counselling is classified or appears under the class of other psychodynamic/psychoanalytic treatments and not under the counselling cluster (see supplementary document B1)	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. All the evidence for counselling that was included in the review for the treatment of a new episode of depression was non-directive counselling, and the committee therefore did not consider it appropriate to recommend a specific intervention (for example, Counselling for Depression/Person-Centred Experiential

							Therapy [PCET]) as the evidence was not reviewed for these interventions. However, based on informal consensus, the committee agreed that counselling should use an empirically validated protocol developed specifically for depression and this was included in the recommendation. No eligible evidence was identified for psychodynamic counselling for treatment of a new episode of depression or for further-line treatment. However, the committee agreed and specified in the protocol that psychodynamic counselling should be categorised with psychodynamic psychotherapies based on the principles of grouping into classes outlined above.

69	SH	Society for Psychotherapy Research	General	General	General	The application of the GRADE system We stressed this point in both prior consultation responses before and will repeat it here because it is still – unfortunately - relevant: We continue to be concerned about the GRADE system upon which the quality assessment of the studies as well as the statistical adjustments and penalisation of studies is based. As stressed during both previous stakeholder consultations, we are particularly concerned that it has not been adapted to studies that investigate psychological treatments. The system follows a medical paradigm that cannot be applied to psychological studies. We maintain that the draft guideline applies GRADE inappropriately. The application of the GRADE system needs to be adapted when psychological studies are investigated. Indeed, the GRADE system was designed to be used flexibly with regard to the nature of the intervention and index problem being assessed. Applying it without modifications reinforces the false belief that the medical paradigm can easily be applied to psychological treatments. A pertinent example is the downgrading of studies that did not follow a double-blind approach, marking this as high risk. We recommend adapting the GRADE system in order to reflect the complex endeavour of comparing medical and psychological treatments. More specifically, the revision of the draft guideline should include the following relevant quality criteria:- The inclusion of end of treatment long-term follow-up data. This would be in line with the draft guideline's emphasis stating the high likelihood of relapse/deterioration in patients with depression in several parts of the document. It is imperative for research to	Thank you for your comment. In assessing risk of bias using GRADE, the non-blinding of participants and intervention administrators presents a risk of bias, although this is more of a problem for psychological than pharmacological trials, it does not negate the fact that participant and intervention administrator knowledge of the treatment being received/delivered is likely to introduce some degree of performance bias due to an individual's inherent beliefs about that intervention. However, in assessing risk of bias, blinding of outcome assessors and the comparator (use of an attention-placebo intervention) is also taken into account. The GRADE system 'quality' rating is not a value judgement on the quality of an individual study but rather an estimate of confidence that an estimate of the effect is correct and is unlikely to change with further research. It is also important to note that the GRADE rating of the evidence is just one factor that the guideline committee took into account when making recommendations. They also considered cost-effectiveness and interpreted all evidence in light of their clinical judgement.

						demonstrate that effects are long-lasting and any randomised controlled trails that aim to do so should be considered stronger and thus be up-graded. The call for the inclusion of long-term follow-ups extending the currently adopted time period of 3 – 6 months to several years after treatment termination has been stressed by many researchers and trial methodologists (e.g. Rawlins, 2008) given the episodic nature of depression.- Adequate sample sizes providing sufficient power to detect true effects. Most psychotherapy studies are not powered enough to detect a true difference (Leichsenring et al., 2013) and relying on statistical significance of effects will create a paradox whereby small effects detected in well-powered studies is used to justify a recommendation, whereas a much larger effect detected in under-powered studies will be disregarded (Wampold et al., 2017).- Utilization of a range of outcome measures, in particular the assessment of functioning in addition to targeted symptoms. As Dijkers (2014) has stressed, the quality for each outcome may differ between outcomes within a single study and across a body of evidence. Thus, we recommend the guideline to adapt the methodology not to penalise but to acknowledge the benefits of inclusion of a range of outcome measures (Wampold et al., 2017).- Adequate statistical and methodological measures taken to control for error rates. The quality of assessment currently adopted does not examine whether studies have controlled for variability across therapist participants (i.e., therapist effects). A review of 71 therapist effect studies by Baldwin and Imel (2013) identified that therapist effects account for approximately 5-8% of patient outcomes:	The committee agree that long-term follow-up, and quality of life and functioning outcomes, are important. The committee considered this data when making its recommendations and based their judgement of the importance of this evidence on the availability and quality of the data. Long-term follow-up, and quality of life and functioning outcomes, are included in the research recommendations in the guideline. Therapist effects was not an area that was prioritised for inclusion in the guideline, therefore the evidence on this has not been reviewed and the committee did not consider it appropriate to make any recommendations on this issue. With regards to the imprecision ratings in the GRADE tables. The thresholds for clinically important SMD effects are -0.5 and 0.5. These thresholds are outlined in Supplement 1. In Table 72, the lower confidence bound is 0.21 and the higher is 0.33. This is therefore rated as 'no serious imprecision' as the confidence interval does not cross any threshold for a clinically

						approximately 7% in naturalistic studies, and 3% in efficacy studies. Considering patient severity, Saxon and Barkham (2012) studied 10,786 patients seen by 119 therapists and identified that therapist effect sizes increased up to 10% as patient non-risk severity increased. Most patients in this sample presented with a level of depression (77.2%) and anxiety (84.6%). The extant empirical evidence points to the presence of therapist effects as an important factor to consider: its robust nature (across research designs) and its increasing contribution to the outcome of more severe patient presentations. We are concerned that the evidence identifying effective treatment does not control for variability between participating therapists within respective studies. We suggest the inclusion of a) a quality criterion to identify trials where therapist effects have been controlled for, and b) if possible, where therapist effects analyses have not been conducted, and data is accessible, to consider post hoc analysis to control for therapist effects. A specific question pertains to inconsistent application of the threshold criterion for clinically important benefit. It is unclear what the threshold criterion is. One assumes it is 0.5, however, it is neither stated nor justified. It furthermore appears to have been applied inconsistently between and within studies. Is the down rating on grounds of Optimal Information Size? In which case what is the OIS being applied and is it being applied consistently across studies? Furthermore, it appears to have been applied inconsistently between and within studies. Compare, for example, Table 72 in which imprecision is rated as 'no serious imprecision' with a lower confidence	important effect and is consistent with no effect wherever the true point estimate is in this 95% confidence interval. This estimate of outcome demonstrates ineffectiveness but is not imprecise. The same is true for the example you cite in Table 71 where confidence intervals include -0.39 to 0.04 and -0.36 to 0.07.

						bound of 0.21 with Table 71, where a rating of 'no serious imprecision' is given for a lower CI bound of 0.04 and 0.07 (evidence review D, p. 361-362).	

70	SH	Society for Psychotherapy Research	General	General	General	Limited generalisability – Exclusion criteria First-line treatment: Studies with > 20% of patients with chronic depression (> 2 years), > 20% of patients with a personality disorder, and > 20% receiving additional treatment (e.g., antidepressants or psychiatric care) were excluded from the NMA.Research has shown that 45% of patients diagnosed with depression were found to also suffer from a comorbid personality disorder (Friborg et al., 2014). In addition, usage of antidepressants is highly prevalent with 17% of the adult population in the UK (7.3 million people) taking antidepressants between 2017-2018 (https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary).Not only is it rather uncommon for meta-analyses of psychotherapy trials for depression to exclude studies with more than 20% use of antidepressants (e.g., Cuijpers et al., 2021a, Cuijpers et al., 2020), exclusion of these and other criteria limits the representativeness and generalisability of the results. Moreover, it is not clear whether this review double-checked whether the studies included had indeed all checked or reported whether participants had co-morbid PD or were receiving medication.Further-line and complex depression: We uphold that there is no evidence that warrants distinguishing between the more complex forms of depression (i.e. chronic depression, treatment-resistant depression, depression with personality disorder and psychotic depression), and that by doing so this guideline provides erroneous and unhelpful classification of research studies with the consequence that treatment	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

						recommendations may also be erroneous and unhelpful. For treatment resistant depression a significant overlap with chronic depression exists (Abbass, 2006; Town & Abbass, 2017; Fonagy et al., 2015). This is true for depression with a comorbid personality disorder (Abbass & Town, 2011; Friborg et al., 2014; Skodol et al., 2011).We have stressed this concern during the first and second consultation and question NICE's decision once more to produce a guideline that is out of step with US and European guidelines. We notice that the review question for further-line treatment has been changed and now includes studies of psychotic depression, depression with personality disorders, chronic depression, and so-called treatment-resistant depression. However, in light of having kept the other reviews, we feel that this change has not really addressed the issue and may in fact have actually led to further confounding evidence. We are in particular concerned that it will be out of step with the clinical understanding of the groupings, especially with respect to chronic depression, and will lead to confusion instead of providing helpful guidance. Specifically, we point to the fact that: Most individuals suffering from chronic or persistent depression lasting for at least two years would have sought previous help, in particular, as highlighted on p. 7, l. 36f when individuals experience functional impairment and suicidality. As such, it does not make sense to us at all, to review the evidence for first-line treatment only for this group. It seems contradictory even to your own description of this sample group which states that it includes "high rates of hospitalisation" (p.7, l.38). At the very least, individuals experiencing persistent depression would	estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

						most likely have been prescribed medication at some point. As previously highlighted, the terms treatment-resistant and chronic depression are often used interchangeably and study populations often meet criteria for both. A brief look at the empirical literature on this topic identified three studies for which that is the case (Fonagy et al, 2015, Kocsis, 2009, and Leuzinger-Bohlber et al, 2018). As McPherson (2020) has pointed out, of the studies included in the 2017 guideline version, approximately half of the studies included under 'further line treatment' do not report the mean duration of episode, making it impossible to ascertain what percentage of participants also met the criteria for chronic depression. Of those that do report episode duration, more than half report a mean duration longer than 24 months.	used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. Given the size of the evidence base it was not possible to contact all authors for missing data, and the review relied on the data reported in the papers. For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of

							psychotic depression, depression with coexisting personality disorder and chronic depression. So, if people with persistent depression had previously sought treatment (an example referenced in your comment) they would be included in the further-line treatment review. As highlighted in your comment, the terms treatment-resistant and chronic are often used interchangeably and study populations often meet criteria for both and this was why further-line treatment of chronic depression was included in the overall further-line treatment review. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee reviewed the European Psychiatric Association classification but did not consider it appropriate to change the term to 'persistent depression' but considered that the grouping together of psychotic

							depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered.

71	SH	Society for Psychotherapy Research	General	General	General	Treatment ranking & Choice We are particularly pleased about the stronger focus on individualised care and the significant emphasis on the importance of service user choice and shared decision-making throughout this third iteration of the treatment guideline. Given a current record-setting demand, and the considerable waiting times for treatment in many parts of the UK, it is crucial to ensure that evidence-based treatment is available to anyone needs it. We This guideline has a direct impact on centralised NHS workforce planning, as well as localised decision making by commissioners. It will have a direct impact on which trainings Health Education England will fund to support increasing capacity in England's IAPT service, where so much of this rising demand is felt. Given the findings that all the listed treatments are clinically and cost-effective, removing the hierarchical ranking of treatments is a simple way to enable capacity-building in the NHS mental health workforce and we strongly recommend doing so. Furthermore, as pointed out by utilising very stringent inclusion criteria, many studies that have shown to provide an evidence base for many interventions were not considered. We notice, for example, the omission and therefore non-recommendation of family therapy, couple therapy for depression, and the creative therapies, which many service users may benefit from (e.g. Albornoz, Y., 2011; Baucom et al., 2018; Nan & Ho, 2017;), and may want to choose.	Thank you for your comment. Based on their overall review of the clinical evidence the committee agreed that some treatment classes and interventions appeared to be more effective than others, but there was otherwise little to choose between treatments. The committee therefore reviewed the results of the health economic modelling which determined which treatments were cost-effective and used this to develop a suggested prioritisation of which treatments should be offered to people with depression, or considered for use. In response to stakeholder comments some changes have been made to the tables guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice. Interventions are arranged in the tables in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to

							recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee did not consider it appropriate to present an entirely non-ranked list based on the evidence reviewed. The committee drew on their knowledge of the IAPT dataset to inform recommendations and to re-structure treatment recommendations in response to stakeholder comments. The committee were also aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to

							stakeholder comments the committee agree that it would be more consistent to name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered

							only in pairwise comparisons (and not included in the NMA). The committee considered the pairwise analysis of behavioural couples therapy for people with depression and problems in the relationship with their partner. This evidence was based on a small, single study which indicated that compared to waitlist, couples' therapy demonstrated benefits in terms of depression symptoms and marital adjustment, but when compared to CBT it did not show a benefit in depression symptoms but did with marital adjustment. CBT compared to waitlist demonstrated benefits only in terms of depression symptoms. The committee discussed that although this was limited evidence, behavioural couples therapy was included in the range of interventions offered by the IAPT services and that it was useful in the specific population and so recommended its use for this group of people. Albornoz 2011 is included in the network meta-analysis for the treatment of a new episode of more severe depression. However, this was the only included study for music therapy, and the committee considered the evidence too limited to

							make a recommendation. The Baucom et al. (2018) study was not appropriate for inclusion in the review as it was not a randomised controlled trial. Nan 2017 is included in the further-line treatment review. However, this was the only included study for art therapy, and the committee considered the evidence too limited to make a recommendation.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

72	SH	UK Council for Psychotherapy	General	General	General	The UK Council for Psychotherapy (UKCP) is the leading professional and regulatory body for psychotherapy in the UK, working to advance psychotherapies for the benefit of all. We exist to promote and maintain the highest standards of practice of psychotherapy and psychotherapeutic counselling for the benefit of the public. Our membership includes more than 11,000 individual therapists and more than 75 training and accrediting organisations. Our individual members work for the NHS, privately, and in third sector organisations offering a wide variety of psychotherapeutic approaches. Our support for the psychological therapies we represent is research-based and recognises the diversity of therapeutic approaches that can improve mental health. We hold the national register of psychotherapists and psychotherapeutic counsellors, which only includes practitioners who meet our exacting standards and training requirements and who agree to abide by our stringent ethical standards. We welcome the opportunity to respond to the consultation on the third draft of this guideline.	Thank you for your comment telling us about your organisation and responding to the consultation.

73	SH	UK Council for Psychotherapy	General	General	General	Couples Therapy We are concerned that couples therapy could become increasingly marginalised by the configuration of the current draft guideline. See below our suggestions.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee considered the pairwise analysis of behavioural couples therapy for people with depression and problems in the relationship with their partner. This evidence was based on a small, single study which indicated that compared to waitlist, couples' therapy demonstrated benefits in terms of depression symptoms and marital adjustment, but when compared to CBT it did not show a benefit in depression symptoms but did with marital adjustment. CBT compared to waitlist demonstrated benefits only in terms of depression symptoms. The committee discussed that although this was limited evidence, behavioural couples therapy was included in the range of interventions offered by the IAPT services and that it was useful in the

							specific population and so recommended its use for this group of people.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

74	SH	UK Council for Psychotherapy	General	General	General	The usage of the term counselling We would like to point out that how the word 'Counselling' as used in this draft is misleading and prejudicial to a particular employment group. In the UK, Counselling is a level of training, it is not a modality of treatment. As such, counsellors can be from a variety of modalities. Looking at the trials included under counselling and they are almost entirely in the Humanistic camp. It appears that 'counselling' is being used as a label for humanistic therapies (including person-centred and experiential therapies) but that this is not at all clear in this draft guideline. This is an important issue of language thus that needs to be clarified. The guideline should specify the modality of counselling (i.e., humanistic, dynamic, couple, family etc.) in the same way that they refer to different families or waves of cognitive and behavioural therapy approaches.Similarly confusing is that psychodynamic counselling is classified or appears under the class of other psychodynamic/psychoanalytic treatments and not under the counselling cluster	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. All the evidence for counselling that was included in the review for the treatment of a new episode of depression was non-directive counselling, and the committee therefore did not consider it appropriate to recommend a specific intervention (for example, Counselling for Depression/Person-Centred Experiential

							Therapy [PCET]) as the evidence was not reviewed for these interventions. However, based on informal consensus, the committee agreed that counselling should use an empirically validated protocol developed specifically for depression and this was included in the recommendation. No eligible evidence was identified for psychodynamic counselling for treatment of a new episode of depression or for further-line treatment. However, the committee agreed and specified in the protocol that psychodynamic counselling should be categorised with psychodynamic psychotherapies based on the principles of grouping into classes outlined above.

75	SH	UK Council for Psychotherapy	General	General	General	Bibliography 5-day DIT training programme. (2022). Anna Freud. https://www.annafreud.org/training/dynamic-interpersonal-therapy/5-day-dit-training-programme/ Aalbers S, Fusar-Poli L, Freeman RE, Spreen M, Ket JCF, Vink AC, Maratos A, Crawford M, Chen X, Gold C. (2017) Music therapy for depression. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD004517. DOI: 10.1002/14651858.CD004517.pub3 Abbass, A. A. (2006). Intensive Short-Term Dynamic Psychotherapy of treatment-resistant depression: a pilot study. Depression and Anxiety, 23(7), 449–452. https://doi.org/10.1002/da.20203 Abbass, A. A., & Town, J. M. (2016). Bona Fide Psychotherapy Models Are Equally Effective for Major Depressive Disorder. JAMA Psychiatry, 73(9), 893. https://doi.org/10.1001/jamapsychiatry.2016.1916 Albornoz, Y. (2011). The effects of group improvisational music therapy on depression in adolescents and adults with substance abuse: a randomized controlled trial. Nordic Journal of Music Therapy, 20(3), 208–224. https://doi.org/10.1080/08098131.2010.522717 Baucom, D. H., Fischer, M. S., Worrell, M., Corrie, S., Belus, J. M., Molyva, E., & Boeding, S. E. (2018). Couple-based Intervention for Depression: An Effectiveness Study in the National Health Service in England. Family Process, 57(2), 275–292. https://doi.org/10.1111/famp.12332 Bower PJ, and Rowland N. (2006). Effectiveness and cost effectiveness of counselling in primary care. Cochrane Database of Systematic Reviews, Issue 3. Art. No.: CD001025. DOI:	Thank you for providing these references. Responses to the points raised in the comments have been addressed in the corresponding comment sections.

						10.1002/14651858.CD001025.pub2. Carmody, T. J., Rush, A. J., Bernstein, I., Warden, D., Brannan, S., Burnham, D., Woo, A., & Trivedi, M. H. (2006). The Montgomery Äsberg and the Hamilton ratings of depression: A comparison of measures. European Neuropsychopharmacology, 16(8), 601–611. https://doi.org/10.1016/j.euroneuro.2006.04.008 Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C. H., Cipriani, A., & Furukawa, T. A. (2020). A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry, 19(1), 92–107. https://doi.org/10.1002/wps.20701 Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C. H., Cipriani, A., & Furukawa, T. A. (2020). A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry, 19(1), 92–107. https://doi.org/10.1002/wps.20701 Cuijpers, P., Quero, S., Noma, H., Ciharova, M., Miguel, C., Karyotaki, E., Cipriani, A., Cristea, I. A., & Furukawa, T. A. (2021). Psychotherapies for depression: a network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. World Psychiatry, 20(2), 283–293. https://doi.org/10.1002/wps.20860 Elliott, R.E., and Freire, E. (2010). The effectiveness of person-centred and experiential therapies: A review of the meta-analyses. In M. Cooper, J.C. Watson and D. Holldampf (eds.), Person-centered and experiential therapies work: A review of the research on counseling, psychotherapy and related practices. Ross-on-Wye: PCCS Books. Faltinsen, E. G., Storebø, O. J., Jakobsen, J. C., Boesen, K., Lange, T., & Gluud, C. (2018).	

						Network meta-analysis: the highest level of medical evidence?. BMJ evidence-based medicine, 23(2), 56–59. https://doi.org/10.1136/bmjebm-2017-110887 Faulkner, A. (2020, December 10). Informing a Decision Guide for Psychological Treatments for Depression. NSUN. https://www.nsun.org.uk/resource/informing-a-decision-guide-for-psychological-treatments-for-depression/ Finazzi, E., & MacBeth, A. (2021). Service users experience of psychological interventions in primary care settings: A qualitative meta-synthesis. Clinical Psychology & Psychotherapy. https://doi.org/10.1002/cpp.2650 Fonagy, P. (2015). The effectiveness of psychodynamic psychotherapies: An update. World Psychiatry, 14(2), 137–150. https://doi.org/10.1002/wps.20235 Freire, E., Williams, C., Martina-Messow, C., Cooper, M., Elliott, R., McConnachie, A., Walker, A., Heard, D. & Morrison, J. (2015). Counselling versus low-intensity cognitive behavioural therapy for persistent sub-threshold and mild depression (CLICD): a pilot/feasibility randomised controlled trial. BMC Psychiatry. doi:10.1186/s12888-015- 0582-y Goddard, E., Wingrove, J., & Moran, P. (2015). The impact of comorbid personality difficulties on response to IAPT treatment for depression and anxiety. Behaviour Research and Therapy, 73, 1–7. https://doi.org/10.1016/j.brat.2015.07.006 Hyvonen, K Pylvainen P, Isotalo E and Lappalainen R (2018) Dance therapy in the treatment of depression: Preliminary results, University of Jyvaskyla, Psychology Department. Available at: https://www.jyu.fi/psykologia/tanssi-liiketerapia Iwakabe, S., & Gazzola, N. (2009). From single-case studies to practice-	

						based knowledge: Aggregating and synthesizing case studies. Psychotherapy Research, 19(4-5), 601–611. https://doi.org/10.1080/10503300802688494 Johnsen, T. J., & Friborg, O. (2015). The effects of cognitive behavioral therapy as an anti-depressive treatment is falling: A meta-analysis. Psychological Bulletin, 141(4), 747–768. https://doi.org/10.1037/bul0000015 Kazdin, A. E. (2007). Mediators and Mechanisms of Change in Psychotherapy Research. Annual Review of Clinical Psychology, 3(1), 1–27. https://doi.org/10.1146/annurev.clinpsy.3.022806.091432 Kazdin, A. E. (2009). Understanding how and why psychotherapy leads to change. Psychotherapy Research, 19(4-5), 418–428. https://doi.org/10.1080/10503300802448899 King M, Marston L, Bower P. (2014) Comparison of nondirective counselling and cognitive behaviour therapy for patients presenting in general practice with an ICD-10 depressive episode: a randomized control trial. Psychological Medicine. 44:1835–44. Knekt, P., Lindfors, O., Härkänen, T., Välikoski, M., Virtala, E., Laaksonen, M. A., Marttunen, M., Kaipainen, M., & Renlund, C. (2007). Randomized trial on the effectiveness of long-and short-term psychodynamic psychotherapy and solution-focused therapy on psychiatric symptoms during a 3-year follow-up. Psychological Medicine, 38(5), 689–703. https://doi.org/10.1017/s003329170700164x Knekt, P., Virtala, E., Härkänen, T., Vaarama, M., Lehtonen, J., & Lindfors, O. (2016). The outcome of short- and long-term	

						psychotherapy 10 years after start of treatment. Psychological Medicine, 46(6), 1175–1188. https://doi.org/10.1017/s0033291715002718 Koch, S., Kunz, T., Lykou, S., & Cruz, R. (2014). Effects of dance movement therapy and dance on health-related psychological outcomes: A meta-analysis. The Arts in Psychotherapy, 41(1), 46–64. https://doi.org/10.1016/j.aip.2013.10.004 Lamph, G., Baker, J., Dickinson, T., & Lovell, K. (2020). Personality disorder co-morbidity in primary care "Improving Access to Psychological Therapy" (IAPT) services: a qualitative study exploring patient perspectives on treatment experience. Behavioural and Cognitive Psychotherapy, 1–15. https://doi.org/10.1017/s1352465820000594 Leichsenring, F., Abbass, A., Luyten, P., Hilsenroth, M., & Rabung, S. (2013). The Emerging Evidence for Long-Term Psychodynamic Therapy. Psychodynamic Psychiatry, 41(3), 361–384. https://doi.org/10.1521/pdps.2013.41.3.361 Leichsenring, F., & Rabung, S. (2014). Long-Term Psychodynamic Psychotherapy in Complex Mental Disorders: Update of a Meta-Analysis. FOCUS, 12(3), 336–346. https://doi.org/10.1176/appi.focus.12.3.336 Leuzinger-Bohleber, M., Kaufhold, J., Kallenbach, L., Negele, A., Ernst, M., Keller, W., Fiedler, G., Hautzinger, M., Bahrke, U., & Beutel, M. (2019). How to measure sustained psychic transformations in long-term treatments of chronically depressed patients: Symptomatic and structural changes in the LAC Depression Study of the outcome of cognitive-behavioural and psychoanalytic long-term treatments. The International Journal of Psychoanalysis, 100(1), 99–	

						127. https://doi.org/10.1080/00207578.2018.1533377 Levitt, H. M., Bamberg, M., Creswell, J. W., Frost, D. M., Josselson, R., & Suárez-Orozco, C. (2018). Journal article reporting standards for qualitative primary, qualitative meta-analytic, and mixed methods research in psychology: The APA Publications and Communications Board task force report. American Psychologist, 73(1), 26– 46. https://doi.org/10.1037/amp0000151 Maj, M., Stein, D. J., Parker, G., Zimmerman, M., Fava, G. A., De Hert, M., Demyttenaere, K., McIntyre, R. S., Widiger, T., & Wittchen, H. (2020). The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry, 19(3), 269– 293. https://doi.org/10.1002/wps.20771 McPherson, S., Wicks, C., & Tercelli, I. (2020). Patient experiences of psychological therapy for depression: a qualitative metasynthesis. BMC Psychiatry, 20(1). https://doi.org/10.1186/s12888-020-02682-1 Medicines Used in Mental Health – England – Quarterly Summary Statistics July to September 2021. (2021, December 1). NHSBSA Statistics. https://www.nhsbsa.nhs.uk/statistical-collections/medicines-used-mental-health-england/medicines-used-mental-health-england-quarterly-summary-statistics-july-september- 2021 Meekums B, Karkou V, Nelson EA. (2015) Dance movement therapy for depression. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD009895. DOI: 10.1002/14651858.CD009895.pub2. Moller, N. P., Ryan, G., Rollings, J., & Barkham, M. (2019). The 2018 UK NHS Digital	

						annual report on the Improving Access to Psychological Therapies programme: a brief commentary. BMC Psychiatry, 19(1). https://doi.org/10.1186/s12888-019-2235-z Nan, J. K. M., & Ho, R. T. H. (2017). Effects of clay art therapy on adults outpatients with major depressive disorder: A randomized controlled trial. Journal of Affective Disorders, 217, 237–245. https://doi.org/10.1016/j.jad.2017.04.013 NHS Mental Health Implementation Plan 2019/20 – 2023/24. (2019, July). NHS England. https://www.longtermplan.nhs.uk/wp-content/uploads/2019/07/nhs-mental-health-implementation-plan-2019-20-2023-24.pdf Person-Centred Experiential Counselling for Depression Training (PCE-CfD). (2022). The University of Nottingham. https://www.nottingham.ac.uk/education/study/counselling-depression/index.aspx Pinquart M, Oslejsek B & Teubert D (2016) Psychotherapy Research Volume 26, 2, 241-257 Psychological Therapies, Annual report on the use of IAPT services, 2020-21. (2021, November 25). NHS Digital. https://digital.nhs.uk/data-and-information/publications/statistical/psychological-therapies-annual-reports-on-the-use-of-iapt-services/annual-report-2020-21 Public health England. (2020, December 3). Prescribed Medicines Review: Summary. Public Health England. https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary Pybis, J, Saxon, D, Hill, A, and Barkham, M. (2017) The comparative effectiveness and efficiency of cognitive behaviour therapy and generic counselling in the treatment of	

						depression: evidence from the 2nd UK National Audit of psychological therapies. BMC Psychiatry 17:215 DOI 10.1186/s12888-017-1370-7 Record high patient numbers completing NHS treatment for common mental illness. (2021, November 25). NHS England. https://www.england.nhs.uk/2021/11/record-high-patient-numbers-completing-nhs-treatment-for-common-mental-illness/ Ritter, M. & Low, K. G. (1996). Effects of dance/movement therapy: A meta-analysis. The Arts in Psychotherapy, 23, 249–260. Available: http://www.sciencedirect.com.edgehill.idm.oclc.org/science/article/pii/0197455696000275 Röhricht F, Papadopoulos N, & Priebe S. (2013). An exploratory randomized controlled trial of body psychotherapy for patients with chronic depression. Journal of Affective Disorders, 151, 85-91. Röhricht F. (2015). Body psychotherapy for the treatment of severe mental disorders–an overview. Body, Movement and Dance in Psychotherapy, 10, 51-67. Rush, A. John., Thase, M. E., & Dubé, S. (2003). Research issues in the study of difficult-to-treat depression. Biological Psychiatry, 53(8), 743–753. https://doi.org/10.1016/s0006-3223(03)00088-x Saxon D, Ashley K, Bishop-Edwards L, Connell J, Harrison P, Ohlsen S, et al. (2017). A pragmatic randomised controlled trial assessing the non-inferiority of counselling for depression versus cognitive-behaviour therapy for patients in primary care meeting a diagnosis of moderate or severe depression (PRaCTICED): study protocol for a randomised controlled trial. Trials. 2017;18:93. DOI: https://doi.org/10.1186/s13063-017-1834-6 Skodol, A. E., Clark, L. A., Bender, D. S., Krueger, R. F.,	

						Morey, L. C., Verheul, R., Alarcon, R. D., Bell, C. C., Siever, L. J., & Oldham, J. M. (2011). Proposed changes in personality and personality disorder assessment and diagnosis for DSM-5 Part I: Description and rationale. Personality Disorders: Theory, Research, and Treatment, 2(1), 4–22. https://doi.org/10.1037/a0021891 Steinert, C, Munder, T, Rabung, S, Hoyer, J, and Leichsenring, F. (2017). Psychodynamic therapy: As efficacious as other empirically supported treatments? A meta-analysis testing equivalence of outcomes. https://doi.org/10.1176/appi.ajp.2017.17010057 Stratton, P. (2011). The evidence base of systemic family and couples therapies. Available: http://www.aft.org.uk/SpringboardWebApp/userfiles/aft/file/Research/Final%20evidence%20base.pdf Last accessed 06/06/2018. Timulak, L. (2009). Meta-analysis of qualitative studies: A tool for reviewing qualitative research findings in psychotherapy. Psychotherapy Research, 19(4-5), 591–600. https://doi.org/10.1080/10503300802477989 Uher, R., Farmer, A., Maier, W., Rietschel, M., Hauser, J., Marusic, A., Mors, O., Elkin, A., Williamson, R. J., Schmael, C., Henigsberg, N., Perez, J., Mendlewicz, J., Janzing, J. G. E., Zobel, A., Skibinska, M., Kozel, D., Stamp, A. S., Bajs, M., & Placentino, A. (2007). Measuring depression: comparison and integration of three scales in the GENDEP study. Psychological Medicine, 38(2), 289–300. https://doi.org/10.1017/s0033291707001730 Van Rijn, B, Wild, C and Moran, P. (2011). Evaluating the outcomes of transactional analysis and integrative counselling psychology	

						within UK primary care settings. International Journal of Transactional Analysis Research & Practice, 2, 34-43. Van Rijn, BV & Wild, C. (2013). Humanistic and integrative therapies for anxiety and depression: Practice-based evaluation of transactional analysis, gestalt, and integrative psychotherapies and person-centred counselling. Transactional Analysis Journal, 43, 150-163. Van Rijn, BV and Wild, C. (2016). Comparison of transactional analysis group and individual psychotherapy in the treatment of depression and anxiety: Routine outcomes evaluation in community clinics. Transactional Analysis Journal, 46, 63-74. Wahl, I., Löwe, B., Bjorner, J. B., Fischer, F., Langs, G., Voderholzer, U., Aita, S. A., Bergemann, N., Brähler, E., & Rose, M. (2014). Standardization of depression measurement: a common metric was developed for 11 self-report depression measures. Journal of Clinical Epidemiology, 67(1), 73–86. https://doi.org/10.1016/j.jclinepi.2013.04.019 Ward E, King M, Lloyd M, Bower P, Sibbald B, Farrelly S, et al. (2000). Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy, and usual general practitioner care for patients with depression. I: Clinical Effectiveness. British Medical Journal 321:1383–8 Windle, E., Tee, H., Sabitova, A., Jovanovic, N., Priebe, S., & Carr, C. (2019). Association of Patient Treatment Preference With Dropout and Clinical Outcomes in Adult Psychosocial Mental Health Interventions. JAMA Psychiatry, 77(3). https://doi.org/10.1001/jamapsychiatry.2019.3750	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

76	SH	Society for Psychotherapy Research	General - all documents	General	General	Adequate referencing We notice that references are not included in all introductions and very much hope that they will be added in the published version. Given this omission it was not possible to check the accuracy of some of the statements made. (NB: A paper that is send for publication with missing references is often rejected on the grounds of potential plagiarism or imprecision.)	Thank you for your comment. The introductions to NICE evidence reviews are written by the committee as a brief introduction to the topic, the current knowledge and the aim of the review and are not referenced. References will therefore not be added prior to publication.
77	SH	NHS England and Improvement	General comment	General	General	We welcome the recommendations for integrated systems of care built on strong collaboration between professions to avoid people falling through gaps in service provision.	Thank you for your comment and support of this recommendation.
78	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	9	20	Risk: Is it mandatory to refer to a specialist service when someone expresses suicidality? Can other frontline services provide sufficient support (e.g. 111 type services) and indeed, is it not more important to have a robust risk management plan in place than the specialist service per se.	Thank you for your comment. The first 3 bullet points in this recommendation relate to provding treatment and limiting risk, and the 4th bullet advises that a referral can be considered, so it is not mandatory to refer a person who expresses suicidal ideation to specialist services.
79	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	10	26	Choice of Treatments: “ensuring they can see the same healthcare provider wherever possible” – we are concerned that this recommendation will set up unrealistic expectations for patients that providers will be unable to deliver, with consequent impact on outcomes.	Thank you for your comment. The evidence showed that people value building a trusted relationship and that a therapeutic relationship can be very helpful, so the committee agreed this was an important recommendation to make, but they added the caveat 'wherever possible' as they recognised that this would not always be possible.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

80	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	23	23	Table 1: What has informed the decision for 8 sessions of Guided Self Help Groups rather than 6 which is consistent with the competency framework.	Thank you for your comment. The usual number of sessions was informed by reported resource use in the RCTs that informed the NMA and the economic analysis. This information has now been included in evidence review B, under Appendix N. The recommendation has been amended to 'usually 6-8' sessions.
81	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	29	23	Table 1 - Treatment for people with new episode of less severe depression: For IPT, Counselling and short-term psychodynamic psychotherapy the session length for all these modalities should be amended to "weekly sessions of 50-60 minutes each" for consistency in order to manage patients' expectations around this. Some services and therapists will be modelled on a "50 minute" therapy hour and others on "60" minutes. It would be helpful, from the provider perspective, to build this flexibility into the recommendation in keeping with current practice in IAPT services and cost implications.	Thank you for your comment. The suggested duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of interventions.
82	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	32	12	Table 2 - Treatment for people with a new episode of more severe depression: For IPT, Counselling and short-term psychodynamic psychotherapy the session length for all these modalities should be amended to "weekly sessions of 50-60 minutes each" for consistency in order to manage patients' expectations. Some services and therapists will be modelled on a "50 minute" therapy hour and other on "60" minutes. It would be helpful in practice, from the provider perspective, to build this flexibility into the recommendation in keeping with current practice in IAPT services and cost implications.	Thank you for your comment. The suggested duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of interventions.

83	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	34	12	Table 2 - Treatment for people with a new episode of more severe depression: Counselling 12-16 sessions. This is a reduction from the 20 session modal for CFD that is standardly offered at present both in IAPT services and, significantly, on the training courses for Counselling for Depression (CFD) for patients with more severe depression. Whilst we acknowledge that reducing this will bring the number of sessions in line with other treatments (i.e. maximum of 16 sessions for IPT and DIT/STPP) we believe this may impact efficacy and outcomes for those with severe depression.	Thank you for your comment. It is noted that all the evidence for counselling that was included in the review for the treatment of a new episode of depression was for non-directive counselling, so the recommendation is not specific to CFD. However, based on informal consensus, the committee agreed that counselling should use an empirically validated protocol developed specifically for depression and this was included in the recommendation. Regarding the recommended number of sessions, this was based on relevant information reported in the RCTs that were considered in the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. This information has now been added in evidence review B, under Appendix N. The recommended ('usually') 12-16 sessions for counselling in more severe depression are consistent with the reported resource use in the respective RCTs; they serve only as a guidance and can be modified depending on individual needs. This has now been clarified in the recommendation.

84	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	43	13	"Changing to a combination of Psychological therapy (e.g. CBT, IPT or STPP) and medication" – why is CFD not specified here?	Thank you for your comment. Where there was limited or no response to an initial antidepressant monotherapy the committee recommended that, based on the evidence, a psychological therapy could be used to augment the antidepressant. There was some evidence for benefits associated with augmenting antidepressant treatment with CBT, IPT or STPP relative to continuing with the antidepressant only and on this basis the committee considered it appropriate to provide these psychological interventions as examples in the recommendation. There was only a single study included for augmenting antidepressant treatment with counselling relative to continuing with antidepressant treatment alone (Kocsis 2009/Klein 2011) and this study did not show clinically important or statistically significant effects of adding counselling to antidepressant treatment on depression symptoms or the rate of remission. Furthermore, this study used brief supportive psychotherapy (BSP) rather than Counselling for Depression (CFD). The committee therefore did not consider it appropriate to recommend Counselling for Depression as the evidence was not reviewed for this intervention.

85	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	48	2	Greater clarity around treatment for people with Personality Disorder who are depressed, for example, would the NICE guidelines be specifying a specialist service with an MDT to support those individuals or not?	Thank you for your comment. Evidence review F reviews interventions for people with depression and a coexisting personality disorder and the corresponding recommendations are in section 1.11 of the guideline. Based on the evidence, the committee recommended that in people with depression and coexisting personality disorder, their depression should be treated with a combination of an antidepressant and a psychological therapy. The committee were aware, based on their clinical experience and knowledge, of the significant problems in engaging, and ensuring uptake of treatment, for people with depression and a coexisting personality disorder. They therefore recommended that support should be provided to encourage uptake and engagement. A multi-disciplinary setting was considered by the committee to be important due to the complexity of the difficulties experienced by this population, as this allows access to appropriate expertise, and this is included in a recommendation. The committee also recommended that referral to a specialist personality disorder treatment programme is considered in line with the NICE guidance on borderline personality disorder.

86	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	68	009-010	Some Evidence for the Cost effectiveness of Counselling: (please also see point 4 above). The cost effectiveness will depend on which model is being delivered. We are concerned that the modality being delivered and number of sessions offered for more severe depression needs to be clearly delivered in line with treatment protocols for CFD and clearly differentiated from 'Generic Counselling' (8-sessions) which is suitable for those with less severe depression. A 12-16 session CFD will be more cost effective but moving away from the treatment protocols risks non-compliance and therapy-drift due to cost pressures.	Thank you for your comment. It is noted that all the evidence for counselling that was included in the review for the treatment of a new episode of depression was for non-directive counselling, so the recommendation is not specific to CFD. However, based on informal consensus, the committee agreed that counselling should use an empirically validated protocol developed specifically for depression and this was included in the recommendation. Regarding the number of sessions tested in economic modelling and the recommended number of sessions, these were based on relevant information reported in the RCTs that were considered in the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. This information has now been added in evidence review B, under Appendix N. The recommended ('usually') 12-16 sessions for counselling in more severe depression are consistent with the reported resource use in the respective RCTs; they serve only as a guidance and can be modified depending on individual needs. This has now been clarified in the recommendation.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

87	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	69	15	The fact that significant Behavioural Couples Therapy data has been considered and others not (as referenced in the other concerns are rather pertinent).	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such eligibility criteria for these interventions was restricted to this subgroup of people with depression.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

88	SH	Big Health Ltd	Guidance	General	General	1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Almost all patients with depression experience sleep disturbance. This is likely because sleep plays a fundamental role in mood and affect regulation. That is, sleep and circadian processes are more likely causally involved in depression rather than mere symptoms. The biggest impact on practice would be the routine adoption of insomnia management as part of standard care for depression. Currently, sleep hygiene advice is often provided within primary care however, it is not an effective or recommended treatment, but CBT for insomnia is. CBT for insomnia is also scalable to population level using Sleepio, a digital CBT for insomnia programme already evaluated by the NHS and by NICE. An implementation toolkit for Sleepio has been developed through a UKRI initiative (https://www.oxfordahsn.org/wp-content/uploads/2020/07/Sleepio-in-the-Thames-Valley_Big-Health-and-Oxford-AHSN-case-study_2020.pdf) which provided population-level access to Sleepio in the Thames Valley through primary care and community settings. This project, using real-world evidence, demonstrated that Sleepio can be made available at scale in the community through primary care. Therefore, Sleepio could be made available to any adult with depression immediately through primary care and with zero waiting list. In addition to improving remission from depression when insomnia symptoms are experienced, availability of evidence-based first line CBT through Sleepio may also reduce harmful prescribing of sleeping pills.2. Would implementation of any of the draft	Thank you for your comment. This guideline is about the treatment and management of depression in adults. People with depression and a chronic physical health problem, such as insomnia, are not within the scope of this guideline. Therefore it is not possible to make recommendations for the treatment of insomnia in this guideline. CG91 on 'Depression in adults with a chronic physical health problem' covers identifying, treating and managing depression in people aged 18 and over who also have a chronic physical health problem such as cancer, heart disease or diabetes. Your feedback will be passed on to the NICE surveillance team so that people with insomnia who are experiencing depression can be considered for inclusion in future updates of CG91.

						recommendations have significant cost implications?Health Economic data shows that it is feasible and cost-effective to make Sleepio available at community level and through primary care (e.g., Sampson et al., 2021; British Journal of General Practice; https://www.oxfordahsn.org/wp-content/uploads/2020/07/Sleepio-in-the-Thames-Valley_Big-Health-and-Oxford-AHSN-case-study_2020.pdf). Indeed, data indicates that Sleepio is cost saving compared to treatment as usual and face-to-face CBT with regards to reducing direct and downstream costs. A recent paper suggests that national adoption of Sleepio could reduce primary care costs by up to £20 million in the first year of rollout (Sampson et al., 2021; British Journal of General Practice). There is also data showing that Sleepio leads to significant improvements in QALYs (Stokes et al., in preparation). 3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)Sleep is a less stigmatised topic than most other mental health complaints. Stigma is a primary challenge for many accessing mental health services and can discourage people from accessing care. Addressing sleep problems would be hugely popular with most patients experiencing mental health problems and would provide a less stigmatised route to addressing mental health. Given that Sleepio can provide instant access to CBT, without any waiting lists Sleepio would lower barriers to self-care. Provision of Sleepio would also help align routine care for individuals experiencing insomnia symptoms in the context of depression with treatment guidelines for addressing insomnia symptoms. 4. Please tell	

						us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.We made Sleepio available to the entire NHS and DHSC workforce during the pandemic, given the substantial burden and mental health difficulties experienced by frontline workers. Provision of care digitally is actually more feasible than face to face care, and much more scalable. Indeed, over the period it was available, over [redacted] NHS and DHSC employees accessed Sleepio. Relatedly, there is evidence from the use of Sleepio in the US that it helps reduce COVID-related distress, in addition to reducing both insomnia and depression symptoms and stress [redacted]	

89	SH	Active Partnerships National Team	Guidance	General	General	Key points summaryWe support the inclusion of exercise as an optional first line treatment for people experiencing mild depression. However, feel there is significant opportunity for clinicians to promote a broader 'move more' message and integrate physical activity in adjunct to all treatment pathways for patients experiencing mild or severe depression.We support the inclusion of peer support in exercise treatment pathways for mild and severe depression.We would welcome the consideration within the methodology of the inclusion of broader research (including real-life setting research, physical activity non-randomised trials and physical inactivity research) to enrich the guideline development. Whilst structured, group exercise may be appropriate for some individuals, broader options that are person-centred and individualised should be considered due to their proven effectiveness such as social prescribing, community provision and self-led activity.We feel the high level of frequency and duration information included within the exercise treatment pathway delivery information could be too ambitious and unrealistic for many people experiencing mild or severe depression.We feel a ranking approach of intervention options on the treatment wheel undermines true patient choice. We are concerned how in practice a patient will be informed of the exercise treatment option, particularly if they have no preference and limited understanding of what could be available to them.We feel the starting point for treatment options should not be the most cost-effective interventions. We suggest a method that starts with understanding patient needs through appropriate questioning and responding with the most relevant treatment	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. The committee considered RCTs as the most appropriate study design to assess clinical and cost effectiveness. This is consistent with the NICE guidelines manual which recognises RCTs as the most valid evidence of the effects of interventions. This was outlined a priori in the review protocols, and on this basis non-randomised trials and real-life research were not included. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this. In addition to the results of the network meta-analysis (NMA), the committee took

						option/s.The barriers to being active for those living with mental health conditions should be addressed in any exercise treatment pathway created. This will support recruitment and patient attrition rates.	other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee agreed that decisions on treatment should be made in discussion with the person with depression and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion.

90	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	General	General	The guideline review should not recommend treatments based solely on patients who recover from depression by end of treatment, but should recognise clinical improvement (i.e. partial recovery) achieved from a severe baseline point. In addition, categorisations of depression severity must be based on validated tools, not un-validated non-transparent functions of them	Thank you for your comment. The guideline includes continuous changes in scores on depression scales as a critical outcome for every treatment question, which will show changes for people who have both fully and partially recovered. This was agreed by the committee to be a better way to capture this data than the use of a dichotomous outcome for partial recovery. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line presentations of depression are managed in primary care). Based on this distinction, an anchor point of 16 on the PHQ-9 was selected as the cut-off between less severe and more severe depression, on the basis of alignment with the clinical judgement of the committee and eligibility criteria in the included studies. Published standardization of depression measurement crosswalk

							tables (Carmody 2006; Rush 2003; Uher 2008; Wahl 2014) were used in order to 'read-across' different symptom severity scales that were used in different studies.
91	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	General	General	While acknowledging the extension by five days of the original deadline, given the importance of this unprecedented third consultation, a closing date not so close to the Christmas and New Year holidays would perhaps have provided an opportunity for greater collaboration and a richer response from stakeholders	Thank you for your comment. The consultation period is scheduled well in advance and, as you state, was extended as well, so it is hoped stakeholders were able to plan resources to enable them to review the guideline and respond. Over 1400 comments were received so it appears this was a successful consultation process.

92	SH	Dorset Healthcare University NHS Foundation Trust	Guidance	General	General	The movement in the recommendations to recognise some of the other features where choice is important and recovery has been demonstrated is valuable.	Thank you for your comment and support for these recommendations.
93	SH	Association for Family Therapy and Systemic Practice	Guideline		General comment	Why was the extremely large IAPT dataset comparing outcomes from different types of therapies, which has been collected for over a decade and is high quality practice-based evidence, not included alongside RCT evidence?	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is

							possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.
94	SH	Association for Family Therapy and Systemic Practice	Guideline		General comment	Why were family interventions for depression not considered such as family therapy for depression based on the McMaster model, (Miller et al., 2005; Ryan et al., 2005); behavioural family therapy for families of depressed mothers of children with disruptive behaviour disorders (Sanders and McFarland, 2000); and various types of individual family and multifamily therapy for older adults with depression (Stahl et al., 2016)?	Thank you for your comment. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

95	SH	Association for Family Therapy and Systemic Practice	Guideline		General comment	The committee made the recommendations on the use of lithium and the use of antipsychotics by informal consensus and based on their knowledge and experience. This seems inconsistent with recommendations made about other interventions including psychological therapies.	Thank you for your comment. The recommendation on use of lithium and use of antipsychotics provide practical information on how these medicines should be used in practice and monitored, and this is not the sort of information that is best obtained from a systematic review of the evidence. These recommendations were therefore based on pre-existing national guidance such as the BNF, and the committee's knowledge and experience. The place in therapy of lithium and antipsychotics was based on systematic reviews of the evidence for the treatment sections of the guideline.
96	SH	NHS England and Improvement	Guideline	1	7	It would be helpful to specifically mention older adults in the description of what the guideline covers or in the title.	Thank you for your comment. The guideline covers adults of all ages, so it was not felt necessary to specify a particular age sub-population in the title.
97	SH	Association for Family Therapy and Systemic Practice	Guideline	002/062	General comment	COVIDThe COVID pandemic has seen a rise in problems that are connected to living circumstances and relational factors, including stresses such as living within family systems. The lack of consideration of systemic factors and deemphasising of behavioural couples therapy seems surprising at such a time. Systemic, family and couples treatments is also another area that the committee could usefully suggest for further research on page 062, line 001.	Thank you for your comment. The committee were aware of the link between the Covid pandemic and difficulties with personal relationships but agreed not to make pandemic-specific recommendations as these may soon become outdated. The committee looked at the evidence for the use of behavioural couples therapy for people with relationship problems and

							found some evidence, so did not prioritise this area for a research recommendation. It is recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
98	SH	NHS England and Improvement	Guideline	5	3	Under the section 'Principles of care': In light of UN report on Ageism it is suggested highlighting the need to ensure that staff should avoid ageism	Thank you for your comment. Based on this and other stakeholder feedback, this recommendation has been amended to highlight the need to be aware of discrimination as well as stigma, and this would include ageism, racism or any other form of discrimination.
99	SH	NHS England and Improvement	Guideline	5	6	Rec 1.1.1 – Include principles of Personalised Care "what matters to you" in the assessment process	Thank you for your comment. The discussion about 'what matters to you' is included in the section of the guideline on discussing treatment choice so it has not been repeated here.
100	SH	The College of Mental Health Pharmacy	Guideline	5	12	"can make it hard for people to access mental health services…." Please delete "mental".	Thank you for your comment. As this recommendation is about accessing treatment for depression, the terminology 'mental health services' has been retained.

101	SH	NHS England and Improvement	Guideline	5	20	Rec 1.1.2 – recommendation should use terminology of supported self-management and peer support groups rather than self-help groups	Thank you for your comment. The committee agreed that the terminology 'self-help groups' was widely used and understood and therefore did not change this. They did, however, agree to add the terminology to 'peer' support groups.
102	SH	The Challenging Behaviour Foundation	Guideline	6	3	Rec 1.1.3 – Recommendation should read: 'Provide people with depression with up to date and evidence-based verbal and written information, in a manner appropriate to their communication needs and in line with the NICE guideline on patient experience in adult NHS services'.	Thank you for your comment. 'Appropriate to their communication needs' has been added to this recommendation as you suggest, but the link the to the NICE guideline on patient experience has been left as a standalone sentence, to avoid a very long sentence.
103	SH	NHS England and Improvement	Guideline	6	7	There is mention of the MH Act in this section. Is there an opportunity here to raise awareness of PHBs as part of s117 aftercare here? The right to have a PHB (and a PCSP) for people who are s117 aftercare eligible should be included in this section that focuses on Advance Decision making and people who have been detained under the MHA	Thank you for your comment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this

							basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).
104	SH	NHS England and Improvement	Guideline	6	15	At point 19 talks about 'supporting families & carers' - consider adding PCSP / access to PHBs for the person and / or their Carer	Thank you for your comment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to

							advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).
105	SH	The Challenging Behaviour Foundation	Guideline	6	15	Rec 1.1.5 – Recommendation should read: 'Advise people with depression that they can set up a Health and Welfare Lasting Power of Attorney, and support them to do so if appropriate, so that…'.	Thank you for your comment. The amendment you suggested has been made.
106	SH	Diabetes UK	Guideline	6	015-018	1.1.5 – We suggest also explicitly stating that a person with depression's capacity to make decisions themselves should be regularly reviewed in this section	Thank you for your comment. The committee has added the need for regular review to the recommendation.
107	SH	The College of Mental Health Pharmacy	Guideline	6	General	Please outline what this "information" should be about. E.g., the illness? Or drug treatments? Or talking therapies? or delete.	Thank you for your comment. The committee added more detail to explain that this was information about depression and its treatment.
108	SH	Association for Family Therapy and Systemic Practice	Guideline	6	General comment	TherapeuticrelationshipThere is no mention within the guidelines that therapeutic relationship is important in the treatment. Omission of this point is likely to impact clinical practice. This could be mentioned within the Principles of Care section	Thank you for your comment. The building of a trusting relationship is already recommended in the section on the principles of care.

109	SH	NHS England and Improvement	Guideline	8	2	Talks about Initial assessment including discussion of social factors e.g. 'living conditions, debt, employment & social isolation' - PCSP / offer of a PHB to help resolve issues impacting health needs/depressive episode to be considered	Thank you for your comment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness). The committee were aware of work

							emanating from the NHS long-term plan which suggested that care should be locality-based and integrated across all aspects of health and social care and so made recommendations (in the access section of the guideline) to advise this.
110	SH	Anxiety UK	Guideline	8	10	We feel that you should specifically mention anxiety disorders when exploring co-existing mental health and/or physical disorders	Thank you for your comment. There is a separate section of the guideline on depression with anxiety, so anxiety has not been mentioned specifically as a co-existing mental health condition in this section of the guideline.
111	SH	NHS England and Improvement	Guideline	8	016 - 017	Rec 1.2.7 – recommendation does not cover a broad enough range of wider determinants, and loneliness is distinct from social isolation. Suggest “personal, social and environmental factors including living conditions and housing, drug and alcohol use and misuse, debt and poverty, employment, caring status, loneliness and social isolation”	Thank you for your comment. Based on your comments and feedback from other stakeholders, this recommendation has been expanded to include loneliness, lifestyle and stress or trauma.

112	SH	NHS England and Improvement	Guideline	8	19	Under the section 'Risk Assessment': Suggest highlighting that risk following self harm has distinct characteristics in older adults and the risk of suicide is higher in older adults Self-harm in older adults: systematic review | The British Journal of Psychiatry | Cambridge Core)	Thank you for your comment. The NICE guideline on self-harm is currently being updated, and a link has been included to it from these recommendations on risk, so more detail on self-harm has not been included here.
113	SH	The College of Mental Health Pharmacy	Guideline	8	General	Please advise practitioners as to commonly used assessment tools such as the PHQ9 which may be used as part of the initial assessment.	Thank you for your comment. As specified in the scope, the recognition, assessment and initial management section from the 2009 guideline was not included in this update. In line with NICE processes, the 2009 content has been carried across to this updated guideline. However, the evidence on recognition, assessment and initial management has not been reviewed and it is therefore not possible to recommend a specific assessment tool as the evidence for the reliability and validity of specific scales has not been assessed as part of this update.
114	SH	The College of Mental Health Pharmacy	Guideline	8	General	Please advise practitioners as to commonly used assessment tools for anxiety which may be used as part of the initial assessment.	Thank you for your comment. As specified in the scope, the recognition, assessment and initial management section from the 2009 guideline was not included in this update. In line with NICE processes, the 2009 content has been carried across to this updated guideline. However, the evidence on recognition, assessment and initial management has not been reviewed and it

							is therefore not possible to make changes to these recommendations. The section of the guideline on Depression with anxiety recommends that the NICE guidance for the relevant anxiety disorder (if available) is consulted.
115	SH	Care To Listen	Guideline	9	25	Concerns that this could lead to an over-simplistic assumption that treatment for depression is prioritised over treatment for anxiety when co-morbidity is so often the case. This can often not be helpful as the client is unable to start looking at some of the causes and underlying emotions/feelings of a situation until the more day-to-day anxiety around engaging with support or functioning are addressed. To have the flexibility to decide which of the two symptoms is tackled first is also an important part of the therapist/triage-client conversation – e.g. what works best for this individual? In the majority of clients we see the scores for anxiety and depression often track each other closely and so it makes sense that being able to decide how best to approach this on a more individual basis is important. Failure to engage with one treatment could undermine the efficacy of or client's willingness to engage in a later treatment.	Thank you for your comment. The recommendation allows flexibility to determine if the depression or the anxiety is the predominant problem and to treat accordingly, and so has not been revised
116	SH	NHS England and Improvement	Guideline	9	25	Could the guidance please highlight that anxiety is a particularly common manifestation of depression in older adults	Thank you for your comment. This recommendation has been expanded to include the fact that anxiety is particularly common in older people.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

117	SH	Anxiety UK	Guideline	9	026 - 027	We are aware this hasn't changed from the last guideline, however we feel that this section is a bit confusing – our experience is that often those with anxiety disorders who have a secondary depression arising from their anxiety disorder often not having been treated in a timely manner, find that their anxiety is not treated as the primary problem and so they get treated for depression when actually the root cause is anxiety. We would like this to be reflected/taken account of in the guidelines.	Thank you for your comment. The recommendation allows flexibility to determine if the depression or the anxiety is the predominant problem and to treat accordingly, and so has not been revised
118	SH	NHS England and Improvement	Guideline	10	1	Suggest under 'Depression in people with acquired cognitive impairments' it could reference the NICE dementia guidelines (consistent with section 1.4 which does reference NICE dementia guidelines)	Thank you for your comment. This link to the dementia guidelines has been included here as well.
119	SH	The Challenging Behaviour Foundation	Guideline	10	13	Rec 1.3.1 – 013 Discussion should also include prior experiences of other treatments besides treatments for depression alone. Prior experiences of treatments and medical interventions will inform preferences, and may have been traumatic for the individual.	Thank you for your comment. This section of the guideline is about the choice of treatments for depression and so recommendation has not been expanded to include experience of treatments for other conditions. However, the section of the guideline on initial assessment has now been expanded to include a discussion about other factors such as previous trauma.
120	SH	UK Council for Psychotherapy	Guideline	10	14	Rec 1.3.1 We welcome this point about what people think might contribute to the development of the depression and suggest that the guidelines advise also that enquiries are also made about people's views regarding what helps/alleviates their depression.Suggested wording:what, if anything, they think might be contributing to the development of their	Thank you for your comment. This recommendation has been revised to include asking people about what has helped their depression in the past.

						depression and what they have noticed helps/alleviates their depression.	
121	SH	Association for Family Therapy and Systemic Practice	Guideline	10	14	Rec 1.3.1 - AFT members welcome the inclusion of perspectives from people with depression on what they think might contribute to the development of their depression, including social/contextual and relational factors. However, it was noted that there was an absence of guidance around how to support professionals in having such conversations. Based on our experience of being guided in systemic work by people's own strengths and resources, we would strongly recommend the guidelines also include discussions about people's views regarding what alleviates their depression. We would suggest the following amendment: "what, if anything, they think might be contributing to the development of their depression and what they have noticed alleviates their depression".	Thank you for your comment. The committee agreed that decisions on treatment should be made in discussion with the person with depression and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion. It was recognised by the committee that people who have had prior episodes of depression may have preferences for their treatment based on prior experience or insight into their own depression patterns. The committee considered your suggested amendment but agreed that people's views on what might alleviate their depression was already covered in the current recommendation by discussing what treatment options people might prefer, the person's experience of any prior episodes of depression or treatments for depression, and what they would expect to gain from treatment.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

122	SH	Diabetes UK	Guideline	10	20	In practice, this question may be perceived negatively by someone with depression depending on tone and body language of the healthcare professional asking it. To avoid this we suggest rephrasing it to ask what outcome they are hoping for from the treatment plan or what their expectations of the treatment is.	Thank you for your comment. This recommendation has been rephrased to include what people hope to gain from treatment, as you suggest.
123	SH	Association for Family Therapy and Systemic Practice	Guideline	10	20	Rec 1.3.1 – There is significant evidence that working with families, carers and significant others improves health outcomes (see Carr, A. (2019), Couple therapy, family therapy and systemic interventions for adult-focused problems: the current evidence base. Journal of Family Therapy, 41: 492-536). We would suggest including in the recommendations to discuss with people with depression "who they would like involved in their treatment"	Thank you for your comment. The subsequent recommendation, 1.3.2, is about involving family members (if agreed) in the discussion and an option to attend treatment with a family member has been added to a later recommendation in this section. It is also recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
124	SH	UK Council for Psychotherapy	Guideline	10	22	Rec 1.3.2 Involving family members, carers or other supporters is important and welcomed by many people. It can aid the assessment and intervention yet is rarely offered or done. This should not be limited to occasions when requested by the person with depression as suggested in the guideline. Making such a request can be too challenging for some and many do not realise it is an option. Involving family members,	Thank you for your comment. This recommendation has been amended to be more pro-active and now states that family members should be involved (as long as this as agreed by the person with depression), and an option to attend treatment with a

						carers or other supporters should be offered routinely. We suggest changing the wording to:Allow adequate time for the initial discussion about treatment options, and routinely offer to involve family members, carers or other supporters in contact with the person with depression.	family member has been added to a later recommendation in this section.
125	SH	Association for Family Therapy and Systemic Practice	Guideline	10	22	Rec 1.3.2 – AFT members are pleased to see recommendation to involve family members in discussions about treatment options. Involving family members, carers or other supporters is important and welcomed by many people with depression who we work with, yet infrequently offered as part of assessment and treatment. We strongly recommend that inclusion of family members should not be dependent on the request of the person with depression as making such a request can be challenging for some and many would not recognise this to be an option. Carers often feel ignored by healthcare professionals in decisions about their loved ones and want to be involved in discussions about treatment options (Healthwatch, 2020). As such, we would suggest involvement of family members, carers or other supporters as part of routine practice and make the following suggestion for amendment: “Allow adequate time for the initial discussion about treatment options, and routinely offer to involve family members, carers or other supporters in contact with the person with depression.”	Thank you for your comment. This recommendation has been amended to be more pro-active and now states that family members should be involved (as long as this as agreed by the person with depression), and an option to attend treatment with a family member has been added to a later recommendation in this section.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

126	SH	The College of Mental Health Pharmacy	Guideline	010-011	General	This whole section reads as though it is to be used in primary care and with patients who have the capacity to discuss all these nuances in treatment choices. Commonly this is not the case, either due to concurrent dementia, acuity of illness (depression) or concurrent illnesses, and is rarely the case for patients in secondary care mental health services.This needs to be acknowledged and provision given for the scenarios when clinicians have to make decisions about initial treatment on behalf of the patients without their full involvement.	Thank you for your comment. This section on choice has been included to increase the emphasis in the guideline on preferences and shared decision-making, People with depression who lack capacity would be treated under the Mental Health Act 2007, in line with the Mental Capacity Act 2005, and this is stated in the section of the guideline on 'Advance decisions and statements.'
127	SH	The Challenging Behaviour Foundation	Guideline	11	3	Rec 1.3.4 - It should also be discussed that, alongside declining treatment, individuals are able to opt-out of any treatment which they feel is non-beneficial or harmful. For individuals with specific communication needs, the way in which they express negative reactions during treatment should be understood and monitored throughout.	Thank you for your comment. The recommendation has been expanded to include the option for people to change their mind about treatment as well as to decline it. The need to recognise specific communication needs has been described in the over-arching recommendations on information and support and so has not been repeated here as well.
128	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	11	003-012	Patient choice - communication. Among the recommended therapeutic approaches, some, such as psychodynamic psychotherapy, can be adapted to accommodate alternative forms of communication such as music or art, if appropriate. Initial discussions with the patient around selecting a therapeutic approach should acknowledge this – although it would be at the therapist's discretion.	Thank you for your comment. Alternative forms of delivery of psychological therapies for people with communication difficulties is covered in the section of the guideline on the delivery of psychological interventions.
129	SH	UK Council for	Guideline	11	5	Rec 1.3.4 Suggest amend 'providing information on what treatments are available' to 'providing information on all	Thank you for your comment. This recommendation has been amended to state that NICE-recommended treatments

		Psychotherapy				treatments available' or practitioners will likely default to those with which they are most familiar.	should be discussed, to clarify the range of treatments that should be included.
130	SH	Association for Family Therapy and Systemic Practice	Guideline	11	5	Rec 1.3.4 – One AFT member noted that professionals often offer what they choose or the models they are more familiar with. We would the following amendment to reflect the range of potential treatments available to people with depression: "providing information on all treatments available".	Thank you for your comment. This recommendation has been amended to state that NICE-recommended treatments should be discussed, to clarify the range of treatments that should be included.

131	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	11	9	Include an extra bullet to the effect: “and an acknowledgment of the variety of community resources, such as arts, cultural, heritage and nature-based activities, that fall outside of these guidelines, which may enhance the recommended approaches. The patient experience should not be limited to their therapeutic experience but should include the wider context for that experience. Highly cited reports that draw together the extensive evidence on these factors include:For arts and culture-based interventions:All-Party Parliamentary Group on Arts, Health and Wellbeing, 2017. Creative Health: The Arts for Health and Wellbeing. Online: https://ncch.org.uk/uploads/Creative_Health_Inquiry_Report_2017_-_Second_Edition.pdf WHO Scoping Review, 2019: What is the evidence on the role of the arts in improving health and well-being?. Online: https://www.euro.who.int/en/publications/abstracts/what-is-the-evidence-on-the-role-of-the-arts-in-improving-health-and-well-being-a-scoping-review-2019For nature-based interventions:Bragg, R. and Atkins, G., 2016. A review of nature-based interventions for mental health care. Online: http://publications.naturalengland.org.uk/publication/4513819616346112?category=127020	Thank you for your comment. Art therapy was listed as an intervention of interest for the treatment reviews. However, no eligible evidence was identified for art therapy as a first-line treatment. The only included study for art therapy (Nan 2017) was in the further-line treatment review. The committee considered the evidence too limited to make a recommendation for art therapy. The Arts on prescription: All Party Parliamentary Group on Arts, Health and Wellbeing (2017) citation was not considered by the committee as it does not meet study design eligibility criteria. Nature-based interventions were not specified in any of the review protocols and thus specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, in response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not as a treatment for depression) and made a new recommendation to reflect this. The recommendation also emphasised the

							benefits of outdoors activities. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

132	SH	UK Council for Psychotherapy	Guideline	11	10	Rec 1.3.4 The phrase: - how they will be delivered (for example individual or group, face to-face or remotely) needs to include the option of couple therapy e.g. - how they will be delivered (for example individual, couple or group, face to-face or remotely)	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to include couple in the recommendation referred to in your comment as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with depression, unlike the other formats covered by this recommendation. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression. On this basis,

							the committee did not consider it appropriate to include family in the recommendation referred to in your comment. There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. There is also a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include procedures to support active involvement of families, partners, and carers.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

133	SH	Association for Family Therapy and Systemic Practice	Guideline	11	10	Rec 1.3.4 –AFT members have noted the absence of family/systemic interventions within the guidelines. We would suggest the following minor amendment here to reflect the availability of a range of options for people with depression: "how they will be delivered (for example individual, family/couple or group, face to-face or remotely)"	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to include couple in the recommendation referred to in your comment as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with depression, unlike the other formats covered by this recommendation. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression. On this basis,

							the committee did not consider it appropriate to include family in the recommendation referred to in your comment. There is a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include procedures to support active involvement of families, partners, and carers. There are also recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

134	SH	UK Council for Psychotherapy	Guideline	11	12	Rec 1.3.4 There should also be a clear choice to attend with a family member if preferred.	Thank you for your comment. An additional point has been added about attendance with a family member, if preferred.
135	SH	Association for Family Therapy and Systemic Practice	Guideline	11	16	Rec 1.3.4 – We would suggest the inclusion of a further bullet point that indicates the choice of a person with depression to attend with a family member: "an option to include family members or other significant people within the treatment, including the choice to include them as a one-off or as part of regular treatment".	Thank you for your comment. An additional point has been added about attendance with a family member, if preferred.
136	SH	Association for Family Therapy and Systemic Practice	Guideline	11	22	Rec 1.3.6 – We would suggest the inclusion of "….in severe depression, that access to them is monitored and preferences for including family and other important people in treatment are taken into account"	Thank you for your comment. There are a number of aspects of choice that could be monitored, but the committee agreed that the main priority was that access to the full range of NICE recommended treatments was available, and so chose to highlight this in their recommendation.

137	SH	NHS England and Improvement	Guideline	12	3	Worth adding something along the lines of consideration of past and current level of engagement? (you would expect the practitioner to assess this anyway, though poor engagement may be an opportunity for further personalisation/consideration of PHBs)Consideration of other options for people who do not / will not access formal treatment should be flagged here - particularly access to PCSP / PHBs as alternatives	Thank you for your comment. An additional point has been added to this recommendation that for all treatments, there should be a discussion with the person with depression about the best way to enable good engagement including positive and negative experiences of previous treatment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to

							the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).
138	SH	Diabetes UK	Guideline	12	003-017	1.4.1 – We think that the guidance here should clearly state that consideration of "any physical health problems" may include long term chronic conditions and, at a minimum, acknowledge and cross-reference to 'Depression in adults with a chronic physical health problem: recognition and management' [CG91].	Thank you for your comment. The link to the NICE guideline on depression in adults with a chronic physical health problem has been included in the previous recommendations on recognition and assessment, so has not been repeated again in this section
139	SH	Association for Family Therapy and Systemic Practice	Guideline	12	11	Rec 1.4.1 – Based on the strong links between social and contextual factors and depression, we would suggest the addition of an additional bullet point, with the suggested wording: "consideration of social and relational factors which impact on mood."	Thank you for your comment. Consideration of the social and relational factors which impact on mood has been included in the recommendations on initial assessment so they have not been repeated in the section on delivery as well.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

140	SH	Anxiety UK	Guideline	12	18	We feel this is very helpful and good to include.	Thank you for your comment and support for this recommendation.
141	SH	NHS England and Improvement	Guideline	12	19	The minimum two-week delay for the assessment of tolerability/adverse effects from antidepressant medication the wording should be reviewed. Although this statement refers to an assessment of "how well" treatment is working an earlier review of tolerability – and assurance should be offered – Although there is a recommendation to review within 7 days for people at risk of suicide – There should be an opportunity for an earlier review for all patients – so that - for all patients any premature decision to stop taking medication can be reviewed and concerns addressed.	Thank you for your comment. The committee agreed that for most people with depression prescribed antidepressants a review after 2 weeks would be appropriate as it would have allowed time for the antidepressant to begin to work, as well as allowing a review of concordance and side-effects, and would be possible to implement in practice. As you have noted, a 1-week review is advised for young people or those at risk of suicide but the committee agreed this would not be achievable for all people.
142	SH	The College of Mental Health Pharmacy	Guideline	12	19	"working" this reviewing should not just be reviewing whether the antidepressant is effective; it should also be looking at adherence (first) and tolerability.	Thank you for your comment. Treatment adherence (concordance) is covered in the next bullet point, and side-effects in the subsequent bullet point so these topics would also be covered in the review.

143	SH	The College of Mental Health Pharmacy	Guideline	12	019-020	The timeframe here is “2-4 weeks”. This should be 2 weeks if it is to be meaningful and help avoid worsening of depression and suicides. Studies show that patients commonly stop new medications within 10 days therefore waiting for 4 weeks to re-assess whether an antidepressant is helping or not is far too late. It is likely that they will have stopped it and therefore will have been untreated for several weeks. Please revise this advice to 2 weeks, and 1 week for younger people and those at high risk of self harm and/or suicide, as per the previous guideline.	Thank you for your comment. The committee agreed that for most people with depression prescribed antidepressants a review after 2 weeks would be appropriate as it would have allowed time for the antidepressant to begin to work, as well as allowing a review for side-effects, and for psychological therapies a review after 4 weeks would be more appropriate. The committee agreed that a review period of 2-4 weeks was also pragmatic and achievable in most cases. The guideline already recommends a review at 1 week for young people or those at risk of suicide, and this is included in and linked from these recommendations.
144	SH	Royal College of Psychiatrists	Guideline	12	26	Section 1.4.2 states “consider routine outcome monitoring (use appropriately validated sessional outcome measures)”. We strongly endorse the use of routine assessments of symptoms or functioning given the evidence for the impact of this on treatment outcome (e.g. see papers cited by Xiao et al. 2021 doi: 10.1038/s41398-021-01638-7). We therefore question the use of the word “consider” in section 1.4.2. This seems at odds with more definitive statements in sections 1.8.11, 1.11.2 and 1.15.8.	Thank you for your comment. The committee agreed that routine outcome monitoring was used more in psychological therapy practice including in IAPT, than in primary care or specialist mental health services. The committee agreed that the evidence on whether routine outcome monitoring improves outcomes was equivocal, but noted that it may be valued by people with depression. On this basis, the committee agreed to keep this recommendation as a 'consider'.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

145	SH	The College of Mental Health Pharmacy	Guideline	12	1.4.2	Frequency of review should be individualised? 2 and 4 weeks maybe not good for patients at risk should it reference 1.4.21	Thank you for your comment. The committee agreed that for most people with depression prescribed antidepressants a review after 2 weeks would be appropriate as it would have allowed time for the antidepressant to begin to work, as well as allowing a review for side-effects, and for psychological therapies a review after 4 weeks would be more appropriate. The committee agreed that a review period of 2-4 weeks was also pragmatic and achievable in most cases. The guideline already recommends a review at 1 week for young people or those at risk of suicide, and this is included in and linked from these recommendations.
146	SH	NHS England and Improvement	Guideline	13	1	Psychological and psychosocial interventions: please could the guidance specifically mention that this also applies to older adults (in light of poor referrals of older adults for psychological interventions). And that those delivering the therapies should have the competencies to deliver to older adults who have depression.	Thank you for your comment. The guideline applies to all adults and so the committee did not think it was necessary to state that these recommendations apply to older adults as well, or to highlight that therapists should be able to deliver to older adults. The committee agreed that the problem may lie with the referral to psychological therapies, not their delivery.

147	SH	NHS England and Improvement	Guideline	13	2	Consider community-based provision and social prescribing – Consider a personal health budget for unmet needs, which would be conducive to the person's psychosocial needs	Thank you for your comment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

148	SH	The Challenging Behaviour Foundation	Guideline	13	2	Rec 1.4.3 - Self-help material will not necessarily be appropriate for all individuals with learning disabilities, and the option for family/carer support while waiting for treatment should be facilitated.	Thank you for your comment. Adaptation of the delivery of psychological interventions for people with learning disabilities is now included in the section on the delivery of psychological interventions, as well as a cross-reference to the NICE guideline on mental health problems for people with learning disabilities, where this is covered in more detail.
149	SH	Association for Family Therapy and Systemic Practice	Guideline	13	5	Rec 1.4.3 – People with depression might be receiving support from family members or others in their network. We would suggest professionals consider including important people within the support network in discussions where people are being asked to wait for a treatment and that this recommendation could be added here. For example, “People with depression should routinely be offered an option to involve family members in these discussions if they would find it helpful.”	Thank you for your comment. The option to involve family members in discussions and treatment is already covered in the recommendations on choice of treatments so has not been repeated here.
150	SH	Society for Psychotherapy Research	Guideline	13	017-027	We are concerned about an inconsistency here. The new Safe Prescribing and Withdrawal Guideline recommends that a ‘Management Plan’ be devised when prescribing drugs associated with dependence (see P. 7, L19) – this should be included and referred to in this Guideline as part of 1.4.7 or 8 for consistency.	Thank you for your comment. This recommendation has now been updated to include the use of a management plan.
151	SH	UK Council for Psychotherapy	Guideline	13	017-027	Withdrawal from medicationThe new Safe Prescribing and Withdrawal Guideline recommends that a ‘Management Plan’ be created when prescribing drugs associated with dependence (P7, L19) – this should be included / referred to in this Guideline as part of 1.4.7 or 8 for consistency.	Thank you for your comment. This recommendation has now been updated to include the use of a management plan.

152	SH	NHS England and Improvement	Guideline	13	19	Although the option for involving a patient in making a decision about which particular antidepressant to take may be implicit – this should be made explicit – for example "If there are a number of different antidepressants equally suitable for an individual patient, then then they should be offered the opportunity to be involved in the decision about which one they would prefer to take"	Thank you for your comment. Discussion of the choice of medication has been added to this recommendation.
153	SH	The College of Mental Health Pharmacy	Guideline	13	023-025	Rephrase to: "Discuss the possible side effects and discontinuation / withdrawal effects….".	Thank you for your comment. The committee agreed to use the terminology withdrawal throughout the guideline so 'discontinuation' has not been added into this recommendation.
154	SH	Diabetes UK	Guideline	13	25	When weight gain is discussed as a potential side effect for people taking anti-depressant medications we feel it is important to include a clear recommendation that action to help mitigate this will be provided. This should include a reference to the current NICE guidance on 'Obesity Prevention' [CG43] and 'Weight Management: preventing, assessing and managing overweight and obesity', which are currently in development: https://www.nice.org.uk/guidance/indevelopment/gid-ng10182.	Thank you for your comment. Weight gain is an example of a side-effect of antidepressants but the committee agreed it would over-complicate the guideline to list the mitigating actions for all possible side-effects.
155	SH	The College of Mental Health Pharmacy	Guideline	13	General	"Starting an antidepressant" Please add that this should normally be an SSRI	Thank you for your comment. The committee agreed that these over-arching recommendations would apply to any antidepressant and so did not add that this would be an SSRI.

156	SH	The Challenging Behaviour Foundation	Guideline	14	3	Rec 1.4.8 - All prescriptions of psychotropic medication, and forthcoming NICE guideline on safe prescribing, must take into account the overmedication and inappropriate medication of individuals with learning disabilities and autistic people. Prescribing should be done only under safe, and well-monitored, conditions, with side effects monitored intensively for individuals who are unable to express verbally how they are reacting to this medication.	Thank you for your comment. The committee agree that people with learning disabilities and autism may require special consideration and, in the section of the guideline on the delivery of all treatments, have included links to the NICE guideline on mental health problems in people with learning disabilities and the NICE guideline on autism spectrum disorder to raise awareness of this.
157	SH	Anxiety UK	Guideline	14	3	We feel again that this is very helpful to include.	Thank you for your comment and support of this recommendation.
158	SH	Anxiety UK	Guideline	14	5	We would also like consideration to be given at the outset by the prescriber as to how easy it is for someone to withdraw from the antidepressant medication, so a conversation about previous experiences of taking such medication and withdrawal as well as checking whether the antidepressant which is to be prescribed is available in liquid format/low doses would be suggested. It is our experience that people can really struggle when the latter is not available.	Thank you for your comment. The last bullet point in this recommendation advises that withdrawal is discussed when starting antidepressants, as you suggest, and the link to recommendations on stopping antidepressants is included to support a more detailed discussion of the withdrawal process, including tapering and the use of liquid preparations.
159	SH	The College of Mental Health Pharmacy	Guideline	14	009-011	The timeframe here is “2-4 weeks”. This should be 2 weeks if it is to be meaningful and help avoid worsening of depression and suicides. Studies show that patients commonly stop new medications within 10 days therefore waiting for 4 weeks to re-assess whether an antidepressant is helping or not is far too late. It is likely that they will have stopped it and therefore will have been untreated for several weeks. Please revise this advice to 2 weeks, and 1 week for younger people and those	Thank you for your comment. This recommendation has been amended to state that the review should be after 2 weeks. This recommendation already includes the advice that review should be after 1 week for younger people and those at high risk.

						at high risk of self-harm and/or suicide, as per the previous guideline.	
160	SH	Diabetes UK	Guideline	14	011-014	We feel that the important point about those under 25 years old at concern for risk of suicide requiring a first review after one week may get missed due to the lengthy wording here and suggest adding a new bullet point for it.	Thank you for your comment. The details on early review for those under 25 years and at higher risk are repeated in this recommendation to ensure they are not missed but are also included in a separate section of the guideline called 'antidepressant medication for people at risk of suicide'.
161	SH	Care To Listen	Guideline	14	018-023	We welcome the emphasis on regular monitoring and review of anti-depressants as too often it feels as though clients have been prescribed antidepressants on a repeat basis and the efficacy is questionable. Likewise we recognise that a combination of medication (once they have taken effect) can offer a client space to engage with counselling in a way that feels safer and less overwhelming. We would ask that particular importance is attached to the timings around this.	Thank you for your comment and support for these recommendations. The committee agreed that regular review and appropriate combinations of treatment was important, and both these points are reflected in their recommendations.
162	SH	The College of Mental Health Pharmacy	Guideline	14	24	"Some side effects may persist throughout treatment" – please add some advice. E.g., balance of tolerability vs benefits and how and when to stop a treatment.	Thank you for your comment. The previous recommendation in this section already advises a discussion on the benefits and harms of antidepressant medication. Other bullet points in this recommendation already advise on the duration of therapy and withdrawal.

163	SH	The College of Mental Health Pharmacy	Guideline	14	General	Please emphasise that antidepressants are not addictive in the sense that individuals will not crave them or require escalating doses to deliver the same benefits.	Thank you for your comment. The committee chose to focus on the withdrawal effects of antidepressants and agreed it was not necessary to declare a negative fact relating to antidepressants and addiction.
164	SH	The Challenging Behaviour Foundation	Guideline	15	2	Recs 1.4.10–1.4.13 - All relevant family members/family carers/support staff etc should be informed of these details, and should be involved in collaboration with clinicians to decide how these courses of action can be navigated safely.	Thank you for your comment. The committee agree that, if people with depression wish their family or carers to be involved, or for people with depression who rely on family or carers for support or help with communication, these details should be shared. However, this applies to large sections of the guideline and so has not been specifically mentioned in this section.

165	SH	Critical Psychiatry Network	Guideline	15	007-019	This is a good list of symptoms (1.4.11), however some symptoms should be added because they are either common, often confusing to patients and doctors or have severe consequences. Feelings of depersonalisation and derealisation are common and can help diagnose the condition. They are common, even more so in clinical practice than in the Rosenbaum et al. 1998 RCT. (Framer, 2021; Hengartner et al., 2020; Lerner and Klein, 2019) Muscle aches, tremor, myoclonus, spasm are relatively uncommon in SSRI/SNRI withdrawal but often lead to mis-diagnosis of a neurological condition like MS, or more commonly, functional neurological disorder and to prevent this mis-diagnosis it would be useful to include them (Cosci and Chouinard, 2020; Rosenbaum et al. 1998)Suicide attempts are increased in the 2 weeks after stopping antidepressants above and beyond that in unmedicated depressed people, suggesting a causal link to the process of withdrawal and not to exposure of the underlying untreated disorder. (Valuck et al 2009)Akathisia is a rare but potentially fatal complication of SSRI/SNRI withdrawal (Haddad, 2001; Kotzalidis et al., 2007; Read, 2019) It is exceedingly difficult to manage when it occurs, especially when left untreated or mis-diagnosed and is best dealt with by early re-instatement of medication. However, this requires early detection; NICE guidance would be prudent to include this to prevent mis-diagnosis. As in a case outlined in Hengartner et al., 2020 people take their lives as a result of SSRI/SNRI withdrawal-induced akathisia. Cosci F, Chouinard G. Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications. Psychother	Thank you for your comment. The list of symptoms is based on the evidence review for the withdrawal of antidepressants conducted as part of the development of the NICE guideline on Safe prescribing and it is not intended to be an exhaustive list. However, this review included 10 randomised trials, and did not identify evidence for feeling unreal or detached more on withdrawal than on continuation, and hence these were not included in the list. Muscle and joint aches are included in the list already, as are suicidal thoughts, restlessness and agitation (aka akathisia).

						Psychosom. 2020;89(5):283–306.Haddad, P. M. (2001). Antidepressant Discontinuation Syndromes. Drug Safety, 24(3), 183–197.Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573.Kotzalidis, G. D., Patrizi, B., Caltagirone, S. S., Koukopoulos, A., Savoja, V., Ruberto, G., Tatarelli, C., Pacchiarotti, I., Lazanio, S., Sani, G., Manfredi, G., Pisa, E. de, Tatarelli, R., & Girardi, P. (2007). The adult SSRI/SNRI withdrawal syndrome: A clinically heterogeneous entity. Clinical Neuropsychiatry, 4(2), 61–75. https://moh-it.pure.elsevier.com/en/publications/the-adult-ssrisnri-withdrawal-syndrome-a-clinically-heterogeneousRead, J. (2019). How common and severe are six withdrawal effects from, and addiction to, antidepressants? The experiences of a large international sample of patients. Addictive Behaviors, 106157. https://doi.org/10.1016/j.addbeh.2019.106157Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. Biol Psychiatry. 1998;44(2):77–87.Valuck RJ, Orton HD, Libby AM. Antidepressant Discontinuation and Risk of Suicide Attempt. J Clin Psychiatry. 2009;70(8):1069–77.	
166	SH	The College of Mental Health Pharmacy	Guideline	15	20	"…withdrawal symptoms can be mild, appear within a few days" please add "MAY appear within a few days"	Thank you for your comment. The word 'may' has been added as you suggest.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

167	SH	Society for Psychotherapy Research	Guideline	15	020-024	We notice that this definition is now out of date and recommend for it to be emended in order to be consistent with the used in the new draft guideline on Safe Prescribing and Withdrawal (see p. 14, Section 1.5.9, L.18f)	Thank you for your comment. This recommendation has now been updated to ensure consistency with the safe prescribing guideline.
168	SH	UK Council for Psychotherapy	Guideline	15	020-024	1.4.12: This is an out-of-date definition. Again for consistency it should be based on the one to be used in the new draft guideline on Safe Prescribing and Withdrawal (P14, Section 1.5.9, L18 onwards) e.g.Explain that withdrawal can be difficult and may take several months or more. Withdrawal symptoms do not affect everyone, and it is not possible to predict who will be affected. They vary widely in both type and severity, can be physical or psychological, vary in intensity, change over time and can last for months or longer.	Thank you for your comment. This recommendation has now been updated to ensure consistency with the safe prescribing guideline.

169	SH	Critical Psychiatry Network	Guideline	15	020-024	We are concerned that this guidance (1.4.12) is misleading to clinicians as well as patients. Evidence of withdrawal symptoms resolving in 1-2 weeks comes from a review of five drug company studies published as Baldwin et al (2007). Some of these studies show that withdrawal symptoms reduced from weeks 1 to week 2. However, the patients in these studies were taking antidepressants for between 6 and 24 weeks, with an average of 12 weeks. The length of time that a patient is on an antidepressant in England is growing such that half are on the drugs for more than 2 years and 20% are on the drugs for more than 3 years. (Johnson et al. 2012) The NICE guidelines as they currently stand recommend months of treatments at least and so studies of people stopping the drugs after 12 weeks are unlikely to be relevant to the wider population. There is evidence that the longer a patient is on antidepressants the more long-lasting (and severe) the symptoms are likely to be. We include some data analysis and relevant graphs from a paper currently under review at CNS Drugs to demonstrate the evidence for a duration of use-dependent gradient for severity and duration of symptoms which helps to explain why the current guidance is misleading (Horowitz, et al., 2022, in review):We examined the relationship between duration of use and incidence of withdrawal symptoms for the double-blind placebo-controlled trials of SSRIs included in the recent systematic review,(Davies and Read 2019) as well as the drug manufacturers' studies selected for a recent opinion piece(Jauhar et al. 2019) by comparing, at the trial level, average duration of use before stopping antidepressants with incidence of withdrawal	Thank you for your comment and for sharing your data on the correlation between duration of antidepressant use and incidence of withdrawal symptoms. The wording of this recommendation has been amended to bring it in line with the recommendations in the NICE guideline on safe prescribing, and the advice on how long withdrawal effects can last has been strengthened, but the duration of treatment is already listed as a consideration in the following recommendation. The details of how to discuss, monitor and manage symptoms that may emerge on dosage reduction are included in the subsequent recommendations and so more detail has not been added about asking people to report symptoms.

						syndrome for different antidepressants (individual patient data were not available). We conducted a meta-analysis with meta-regression with an inverse-variance random-effects model (DerSimonian-Laird method) with the metafor package for R.(Viechtbauer 2010) We conducted two analyses for the groups of studies where there was enough data to do so – SSRIs (excluding fluoxetine) and paroxetine alone. Meta-regression for the RCTs for the SSRIs citalopram (1 study), escitalopram (6 studies), fluvoxamine (1 study), paroxetine (6 studies) and sertraline (2 studies) showed that average treatment duration per study (range 2-15 months) was a significant effect moderator (p=0.022). Across these drugs and within this range of treatment duration each additional month of treatment was associated with a 2.0 percentage point increase in withdrawal incidence (95%-CI: 0.3 percentage point to 3.8 percentage point) (Figure 3a). Average treatment duration explained 26.1% of between-study variation (heterogeneity) in withdrawal incidence. Fluoxetine trials were not included because short observation periods of about 1 week after treatment cessation/interruption are too brief to reliably detect withdrawal events due to the drug's long elimination half-life. Moreover, heterogeneity was substantial (I2=91.8%), suggesting that the meta-analytic results must be interpreted with caution; there are many potential other factors that influence incidence of withdrawal including method of drug withdrawal, drug dose, other medications used, amongst others. The only individual drug that we were able to study separately, owing to a sufficiently large number of studies (n=6) and adequate variability in average treatment	

						duration (3-15 months), was paroxetine. The meta-analysis with meta-regression for paroxetine likewise showed that average treatment duration was a statistically significant moderator (p=0.001) (Figure 3b). Within the range of treatment duration studied (i.e. 3-15 months), each additional month of treatment was associated with a 3.4 percentage point increase in withdrawal incidence (95%-CI: 1.4 percentage points to 5.4 percentage points). Average treatment duration explained 73.3% of between-study variation in withdrawal incidence. The heterogeneity in the subgroup of paroxetine trials was lower but still substantial (I2=65.3%). The relationship between duration of use and incidence of withdrawal symptoms in these studies of SSRIs (excluding fluoxetine), and paroxetine alone is shown in Figure 3. The five studies hand-picked for the opinion piece examined a group of patients who had received antidepressants for 8 to 24 weeks with the average duration of use being 12 weeks.(Jauhar et al. 2019) This study subtracted an estimated nocebo response of 12% (larger than found in the majority of studies) to determine a rate of incidence of paroxetine withdrawal syndrome of 23%. It is probable the smaller incidence of withdrawal effects in these studies compared to others is due to the shorter duration of use in this group, as the line of best fit passes through these five data points (Figures 3a and 3b). Although survey data included in the recent systematic review (Davies and Read 2019) is excluded from this analysis as uncontrolled data, it is noteworthy that this data is largely consistent with the controlled data presented.	

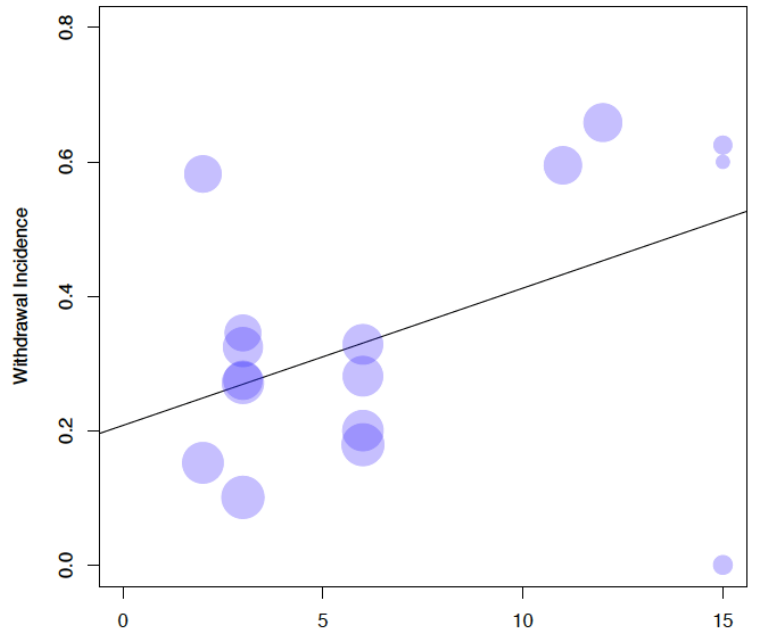
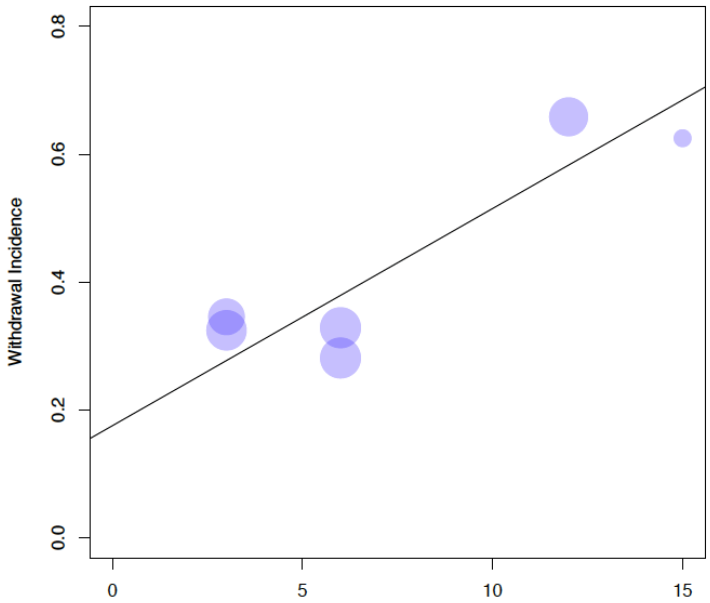

Withdrawal Incidence
0.0
0.2
0.4
0.6
0.8
0
5
10
15
Treatment duration (months)

Figure 3a

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022



Treatment duration (months)

Figure 3b

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

170	SH	Critical Psychiatry Network	Guideline	15	020-024	Chart, scatter chart, bubble chart Description automatically generatedTreatment duration (months)Figure 3a Chart, scatter chart, bubble chart Description automatically generatedTreatment duration (months)Figure 3b Figure 3. Bubble plot of relationship between duration of use of antidepressant and incidence of withdrawal syndrome for a) SSRIs (excluding fluoxetine) and b) paroxetine, with treatment duration in months. Weighted lines of best fit are shown in the graphs. Areas of bubbles are proportional to the sample size of the studies. Data sources are double-blind RCTs derived from Davies and Read (2019) and Jauhar et al. (2019). In (a) withdrawal incidence increases by 2.0 percentage points per month treated and in (b) by 3.4 percentage points per month treated.Although no RCTs examined the severity of withdrawal symptoms in association with treatment duration (rather, they only counted the number of symptoms), online surveys of patients did so.(Read, Cartwright, and Gibson 2014, 2018) Although these surveys may have captured skewed samples, the line of best fit suggests a clear gradient between duration of use and severity of withdrawal syndrome (Figure 4a and Table 2a).(Read, Cartwright, and Gibson 2018) This suggests that for patients who are on antidepressants for more than three years, more than half will experience severe withdrawal symptoms, although this should be interpreted cautiously due to the design of the study. However, this provides support for	This is a continuation of the comment as above so no separate response required.

						the relationship between duration of antidepressant use (leading to greater physiological adaptations) and severity of withdrawal symptoms.(Read, Cartwright, and Gibson 2018) Chart, scatter chart Description automatically generatedFigure 4a Shape Description automatically generated with medium confidenceFigure 4bFigure 4. Relationship between duration of treatment and severity and duration of withdrawal symptoms from surveys of antidepressant users and observational studies. a) Relationship between duration of treatment of antidepressants and incidence of moderate or severe withdrawal symptoms. Graph is derived from data in Read et al. (2018)(Read, Cartwright, and Gibson 2018). b) Relationship between duration of use of antidepressants and duration of withdrawal symptoms in studies captured in the systematic review.(Davies and Read 2019) There were five studies for which duration of antidepressant use and duration of withdrawal symptoms were available (Figure 4b and Table 2b).(Bogetto et al. 2002; Stockmann et al. 2018; Zajecka et al. 1998; Davies, Regina, and Montagu 2018; Narayan and Haddad 2010) Although a relationship appears to exist between duration of use and duration of withdrawal symptoms, the data was heterogenous. Both studies with a longer duration of use involved samples of patients who self-	

						identified as having trouble with withdrawal, likely to represent a more severe group than average.(Stockmann et al. 2018; Davies, Regina, and Montagu 2018) Additionally, the length of time recorded for withdrawal effects included the period over which the drugs were tapered, perhaps artificially inflating the duration of withdrawal symptoms. However, it does appear that a portion of patients will experience withdrawal symptoms for several months or longer than a year, perhaps related to length of treatment. There are several records of studies which find that antidepressant withdrawal symptoms can last for years – references to these papers can be found in the Davies and Read (2019) review and a paper looking at a case series of protracted withdrawal in Hengartner (2020), where symptoms last for years. It is particularly important for NICE advice to be explicit about the possibility of years of symptoms because people who experience protracted withdrawal are often told that this is physiologically impossible and that it must be a return of their underlying mental health condition or onset of a new disorder. This misdiagnosis leads to all manner of inappropriate advice, mis-diagnosis, mis-management and huge emotional costs to the patient as detailed in Guy et al. (2020). In this current NICE draft advice, it is also not accurate to say that severe symptoms will only occur if antidepressants are 'stopped suddenly'. Severe symptoms occur if the drugs are stopped too quickly for an individual – which can mean anything from weeks to months if the taper is not slow enough for the person. It would be accurate for NICE advice to say - severe symptoms can occur if the antidepressant	

						medication is stopped suddenly or too quickly for the individual patient (who might need months or years to stop the medication in a tolerable fashion)..Lastly, drugs with long half-lives such as fluoxetine can have onset of symptoms weeks or months after reducing or stopping the drug; withdrawal from which can be particularly prone to mis-diagnosis as relapse. This should be specified in NICE advice. Additionally, it has been observed that even drugs with short half-lives can have withdrawal effects with onset several weeks after stopping the drug (including the presence of physical symptoms which distinguishes them for relapse). (Chouinard & Chouinard, 2015; Framer, 2021)Therefore, the NICE advice that “withdrawal symptoms can be mild, appear in a few days of reducing or stopping antidepressants medication, and go away within 1 to 2 weeks” is not substantiated by current research. It may be made accurate by prefacing it with the qualifier - for patients who have only used antidepressants for several weeks, withdrawal symptoms can be mild, appear in a few days of reducing or stopping antidepressants medication, and go away within 1 to 2 weeks. However, given that this relates to a very small number of patients it would be more accurate for NICE advice to say:For patients using antidepressant for only a few weeks, withdrawal symptoms can be mild, appear within a few days of reducing or stopping medication, and go away within 1 to 2 weeks. However for patients who have been on these medications for months or years, many people will experience withdrawal symptoms that can be severe and last months or years. They appear to be less likely to be severe and long-	

						lasting if medications are tapered to individual tolerance, which can take months or years.. Withdrawal symptoms from antidepressants, especially those with long half-lives, can be delayed by weeks or sometimes months.Further, in reassuring patients that withdrawal symptoms can be mild and of short duration (1.4.12), clinicians may elide the essential instruction that patients report withdrawal symptoms immediately for clinical assessment so they may be addressed appropriately (Steinman, 2013), with dosage adjustment, if necessary. (Framer, 2021; Zwiebel & Viguera, 2022) NICE advice should include:- It is essential that patients understand that because withdrawal symptoms may advance if they are not addressed appropriately, they should promptly report emergence of any unusual symptoms after a dosage reduction.Baldwin DS, Montgomery SA, Nil R, Lader M. Discontinuation symptoms in depression and anxiety disorders. Int J Neuropsychopharmacol. 2007;10(1):73–84.Chouinard, G., & Chouinard, V.-A. (2015). New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. Psychotherapy and Psychosomatics, 84(2), 63–71. https://doi.org/10.1159/000371865 Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? Addict Behav. 2019;97(August):111–21.Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274Guy A, Brown M, Lewis S. The “patient voice”: patients who experience	

						antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. Therapeutic Advances in [Internet]. 2020; Available from: https://journals.sagepub.com/doi/abs/10.1177/2045125320967183Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573.Horowitz, M. A., Framer, A., Hengartner, M. P., Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs (in review).Jauhar, S., & Hayes, J. (2019). The war on antidepressants: What we can, and can't conclude, from the systematic review of antidepressant withdrawal effects by Davies and Read. Addictive Behaviors, 97, 122–125. https://doi.org/10.1016/j.addbeh.2019.01.025Johnson CF, Macdonald HJ, Atkinson P, Buchanan AI, Downes N, Dougall N. Reviewing long-term antidepressants can reduce drug burden: a prospective observational cohort study. Br J Gen Pract. 2012 Nov 1;62(604):e773–9.Public Health England. Dependence and withdrawal associated with some prescribed medicines. An evidence review [Internet]. 2019. Available from: https://www.gov.uk/government/publications/prescribed-medicines-review-reportSteinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394.	

						https://doi.org/10.1001/jamainternmed.2013.2965Zwiebel, S. J., & Viguera, A. C. (2022). Discontinuing antidepressants: Pearls and pitfalls. Cleveland Clinic Journal of Medicine, 89(1), 18–26. https://doi.org/10.3949/ccjm.89a.21020	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

171	SH	The College of Mental Health Pharmacy	Guideline	15	22	Please start the following sentence with “Rarely”; “However, they can last longer…..”	Thank you for your comment. The wording of this recommendation has been amended to bring it in line with the recommendations in the NICE guideline on safe prescribing which increases the emphasis on the fact that symptoms can last longer. The word 'rarely' has not been added as this was not included in the Safe prescribing guidleine.
172	SH	Critical Psychiatry Network	Guideline	15	30	This is useful advice (1.4.13). Specific online or written resources should be referred to or doctors will not know where to look – for example, the Royal College of Psychiatrists guide to Stopping Antidepressants. Royal College of Psychiatrists. (2020). Stopping antidepressants. Royal Colllege of Psychiatrists. https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants	Thank you for your comment. NICE guidelines do not usually cross-refer to external sources of information so this link has not been added.
173	SH	The College of Mental Health Pharmacy	Guideline	15	General	This whole section on “Stopping antidepressant medication” feels very imbalanced. There are three pages of text emphasising how to stop these when there is not yet any detailed advice given about how to start them, or what benefits that may confer. The overall impression given is that these have no purpose, and should be stopped.Please readdress this balance and set out that these can be beneficial and how to optimise this. For example the text doesn’t address adherence; the need to take them regularly in order to actually gain clinical benefit from them. Please re-order the text so that the advice on what to start, and how to prescribe well, is read before the extensive advice on stopping. Advise clinicians on which antidepressants to use first. Please advice that these should be used as monotherapy first – this has	Thank you for your comment. The section of the guideline directly before the section on stopping antidepressants is entitled 'starting antidepressant medication' and provides one and a half pages of text on starting antidepressants, including advice on the benefits (and harms), and the importance of taking the medication for a sufficient length of time to see the benefits. The committee discussed whether to make more detailed recommendations about the choice of antidepressants but agreed that there was a lack of head-to-head comparisons, that choice should be individualised , and that

						been omitted. Please advise prescribers to remember to check that other antidepressants aren't already prescribed for other indications such that this would lead to polypharmacy. e.g., patients already on antidepressants at doses for neuropathic pain, or Stress Urinary Incontinence (SUI).	naming specific drugs might affect the longevity of the guideline as the choice of available antidepressants may change. A healthcare professional prescribing medication has a duty of care to ascertain if the person is already taking any other medication which may interact, and as this applies to any clinical situation it has not been mentioned specifically in the guideline.
174	SH	The College of Mental Health Pharmacy	Guideline	15	General	Please balance this message to say that these mild withdrawal symptoms are separate from a relapse in depression.	Thank you for your comment. This recommendation includes advice relating to the concerns people might have about stopping antidepressants, and a valid concern is that their depression will return so the wording of this recommendation has not been changed.
175	SH	The College of Mental Health Pharmacy	Guideline	15	General	This would not happen with fluoxetine due to the long half life. Please add context to keep this section balanced as currently it reads as though this is true for every antidepressant. Please outline which antidepressants are more likely to induce withdrawal effects due to their short half lives, vs others such as fluoxetine.	Thank you for your comment. Details about the likelihood of withdrawal effects with different antidepressants depending on their pharmacokinetic parameters is already included in a subsequent recommendation so this detail has not been repeated here.

176	SH	Critical Psychiatry Network	Guideline	16	005 - 007	We are concerned that, as written, this advice (1.4.14) does not provide a complete view of the factors that may contribute to risk of antidepressant withdrawal symptoms for an individual. Drug half-life may not be the most prominent factor. (Kotzalidis et al., 2007) The following characteristics are likely to affect risk of withdrawal for an individual patient (Horowitz et al., 2022 (in review); Zwiebel & Viguera, 2022):past experience of withdrawal after switching drugs, stopping or reducingtype of antidepressant they are on (which may include half-life)duration of usedosageThese should all be considered by a clinician when deciding on a tapering approach. The NICE draft guideline for safe withdrawal of medications including antidepressants ((NICE, 2021, pp.13-14; lines 16-30, 1-9) outlines the following, which should also be included in this guideline:“Factors that might increase the person’s risk of problems during withdrawal, including:long duration of medicine usehigh dose of medicinehistory of withdrawal symptomstaking an antidepressant with- a short half-life or- anticholinergic properties”Regarding the drug half-life factor, this draft advice does not specify what “short half-life” means. In fact, all antidepressants but one, fluoxetine, have half-lives short enough to be high-risk for withdrawal symptoms if even one dose is missed or reduced. (Keks, et al., 2016; Sorensen et al., 2021) Among the other risk factors, we urge a clearer explanation of half-life, such astake into account the pharmacokinetic profile, including the half-life of the medication; most antidepressants, having a half-life shorter than that of fluoxetine, will need to be tapered more slowly.Horowitz, M. A., Framer, A., Hengartner, M. P.,	Thank you for your comment. The committee agree that the other factors you have listed are also important when considering the risk of antidepressant withdrawal and all are already included in other recommendations in this section: past experience of withdrawal is mentioned in the previous recommendation; duration of use and dose are mentioned in this recommendation. More detail about specific drugs, such as the difference between fluoxetine and other antidepressants is also described in a later recommendation.

						Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs (in review).Keks, N., Hope, J., & Keogh, S. (2016). Switching and stopping antidepressants. Australian Prescriber, 39(3), 76–83. https://doi.org/10.18773/austprescr.2016.039Kotzalidis, G. D., Patrizi, B., Caltagirone, S. S., Koukopoulos, A., Savoja, V., Ruberto, G., Tatarelli, C., Pacchiarotti, I., Lazanio, S., Sani, G., Manfredi, G., Pisa, E. de, Tatarelli, R., & Girardi, P. (2007). The adult SSRI/SNRI withdrawal syndrome: A clinically heterogeneous entity. Clinical Neuropsychiatry, 4(2), 61–75. https://moh-it.pure.elsevier.com/en/publications/the-adult-ssrisnri-withdrawal-syndrome-a-clinically-heterogeneousNICE. (2021). Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90Sorensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-wZwiebel, S. J., & Viguera, A. C. (2022). Discontinuing antidepressants: Pearls and pitfalls. Cleveland Clinic Journal of Medicine, 89(1), 18–26. https://doi.org/10.3949/ccjm.89a.21020	

177	SH	Critical Psychiatry Network	Guideline	16	008-010	As written, this advice (1.4.14) "slowly reduce the dose to a proportion of the previous dose (for example, prescribe 75% or 50% of the previous dose), rather than by a fixed dose reduction" is not clear and it is unlikely that doctors will be able to follow these directions. This instruction does not indicate a series of steps to follow but implies perhaps only a single step.Clinicians may interpret the suggestion of reduction to 50% or 75% of the original dosage as advice to fall back on the common practice of reducing dosage by half or more for an unspecified period and then stopping the medication. This status quo has been found to generate unnecessary cases of withdrawal syndrome, where patients developed severe, intractable withdrawal from such abrupt reduction schedules (Davies & Read, 2019; Framer, 2021; Guy et al., 2020; Hengartner et al., 2020).As this may be the most critical element of this section of the guidance, advice should be explicit about these steps so that clinicians are able to understand and implement the guidance. In the NICE draft guidance on safe withdrawal of medications including antidepressants, the following language was used, including useful words such as 'slow', 'step-wise' and the explanation "rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered." (NICE, 2021, p.15, lines 7-10). This level of detail at least should be included for this guideline as well. From our clinical practice and some preliminary data analysis, many patients on long-term antidepressants are unlikely to be able to reduce their dosage at a rate of 25-50%-75% per month (although the interval of reduction is not specified in the current guidance).	Thank you for your comment. This recommendation has been amended to clarify that the tapering process involves a number of reduction steps, and wording from the NICE guideline on Safe prescribing has been adopted to ensure consistency between the 2 guidelines. The reduction rate suggested in the guideline has been clarified to state that 50% may be appropriate, but that smaller decrements such as 25% may be needed. The recommendations already include advice on only reducing the dose at a rate tolerated by the patient and monitoring regularly. The committee agreed not to stratify the recommendations based on those likely to tolerate quicker or slower withdrawal as they agreed that the tapering process should be individualised for each patient and noted that this stratification had not been included in the Safe prescribing guideline either.

						Many patients will only be able to reduce their dose at 10% of the most recent dose per month, approximating a hyperbolic taper (Framer, 2021; Horowitz and Taylor, 2019; Zwiebel & Viguera, 2022). In order to stop these medications in a tolerable manner (Neimark, 2009), this process, which should include a new practice of close, frequent monitoring in case dosage adjustment is necessary (Jha et al., 2018; Jha, 2019; Steinman et al., 2011; Steinman, 2013), will take more than a year and for some patients several years.It would be clearer to advise as follows:- Rather than reducing dose in a linear manner (e.g. 5mg every 2 to 4 weeks) dose should be reduced in a proportionate manner (that is by a proportion of the most recent dose so that the size of the reduction gets smaller and smaller with each reduction). For example, the dose might be reduced by 25% or 50% of the most recent dose every 2 to 4 weeks (so that reductions become smaller and smaller as the total dose gets lower) if close, frequent monitoring shows this is well tolerated by the patient. Some patients can only tolerate reductions of 10% of their most recent dose a month, or even less."It may also be worth including some manner to stratify the patient population into quicker or slower reductions as for example (or any version of this the committee deems suitable):"Patients who have had little difficulty stopping antidepressants in the past, on short term medication (<6 weeks), and on antidepressants less likely to cause withdrawal such as fluoxetine may be able to reduce at 50% of their most recent dose a monthPatients who have had difficulty stopping antidepressants in the past (or been unable to), on long term medication (>2 years) and on	

						antidepressants most likely to cause withdrawal problems such as paroxetine, duloxetine, mirtazapine and venlafaxine may only be able to reduce their dose at 10% or less per monthPatient with intermediate risk factors may be able to reduce at about 20% of their most recent dose per month"The absence of any advice on how to start reductions may make it difficult for clinicians to know how to commence the process. Unfortunately, as written, this guidance is incomplete and vague, and may have the unintended effect of reinforcing a high-risk status quo rather than moving forward in drug discontinuation advice and improving patient outcomes.Davies, J., & Read, J. (2019). A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? Addictive Behaviors, S0306460318308347. https://doi.org/10.1016/j.addbeh.2018.08.027Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274Guy, A. et al. (2020) 'The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition', Therapeutic Advances in Psychopharmacology. SAGE Publications Ltd STM, 10, p. 204512532096718. doi: 10.1177/2045125320967183.Hengartner, M. P., Schulthess, L., Sorensen, A., & Framer, A. (2020). Protracted withdrawal syndrome after stopping antidepressants: A descriptive quantitative analysis of consumer narratives from a large	

						internet forum. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125320980573Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry, 6(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-XHorowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047Leeuwen, E. van, van Driel, M., De Sutter, A., Robertson, L., Kendrick, T., Horowitz, M., Donald, M., & Christiaens, T. (2021). Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults (Review). Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD013495.pub2Neimark, G. (2009). Help “sensitive” patients tolerate medication. Current Psychiatry, 8(11), 78. https://www.mdedge.com/psychiatry/article/65209/help-sensitive-patients-tolerate-medicationNICE. (2021). Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National	

						Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90Schuck, R. N., Pacanowski, M., Kim, S., Madabushi, R., & Zineh, I. (2019). Use of Titration as a Therapeutic Individualization Strategy: An Analysis of Food and Drug Administration–Approved Drugs. Clinical and Translational Science, 12(3), 236–239. https://doi.org/10.1111/cts.12626Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965Zwiebel, S. J., & Viguera, A. C. (2022). Discontinuing antidepressants: Pearls and pitfalls. Cleveland Clinic Journal of Medicine, 89(1), 18–26. https://doi.org/10.3949/ccjm.89a.21020	

178	SH	The College of Mental Health Pharmacy	Guideline	16	011-012	This reads as though it is advice for every antidepressant every time it is stopped in a planned manner. This is not always necessary, plus not every antidepressant is available as a liquid. Please add balance and context to this advice.	Thank you for your comment. This recommendation has been amended to clarify that liquid preparations should only be used when other methods (such as splitting or dispersing solid oral preparations) are not possible.

179	SH	Critical Psychiatry Network	Guideline	16	011-012	This is helpful advice, “use liquid preparations if necessary to allow slow tapering, once small doses have been reached” (1.4.14), but it does not capture all the circumstances for which liquids may be necessary. This recommendation for the use of liquid preparations in the last phase of tapering should be expanded to advise use of liquid preparations throughout the taper. For example, if the dose of citalopram is to be reduced by 25% from 15mg it may be necessary to use a liquid preparation of the drug because it would be impossible to make up 11.25mg of citalopram using currently available tablet formulations (or splitting with tablet-cutters). If tablet-splitting does not suffice to provide a smoother taper for those patients sensitive to dosage reduction, clinicians can use liquid preparations, possibly in conjunction with a range of tablet sizes or tablet fractions, to make up more precise, progressively smaller intermediary doses. (Framer, 2021; Horowitz and Taylor, 2019; Schuck et al., 2019; Zwiebel & Viguera, 2022)We suggest this wording “use liquid preparations if necessary to allow slow tapering, once small doses have been reached” be changed to - use liquid preparations, in conjunction with lower tablet sizes, to allow more precise, gradual tapering for those patients sensitive to dosage reductions.- liquid preparations will be especially useful for titration once small doses have been reached.There is also the issue that some commonly used antidepressant formulations such as duloxetine, venlafaxine and sertraline are not amenable to titration by tablet-splitting. Sertraline and venlafaxine liquids are available as ‘Specials’. (MHRA, 2014) NICE guidanace should give explicit direction for	Thank you for your comment. The committee agreed that slow tapering was necessary and that in some cases it was necessary to use liquid preparations but were also aware that these were expensive and not available for all antidepressants. This recommendation has therefore been amended to clarify that liquid preparations should only be used when other methods (such as splitting or dispersing solid oral preparations) are not possible. The committee agreed it was not necessary to provide details for individual antidepressants in the guideline as tapering rates would vary and the process may need to be individualised with advice from a pharmacist.

						doctors to prescribe liquid versions of venlafaxine and sertraline as 'Specials'. For duloxetine, there are no liquid preparations available. Patients often open up capsules to count beads as outlined in Framer (2021). The drug label advises against sprinkling contents onto food or mixing with liquids because these actions might affect its enteric coating; however, a formal analysis conducted by the manufacturer, Eli Lilly, concluded that duloxetine beads were stable and their absorption profile was not altered by opening the capsule and mixing the beads with apple juice or apple sauce.(Wells and Losin, 2008)If the committee deems that this advice cannot be given, patients should be told when commencing duloxetine that there is no sanctioned method to stop the medication and they will either have to stop abruptly, risking severe and prolonged withdrawal reactions, or they will have to remain on the drug for their entire lives. Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry, 6(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-X MHRA. (2014). MHRA Guidance Note 14 The supply of unlicensed medicinal products ("specials"). Medicines and Healthcare Products Regulatory Agency. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdfSchuck, R. N.,	

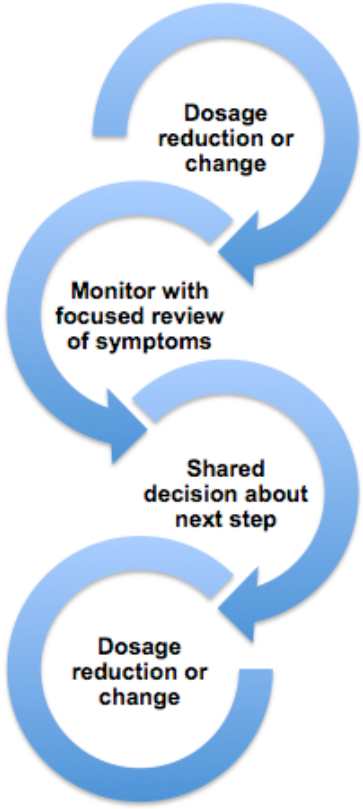
						Pacanowski, M., Kim, S., Madabushi, R., & Zineh, I. (2019). Use of Titration as a Therapeutic Individualization Strategy: An Analysis of Food and Drug Administration–Approved Drugs. Clinical and Translational Science, 12(3), 236–239. https://doi.org/10.1111/cts.12626Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300–8.Zwiebel, S. J., & Viguera, A. C. (2022). Discontinuing antidepressants: Pearls and pitfalls. Cleveland Clinic Journal of Medicine, 89(1), 18–26. https://doi.org/10.3949/ccjm.89a.21020	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

180	SH	Critical Psychiatry Network	Guideline	16	013-016	The guidance (1.4.14) appropriately advises clinicians to "ensure the speed and duration of withdrawal is led by and agreed with the person taking the prescribed medication, ensuring that any withdrawal symptoms have resolved before making the next dose reduction." This is helpful but may be impossible. Withdrawal symptoms, even after small reductions, can persist for weeks or sometimes months; waiting until symptoms have resolved completely may mean the process to come off takes decades. Practically, clinicians may advise patients to make reductions when their withdrawal symptoms have returned to a tolerable level (perhaps 1 to 2 in an intensity scale of 10). (Horowitz and Taylor, 2022) It would be better to phrase this as:- ensure the speed and duration of withdrawal is led by and agreed with the person taking the prescribed medication, ensuring that any withdrawal symptoms have reduced to tolerable levels or resolved before making the next dose reduction.Ascertaining the result of a dosage reduction requires a period of observation after the event. Horowitz & Taylor, 2019 suggests intervals of a month between reductions to account for delayed withdrawal symptoms and washout of the dosage change. This has been confirmed by observation from patients themselves (Framer, 2021). However, withdrawal symptoms may emerge any time within the month. It is the clinician's responsibilty to frequently and closely monitor patients who are reducing their antidepressant drug dosage, as well as urge patients to report withdrawal reactions promptly, in order to quickly redress should withdrawal symptoms emerge. (Jha et al., 2018; Jha, 2019; Steinman, et al., 2011; Steinman, 2013)	Thank you for your comment. This recommendation has been amended to include progressing with tapering when symptoms 'have resolved or are tolerable' as you suggest. An exact timescale has not been included in the recommendation as this will vary between patients. The need for monitoring is included in the next recommendation, and action to take if withdrawal symptoms are experienced is included in a subsequent recommendation, including the need to restore the dose.

						Such redress may be quick restoration of the dosage prior to reduction, then proceed to taper more gradually after withdrawal symptoms have resolved. (Horowitz and Taylor, 2019; Horowitz and Taylor, 2022; Jha et al., 2018; Jha, 2019)This iterative process may be visualized as in Figure 1:	



- In shared decision-making, clinicilian & patient decide on the amount of dosage change according to explained risk facto (informed consent)
- Clinician should closely monitor throughout dosage changes, wi frequent contact to identify emerging symptoms
- While tapering, clinician evaluat new symptoms for severity, safe & tolerability, referring to guidan describing withdrawal symptom
- Depending on outcome of revie
  - Continue with dosage reductio at same rate
  - Maintain dosage until sympton resolve
  - Continue with dosage reductio at slower rate
  - Restore dosage to prior level, make smaller changes later

Figure 1. Process of dosage reduction or change with shared decision-making and fr monitoring. After Jha et al., 2018 and Jha, 2019

Diagram, timeline

Description automatically generated with medium

						confidenceFramer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry, 6(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-XHorowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	

181	SH	Critical Psychiatry Network	Guideline	16	017-019	This is reasonable advice. The existence of concerning or severe adverse effects should be introduced into the calculus at what rate of reduction should be pursued. However, too rapid withdrawal can cause even greater problems than adverse effects. Fast or abrupt discontinuation might be reserved for when organs, health, or life are threatened. (Carvalho et al., 2016; Talton, 2020) NICE advice should remind clinicians of the serious health risks that might arise from antidepressant use. (NHS, 2021) It would be wise to add a proviso to this: - take into account the broader clinical context such as the potential benefit of more rapid withdrawal where there are significant adverse effects, noting that an overly rapid withdrawal can cause severe effects that may be worse than adverse effects It is also misleading to call adverse effects 'side effects' when some 'side effects' have a more than 50% incidence (Aydemir et al., 2018; Opbroek et al., 2002; Read & Williams, 2018; Serretti & Chiesa, 2009); while at most 15% of people experience benefit from antidepressants over placebo(McCormack and Korownyk, 2018). Terming these as 'side effects', misleadingly prioritises the single effect for which the manufacturer secured marketing authorisation. Aydemir, E., Aslan, E., & Yazici, M. (2018). SSRI Induced Apathy Syndrome. Psychiatry and Behavioral Sciences, 8(2), 63. https://doi.org/10.5455/PBS.20180115111230Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychotherapy and Psychosomatics, 85(5),	Thank you for your comment. This recommendation has been amended to clarify that more rapid withdrawal will likely be reserved for situations where there are serious or intolerable side-effects as this is in-line with the wording used in the NICE guideline on Safe prescribing. The NICE style is to use the term 'side effects' and not 'adverse effects' so this has not been changed.

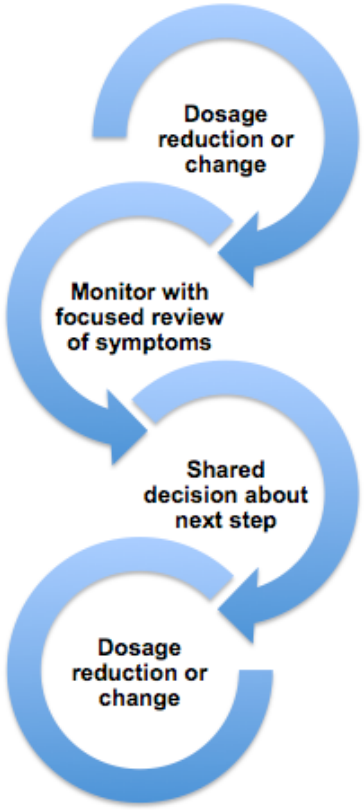
						270–288. https://doi.org/10.1159/000447034 McCormack J, Korownyk C. Effectiveness of antidepressants. BMJ. 2018 Mar 9;360:k1073.NHS. (2021, February 5). Side effects—Antidepressants. Nhs.Uk. https://www.nhs.uk/mental-health/talking-therapies-medicine-treatments/medicines-and-psychiatry/antidepressants/side-effects/ Opbroek, A., Delgado, P. L., Laukes, C., McGahuey, C., Katsanis, J., Moreno, F. A., & Manber, R. (2002). Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? The International Journal of Neuropsychopharmacology, 5(2), 147–151. https://doi.org/10.1017/S1461145702002870Read, J., & Williams, J. (2018). Adverse Effects of Antidepressants Reported by a Large International Cohort: Emotional Blunting, Suicidality, and Withdrawal Effects. Current Drug Safety, 13(3), 176–186. https://doi.org/10.2174/1574886313666180605095130Serretti, A., & Chiesa, A. (2009). Treatment-Emergent Sexual Dysfunction Related to Antidepressants: A Meta-Analysis. Journal of Clinical Psychopharmacology, 29(3). https://journals.lww.com/psychopharmacology/Fulltext/2009/06000/Treatment_Emergent_Sexual_Dysfunction_Related_to.11.aspxTalton, C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042	

182	SH	Critical Psychiatry Network	Guideline	16	020-021	Withdrawal effects can last for years and a lack of understanding of this by clinicians leads to mis-diagnosis, mis-treatment, and huge suffering for patients (Guy et al. 2020; see selection from Horowitz et al., 2022, below). As a consequence, the process of stopping antidepressants can take months or years – this should be made explicit in this guidance (1.4.14). It is probably clearer to use the phrase 'process of stopping' or 'process of discontinuation' here rather than the word 'withdrawal' as this could be seen to be referring to the symptoms, not the process. This section would better read:- recognise that the process of safe discontinuation may take months or year to complete successfully, especially for those people on long-term medicationSelection from Horowitz et al., 2022 (in review):There is significant evidence that withdrawal symptoms can last for weeks, months, or even years in some cases,(Hengartner et al. 2020) but a weighted average of the ten studies included in the recent systematic review was not possible, owing to methodological heterogeneity.(Davies and Read 2019) One study examining reports from doctors to the Medicines and Healthcare products Regulatory Agency (MHRA), described a duration of withdrawal symptoms from 1 to 52 days, with an average of 10.5 days, although this is likely to represent an underestimate as a number of patients on paroxetine had to be re-started on the drug because their withdrawal symptoms were too severe.(Price et al. 1996) A Royal College of Psychiatry online survey found that for the 512 users who experienced withdrawal the symptoms lasted for up to six weeks, and a quarter of the group reported	Thank you for your comment. The recommendation advises that withdrawal may take weeks or months, and the committee agreed that taking 'years' would be uncommon and so did not include it in their recommendations. The committee agreed to use the terminology withdrawal throughout the guideline so 'discontinuation' has not been added into this recommendation. The duration of withdrawal symptoms (which the guidelines states may go away in 1 to 2 weeks) have been conflated in your comment with the duration of the withdrawal process, and these are not the same thing, and the guideline recognises that the withdrawal process may be very protracted.

						anxiety lasting more than 12 weeks.(Psychiatrists 2012) This is consistent with an earlier study which found withdrawal symptoms lasted at least six weeks in 40% of people.(Zajecka et al. 1998) In another online study of 580 people who had withdrawn from antidepressant medication, 86.7% responded that the syndrome had lasted at least two months, 58.6% at least one year and 16.2% for more than three years,(Davies, Regina, and Montagu 2018) although this study may have surveyed a population with a more severe experience of withdrawal than average. Other studies also report longer durations of withdrawal symptoms - in at least some cases symptoms can persist for years.(Fava et al. 2007; Bhanji et al. 2006; Hengartner et al. 2020) It is difficult to establish to what extent these very long-lasting syndromes represent outliers, but it seems likely that withdrawal symptoms routinely persist significantly longer than the one or two-week periods that have been previously ascribed to them for a sizable proportion of patients.(Davies et al. 2019)Horowitz, M. A., Framer, A., Hengartner, M. P., Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs (in review).	
183	SH	The Challenging Behaviour Foundation	Guideline	16	22	Rec 1.4.15 – Recommendation should read: 'Base the frequency and methods of monitoring on the person's clinical and support needs'.	Thank you for your comment. The committee agreed that basing monitoring on clinical and support needs would determine the method of monitoring.

184	SH	The College of Mental Health Pharmacy	Guideline	16	22	"Monitor and review" – what? Please spell out, as this is also about a relapse in their illness of depression, not just about possible withdrawal symptoms.	Thank you for your comment. This recommendation has been expanded to clarify that the monitoring is for both withdrawal symptoms and possible relapse.

185	SH	Critical Psychiatry Network	Guideline	16	022-024	As written, this guidance (1.4.15) is not sufficiently specific about monitoring during tapering. GPs depend on updated NICE advice to prepare them for this unprecedented psychotropic era. GPs may not be aware that with their individual variances in dosing, treatment-emergent effects arising from physiolological dependence (Fava & Rafanelli, 2019), and withdrawal difficulties, antidepressants demand deeper pharmacological understanding and a new practice of close, frequent monitoring (Jha et al., 2018; Jha, 2019; Steinman et al., 2011; Steinman, 2013). Initiation of a drug, dosage changes (including reduction), and drug changes are known to be the highest risk periods for adverse effects (Avery, 2013; GMC, 2021). It is the clinician's responsibility to take the initiative in actively closely monitoring the process (Jha et al., 2018; Jha, 2019; Steinman, et al., 2011) (Figure 1), as well as urging patients to report withdrawal reactions promptly so they may be addressed appropriately (Steinman, 2013).	Thank you for your comment. This recommendation has been expanded to clarify that the monitoring is for both withdrawal symptoms and possible relapse.



- In shared decision-making, clinicilan & patient decide on the amount of dosage change according to explained risk facto (informed consent)
- Clinician should closely monitor throughout dosage changes, wi frequent contact to identify emerging symptoms
- While tapering, clinician evaluat new symptoms for severity, safe & tolerability, referring to guidan describing withdrawal symptom
- Depending on outcome of revie
  - Continue with dosage reductio at same rate
  - Maintain dosage until sympton resolve
  - Continue with dosage reductio at slower rate
  - Restore dosage to prior level, make smaller changes later

Figure 1. Process of dosage reduction or change with shared decision-making and fr monitoring. After Jha et al., 2018 and Jha, 2019

						In addition, NICE guidance should advise clinicians to remind the patient to report suspected adverse drug effects to the MHRA. (GMC, 2021) As it leaves the follow-up process vague, this recommendation as written does not explicitly remind clinicians of optimal clinical practice regarding antidepressants and other prescribed psychotropics. We suggest that the phrase “Monitor and review people taking antidepressant medication while their dose is being reduced. Base the frequency of monitoring on the person’s clinical and support needs.” be modified to say *Actively and closely monitor patients who are reducing their antidepressant drug dosage, in order to quickly redress should withdrawal symptoms emerge.* Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368 GMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf	

						Fava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151 Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	

186	SH	Critical Psychiatry Network	Guideline	016-017	025-029, 001-011	We include an excerpt from a paper currently under review (Horowitz, M. A., Framer, A., Hengartner, M. P., Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs) outlining current evidence on these issues (1.4.14). --- --- --AUTHORS' DRAFT IN REVIEW Horowitz, M. A., Framer, A., Hengartner, M. P., Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs How to taper antidepressants in clinical practice - Part 1: Estimating risk of withdrawal from a review of published data Abstract <u>Background:</u> It is thought that longer duration of use, higher dose and specific antidepressants affect risk of antidepressant withdrawal effects. <u>Method:</u> We conducted a narrative review summarising existing data on determinants of antidepressant withdrawal incidence, severity and duration from studies in a recent systematic review, data from a Committee on the Safety of Medicine review, and other relevant reviews. <u>Results:</u> Meta-regression of double-blind randomised controlled trials revealed a significant association between duration of use and likelihood of experiencing withdrawal symptoms. After three	Thank you for your comment and for sharing this draft paper. The consideration of duration of therapy as a factor when stopping antidepressant treatment is already included in the recommendations, and the committee agreed that the paper produced an interesting rationale for this.

						months of use about a quarter of people will experience withdrawal effects from SSRIs (excluding fluoxetine), increasing by 2.0 percentage points (p.p.) each month, reaching about 40% after 12 months of use. The relevant figures for paroxetine were one-third after three months of use, rising 3.4 p.p. each month. However, there was high heterogeneity in these analyses, suggesting cautious interpretation. A similar duration-response effect is evident for severity of withdrawal symptoms from survey data. After about three years of use, around half of patients report moderately severe or severe withdrawal symptoms. Data on duration of withdrawal symptoms is more sparse but it may be related to duration of use. Effect of type of antidepressant on risk of withdrawal is summarised. Conclusion: Longer use of antidepressants increased incidence of withdrawal, its severity and perhaps its duration. Increased dose also increases risk. Based on these data, we outline a preliminary rubric for determining risk of withdrawal symptoms in a particular patient, which may have relevance for determining tapering rates. Introduction In 2019/2020 1 in 6 adults in England were given a prescription for an antidepressant, representing 7.8 million people,(NHS Business Services Authority 2020) with approximately half of those on antidepressants estimated to be taking them for more than 2 years(Johnson et al. 2012) (roughly 3.5 million people), and at least 930,000 taking them for at least 3 years.(Public Health England 2019) Although there is uncertainty about the precise number, about one-third to one-half of those taking antidepressants will experience withdrawal effects when they stop them.(Jauhar et al. 2019; Davies and Read 2019) Severe	

						withdrawal effects can lead to misdiagnosis of other medical conditions or misdiagnosis of relapse,(Guy et al. 2020; Hengartner 2020) presentations to the emergency department,(P. M. Haddad and Anderson 2007) and suicide attempts.(Valuck, Orton, and Libby 2009) Some people will find withdrawal effects so aversive that they will recommence their antidepressant, leading to long-term unwarranted use and unnecessary exposure to adverse effects.(P. M. Haddad and Anderson 2007; Young and Haddad 2000) The estimated cost of antidepressant withdrawal syndrome has not yet been evaluated, but costs to the health system and social costs may be substantial. There has been widespread debate on how commonly withdrawal symptoms from antidepressants occur as well as their severity and duration.(Jauhar et al. 2019; Jauhar and Hayes 2019; Davies and Read 2019) It has also been thought that various aspects of antidepressant use are likely to affect risk of withdrawal, including dosage, duration of use and characteristics of the antidepressant.(P. M. Haddad and Anderson 2007; Henssler et al. 2019; Renoir 2013) In this paper, the first of two outlining how to implement tapering of antidepressants in clinical practice, we briefly review the neurobiological causes of withdrawal symptoms before examining what is known about the determinants of antidepressant withdrawal from existing literature on the subject. From this review we develop a simple risk calculator to determine the risk of withdrawal symptoms in a given patient. In the second paper we outline a procedure to taper patients off their antidepressant according to this risk stratification and the receptor occupancy of different antidepressants. Neurobiology of physiological dependence and withdrawal symptoms from antidepressants	

						All major classes of antidepressants (SSRIs, SNRIs, MAOIs, TCAs, NaSSAs) are associated with physiological dependence (a normal neurobiological response to drugs that act on the central nervous system) and withdrawal symptoms on cessation or dose reduction.(Howland 2010; P. M. Haddad and Anderson 2007; Public Health England 2019; Taylor, Stewart, and Connolly 2006; Lerner and Klein 2019; O'Brien 2011) Physiological dependence arises because the body and brain undergo adaptations to the presence of a drug, countering its effect in order to maintain homeostasis.(Hyman and Nestler 1996; Turton and Lingford-Hughes 2016; O'Brien 2011) As a physiological consequence of chronic exposure to an antidepressant, dependence is distinct from addiction, in which there are additional impairments of behavioural control not associated with antidepressant use, such as craving, compulsion, and use despite aversive consequences.(Jauhar et al. 2019; Lerner and Klein 2019) Withdrawal symptoms are the cardinal sign of physiological dependence.(Brunton, Chabner, and Knollmann 2011) The exact nature of neurobiological adaptation to antidepressants has received relatively little study, but it is thought to involve down-regulation of serotonergic receptors in response to higher levels of synaptic serotonin arising as a consequence of serotonin transporter (SERT) antagonism, the primary target of antidepressants.(Renoir 2013; Olver, Burrows, and Norman 1999) There is evidence this occurs in humans: even short-term SSRI use causes reduces the sensitivity of cortical 5-HT_{2A} receptors(J. Meyer et al. 2001) in depressed patients and 5-HT_4 receptor in healthy controls(Haahr et al. 2014) as measured by PET binding studies. Consistent with this, in animals long-term treatment with antidepressants produces a reduction in endogenously synthesised levels of serotonin detected(Bosker et al. 2010) after an initial increase,(Kitaichi et al. 2010) although this phenomenon has not been studied in humans. There are many other systems	

						downstream of effects at the target receptor, including norepinephrine, dopamine, glutamate and GABA-ergic pathways, which may also adapt to long-term administration of antidepressants.(Renoir 2013) Another corollary of the neurobiological process of adaptation is tolerance, defined pharmacodynamically as a medication producing less effect over time or, clinically, when higher doses are required for the same effect.(Hyman and Nestler 1996; Turton and Lingford-Hughes 2016; Lerner and Klein 2019) There is evidence of tolerance in animals administered long-term antidepressants.(Popa et al. 2010) In one longitudinal study it was observed that 25% of patients required increased dosages of antidepressant over time,(Solomon et al. 2005) consistent with the development of tolerance. A systematic review found that rates of tachyphylaxis (the clinical consequence of tolerance) occurred in 9% to 57% of patients with depression treated with antidepressants.(Kinrys et al. 2019) Given the common experience of withdrawal symptoms, which indicate a parallel physiological adaptation, development of tolerance to antidepressants should be unsurprising.(Reidenberg 2011; Lerner and Klein 2019) During ongoing administration of antidepressants, neuroadaptation establishes a new homeostatic equilibrium, in which the system accommodates to alterations produced by the drug. When the medication is reduced or stopped, the homeostasis is perturbed, resulting in withdrawal symptoms.(Reidenberg 2011; Turton and Lingford-Hughes 2016; Hyman and Nestler 1996) Due to wide-ranging adaptations in brain and body, withdrawal symptoms can be both physical and psychological.(Schatzberg et al. 1997; P. M. Haddad and Anderson 2007) Indeed, it has been said that “drug discontinuation effects are part of the pharmacology of a drug” when the body eliminates a drug faster than adaptations to the presence of the drug can subside (Figure 1).(Reidenberg 2011)	

This pathophysiological principle makes it clear why the major determinant of how long withdrawal symptoms persist is not a drug characteristic such as half-life, but how long it takes neurobiological adaptations to the drug to resolve to a pre-drug state.(Reidenberg 2011)

[Figure 1 about here]

Incidence of antidepressant withdrawal symptoms

A 2019 systematic review identified 14 relevant studies from which to calculate the incidence of antidepressant withdrawal symptoms. It was found that antidepressant withdrawal effects are common, occurring in about half of patients who stop antidepressants.(Davies and Read 2019) The incidence rates ranged from 27% to 86%, with a median of 55% and a weighted average of 56.4%.(Davies and Read 2019) Restricting the analysis only to double-blind RCTs from this review the incidence of withdrawal effects was 53.9% (6 RCTs, 731 participants).

A potential limitation of this review was that, in addition to randomised controlled trials and observational studies, it included three online surveys; critics point out it is possible that surveys may capture a skewed sample of patients motivated to answer the survey because of their experience with more severe withdrawal symptoms than average.(Jauhar and Hayes 2019; Jauhar et al. 2019) However, the weighted average incidence of withdrawal symptoms was similar in the six randomized controlled trials (53.9%) to the five observational studies (52.5%) and the three online surveys (57.1%).(Davies and Read 2019) Restricting analysis to studies of SSRIs, the most widely used class of antidepressants, discontinuation syndromes occurred with a

						median rate of 53.6%, and a weighted average of 50.5%.(Davies and Read 2019) Some have suggested that withdrawal symptoms may be a psychosomatic response rather than genuine physiological symptoms.(Jauhar et al. 2019) The presence of antidepressant withdrawal symptoms in both animals(Renoir, Pang, and Lanfumey 2012) and neonates of antidepressant-using mothers(Levinson-Castiel et al. 2006) suggests that the process is primarily physiological rather than psychosomatic. Randomised controlled trials conducted to detect withdrawal symptoms used double-blind placebo-controlled designs so that patient and doctor were unaware whether the patient was receiving a continuation of their antidepressant or identical placebo pills for several days.(Rosenbaum et al. 1998; Hindmarch, Kimber, and Cockle 2000) This design minimises the role of psychological expectation or nocebo effects and therefore suggests that withdrawal effects are physiological consequences of stopping the medication.(Rosenbaum et al. 1998) In one carefully conducted study the average number of new symptoms recorded on the Discontinuation-Emergent Signs and Symptoms (DESS) scale was 5.7 (SD 6.96) for sertraline patients and 7.8 (SD 8.55) for paroxetine patients, suggesting a large number of symptoms, including physical symptoms (such as dizziness, and headache) with onset at the same time, consistent with a physiological syndrome.(Rosenbaum et al. 1998) Furthermore, cessation of fluoxetine (whose half-life of 7-15 days makes withdrawal symptoms unlikely in the 5-8 days of the study) produced a non-significant increase of 0.2 symptoms, serving as a useful negative control group.(Rosenbaum et al. 1998) Severity of antidepressant withdrawal symptoms	

						The severity of the withdrawal syndrome from SSRIs varies widely, ranging from mild, short-lasting cases that can be managed with education and reassurance, to severe cases which cause significant disruptions to normal functioning.(P. M. Haddad and Anderson 2007; Davies and Read 2019) This variability presumably relates to differing degrees of neurobiological adaptation and tolerance to antidepressants amongst individuals. In its severe form, the SSRI withdrawal syndrome has been reported to be associated with ataxia leading to falls, electric shock sensations that impair walking and driving,(P. M. Haddad and Anderson 2007) and urgent consultations at emergency departments.(Pacheco et al. 1996; P. Haddad, Devarajan, and Dursun 2001) The discontinuation period is also associated with a 60% increase in suicide attempts, compared with previous users of antidepressants.(Valuck, Orton, and Libby 2009) The systematic review also identified five studies that evaluated the severity of withdrawal effects,(Davies and Read 2019) with nearly half of participants who had experienced withdrawal effects choosing the most extreme option in the scale offered to them to describe the severity of those effects.(Davies and Read 2019) For example, in response to a question 'How severely do you feel withdrawal has affected your life?' on a scale of 0-10 given to 580 people who had attempted withdrawal from antidepressants, mostly SSRIs, the mean response was 8.35 (SD 2.05), indicating that the majority experienced severe reactions, with 43% (249) of participants choosing 10, the highest level of the scale.(Davies, Regina, and Montagu 2018) As above, it is possible that the online survey method employed by four of these studies may be biased by patients with more negative experiences; however, it is notable that somewhat more than half of the participants surveyed in these studies had used antidepressants for more than 3 years,(Read and Williams 2018) similar to the wider English population (where	

about half of antidepressant users have been on them for more than two years).(Johnson et al. 2012) The remaining study, conducted by Pfizer, found that 34.3% of patients treated with sertraline for 8 weeks experienced moderately severe symptoms (as rated by an investigator on global assessment), 23.9% of them experienced a mild withdrawal reaction, while 23.9% reported a minimal one.(Sir et al. 2005) For venlafaxine, after only 8 weeks of use, 38.7% of patients were rated by study researchers as experiencing moderately severe withdrawal symptoms, with 3.2% as 'severe' and 1.6% as 'very severe'.(Sir et al. 2005) As longer duration of treatment appears to be associated with a greater incidence and severity of withdrawal symptoms (see below),(Read and Williams 2018; Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) patients who are on antidepressants for longer than 8 weeks are more likely to suffer more severe withdrawal symptoms.

Duration of withdrawal symptoms

There is significant evidence that withdrawal symptoms can last for weeks, months, or even years in some cases,(Hengartner et al. 2020) but a weighted average of the ten studies included in the recent systematic review was not possible, owing to methodological heterogeneity.(Davies and Read 2019) One study examining reports from doctors to the Medicines and Healthcare products Regulatory Agency (MHRA), described a duration of withdrawal symptoms from 1 to 52 days, with an average of 10.5 days, although this is likely to represent an underestimate as a number of patients on paroxetine had to be re-started on the drug because their withdrawal symptoms were too severe.(Price et al. 1996) A Royal College of Psychiatry online survey found that for

						the 512 users who experienced withdrawal the symptoms lasted for up to six weeks, and a quarter of the group reported anxiety lasting more than 12 weeks.(Psychiatrists 2012) This is consistent with an earlier study which found withdrawal symptoms lasted at least six weeks in 40% of people.(Zajecka et al. 1998) In another online study of 580 people who had withdrawn from antidepressant medication, 86.7% responded that the syndrome had lasted at least two months, 58.6% at least one year and 16.2% for more than three years,(Davies, Regina, and Montagu 2018) although this study may have surveyed a population with a more severe experience of withdrawal than average. Other studies also report longer durations of withdrawal symptoms - in at least some cases symptoms can persist for years.(Fava et al. 2007; Bhanji et al. 2006; Hengartner et al. 2020) It is difficult to establish to what extent these very long-lasting syndromes represent outliers, but it seems likely that withdrawal symptoms routinely persist significantly longer than the one or two-week periods that have been previously ascribed to them for a sizable proportion of patients.(Davies et al. 2019) Determinants of antidepressant withdrawal symptoms As adaptations to the presence of the drug are thought to underlie withdrawal symptoms, longer duration of use, higher dosage and drug type or half-life would be expected to contribute to the incidence and thus the severity and duration of withdrawal symptoms. Individual physiological differences(P. M. Haddad and Anderson 2007; Reidenberg 2011) may also affect the degree of adaptation to the drug and thus the risk of withdrawal symptoms. We explore evidence for all of these determinants. The effect of duration of use on incidence, severity, and duration of withdrawal symptoms	

						Although the primary data is not publicly available, the Committee on the Safety of Medicines (CSM) was granted access to the manufacturer's data for antidepressant withdrawal effects of a variety of antidepressants.(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) Duration of use of paroxetine was found to be related to incidence of withdrawal symptoms on stopping (Table 1a and Figure 2).(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) Data from people who stopped placebo is also shown and quickly diverges from paroxetine (although it is hard to establish whether symptoms reported in the placebo group correspond in number and severity to those discontinuing paroxetine). Data from the manufacturer of fluoxetine showed higher rates of withdrawal symptoms from patients discontinued from fluoxetine after 28 weeks compared with 12 weeks (Table 1b), although there was no further increase in incidence after 52 weeks of use; details of number or the severity of symptoms were not provided.(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) Although it is surprising to see higher rates of withdrawal effects for fluoxetine than paroxetine, this may be because of the longer duration of treatment or different thresholds for detection of withdrawal effects (but this information was not provided). [Table 1 about here] [Figure 2 about here] We examined the relationship between duration of use and incidence of withdrawal symptoms for the double-blind placebo-controlled trials of SSRIs included in the recent systematic	

						review,(Davies and Read 2019) as well as the drug manufacturers' studies selected for a recent opinion piece(Jauhar et al. 2019) by comparing, at the trial level, average duration of use before stopping antidepressants with incidence of withdrawal syndrome for different antidepressants (individual patient data were not available). We conducted a meta-analysis with meta-regression with an inverse-variance random-effects model (DerSimonian-Laird method) with the metafor package for R.(Viechtbauer 2010) We conducted two analyses for the groups of studies where there was enough data to do so – SSRIs (excluding fluoxetine) and paroxetine alone. Meta-regression for the RCTs for the SSRIs citalopram (1 study), escitalopram (6 studies), fluvoxamine (1 study), paroxetine (6 studies) and sertraline (2 studies) showed that average treatment duration per study (range 2-15 months) was a significant effect moderator (p=0.022). Across these drugs and within this range of treatment duration each additional month of treatment was associated with a 2.0 percentage point increase in withdrawal incidence (95%-CI: 0.3 percentage point to 3.8 percentage point) (Figure 3a). Average treatment duration explained 26.1% of between-study variation (heterogeneity) in withdrawal incidence. Fluoxetine trials were not included because short observation periods of about 1 week after treatment cessation/interruption are too brief to reliably detect withdrawal events due to the drug's long elimination half-life. Moreover, heterogeneity was substantial (I^2=91.8%), suggesting that the meta-analytic results must be interpreted with caution; there are many potential other factors that influence incidence of withdrawal including method of drug withdrawal, drug dose, other medications used, amongst others. The only individual drug that we were able to study separately, owing to a sufficiently large number of studies (n=6) and adequate variability in average treatment duration (3-15 months), was paroxetine. The meta-analysis with meta-regression for paroxetine	

likewise showed that average treatment duration was a statistically significant moderator (p=0.001) (Figure 3b). Within the range of treatment duration studied (i.e. 3-15 months), each additional month of treatment was associated with a 3.4 percentage point increase in withdrawal incidence (95%-CI: 1.4 percentage points to 5.4 percentage points). Average treatment duration explained 73.3% of between-study variation in withdrawal incidence. The heterogeneity in the subgroup of paroxetine trials was lower but still substantial (I^2=65.3%).

The relationship between duration of use and incidence of withdrawal symptoms in these studies of SSRIs (excluding fluoxetine), and paroxetine alone is shown in Figure 3. The five studies hand-picked for the opinion piece examined a group of patients who had received antidepressants for 8 to 24 weeks with the average duration of use being 12 weeks.(Jauhar et al. 2019) This study subtracted an estimated nocebo response of 12% (larger than found in the majority of studies) to determine a rate of incidence of paroxetine withdrawal syndrome of 23%. It is probable the smaller incidence of withdrawal effects in these studies compared to others is due to the shorter duration of use in this group, as the line of best fit passes through these five data points (Figures 3a and 3b). Although survey data included in the recent systematic review(Davies and Read 2019) is excluded from this analysis as uncontrolled data, it is noteworthy that this data is largely consistent with the controlled data presented.

[Figure 3 about here]

Although no RCTs examined the severity of withdrawal symptoms in association with treatment duration (rather, they only counted the number of symptoms), online surveys of patients did so.(Read, Cartwright, and Gibson 2014, 2018) Although these surveys may have captured skewed samples, the line of best fit suggests a clear

gradient between duration of use and severity of withdrawal syndrome (Figure 4a and Table 2a).(Read, Cartwright, and Gibson 2018) This suggests that for patients who are on antidepressants for more than three years, more than half will experience severe withdrawal symptoms, although this should be interpreted cautiously due to the design of the study. However, this provides support for the relationship between duration of antidepressant use (leading to greater physiological adaptations) and severity of withdrawal symptoms.(Read, Cartwright, and Gibson 2018)

[Figure 4 about here]

There were five studies for which duration of antidepressant use and duration of withdrawal symptoms were available (Figure 4b and Table 2b).(Bogetto et al. 2002; Stockmann et al. 2018; Zajecka et al. 1998; Davies, Regina, and Montagu 2018; Narayan and Haddad 2010) Although a relationship appears to exist between duration of use and duration of withdrawal symptoms, the data was heterogenous. Both studies with a longer duration of use involved samples of patients who self-identified as having trouble with withdrawal, likely to represent a more severe group than average.(Stockmann et al. 2018; Davies, Regina, and Montagu 2018) Additionally, the length of time recorded for withdrawal effects included the period over which the drugs were tapered, perhaps artificially inflating the duration of withdrawal symptoms. However, it does appear that a portion of patients will experience withdrawal symptoms for several months or longer than a year, perhaps related to length of treatment.

[Table 2 about here]

Dosage level

						There was also a higher incidence of withdrawal effects for higher dosages of paroxetine in the analysis by the CSM,(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) although the effect reached a threshold at 20mg (Table 3a), probably because of the hyperbolic relationship between antidepressant dosage and effect on its target receptors.(Horowitz and Taylor 2019a; Holford 2018; J. H. Meyer et al. 2004; Furukawa et al. 2019) There was a more pronounced dose-dependent relationship for venlafaxine withdrawal effects (Table 3b),(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) with increased incidence at higher dosages possibly related to greater noradrenergic effects at these dosages.(Debonnel et al. 2007) Fluvoxamine and mirtazapine did not demonstrate clear dose-dependent effects, however the CSM cautioned that the pooled analysis applied may not have been appropriate to detect these effects.(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) Overall, dosage does appear to have some relationship to risk of withdrawal symptoms, but its influence may not be as strong as duration of use, perhaps because higher dosages have only small additional pharmacological effects over minimum clinically employed dosages because of the hyperbolic shape of their dose-response curves.(Holford 2018; Horowitz and Taylor 2019b; Furukawa et al. 2019; Horowitz, Murray, and Taylor 2020; Horowitz et al. 2021) [Table 3 about here] *Drug type*	

						It has been suggested that the risk of withdrawal symptoms varies between different antidepressants. This could be due to differing half-lives, with drugs with shorter half-lives being eliminated more quickly and therefore producing more precipitous drops in inputs 'expected' by the system (See Figure 1).(Henssler et al. 2019) This is supported by the finding that percentage reductions in plasma concentration of fluoxetine, sertraline and paroxetine, following cessation, showed a significant correlation with the appearance of withdrawal symptoms.(Michelson et al. 2000) Cessation of paroxetine for several days causes withdrawal symptoms in 66-100% of patients,(Rosenbaum et al. 1998; Hindmarch, Kimber, and Cockle 2000) cessation of sertraline in 59-60% of patients,(Rosenbaum et al. 1998; Hindmarch, Kimber, and Cockle 2000) and fluoxetine in 14-77% of patients.(Rosenbaum et al. 1998; Hindmarch, Kimber, and Cockle 2000) In surveys, which may include a self-selected population, these differences among common SSRIs are roughly preserved: 69%, 62% and 44% of patients stopping paroxetine, sertraline, and fluoxetine, respectively, report withdrawal symptoms.(Psychiatrists 2012) However, withdrawal symptoms following the cessation of fluoxetine, the SSRI with the longest half-life (7-15 days), has been observed to occur with a delay of onset of four to six weeks after discontinuation in one study,(Zajecka et al. 1998) and two weeks after discontinuation in another.(Fava et al. 2015) Notably, 77% of patients in one study experienced withdrawal symptoms when stopping fluoxetine, so although it may be rarer than for other antidepressants, a withdrawal syndrome often does occur.(Hindmarch, Kimber, and Cockle 2000) Paroxetine and fluoxetine are both metabolised by cytochrome p450 2D6 (while fluoxetine's active metabolite, norfluoxetine is metabolised by p450 3A4) and inhibit their own metabolism,	

resulting in non-linear kinetics.(Preskorn 1997) This predicts disproportionate declines in plasma concentrations during dose reduction. While this effect may not be clinically significant for fluoxetine because of its long half-life, it is likely to be significant for paroxetine.(Olver, Burrows, and Norman 1999) In addition, paroxetine may produce a more severe withdrawal syndrome than other SSRIs because it exhibits the highest known binding affinity for the central site of SERT,(Coleman et al. 2020) and demonstrates muscarinic antagonist effects and moderate norepinephrine transporter-inhibiting effects as well.(Renoir 2013; Olver, Burrows, and Norman 1999)

Tiers of risk based on drug type

A recent systematic review by Henssler et al. (2019) attempted to quantify the relative risks of different antidepressants based on controlled trials, cohort studies, retrospective analyses, and case reports.(Henssler et al. 2019) We have supplemented this review with data from the CSM, and an analysis of calls to an English medication helpline for issues related to withdrawal, normalised to prescription numbers(Taylor, Stewart, and Connolly 2006) to provide a summary table of three levels of risk for antidepressants (Table 4). However, for some of the antidepressants outlined here only case reports were available(Henssler et al. 2019) so this summary can only be considered preliminary.

[Table 4 about here]

Other determinants of withdrawal risk

						Individual characteristics may influence the risk of antidepressant withdrawal symptoms, related to metabolism of the SSRI, sensitivity of SERT to inhibition, and psychological factors.(P. M. Haddad and Anderson 2007; Bitter, Filipovits, and Czobor 2011) Patients who are rapid metabolisers of drugs will experience a more precipitous decrease in drug levels and may be more likely to experience more severe withdrawal symptoms;(Harvey and Slabbert 2014) on the other hand, rapid metabolisers will be exposed to lower levels of the drug over time so may develop less dependence.(Hicks et al. 2015) The likelihood of withdrawal symptoms has been be associated with the C(-1019)G polymorphism of the $5HT_{1A}$ receptor gene, known to be affected by long-term antidepressant treatment.(Murata et al. 2010) There are likely to be other factors which determine incidence and severity of withdrawal but this has not been widely studied. Stratifying patients for reduction Based on the above characteristics that influence risk of withdrawal symptoms, we have derived a broad means of stratifying patients with regards to their risk of withdrawal symptoms. From clinical experience, the strongest predictor of withdrawal symptoms is past experience of withdrawal symptoms (in a previous attempt at discontinuation, a drug switch, or after skipped doses), as recognised in similar efforts to determine risk,(Ruhe et al. 2019) and so this is given strong weighting (3 points) (Table 5). Duration of use appears to have a strong effect on risk of withdrawal symptoms, including their severity and possibly their duration and therefore this has been given strong emphasis (3 points). Antidepressant type (4 points) has been associated with varying risk, and higher doses (1 point) though to	

a lesser extent. This approach can only be seen as preliminary and will need to be further clarified with empirical data. However, we have found this approach useful in clinical practice.

[Table 5 about here]

Conclusion

We have reviewed the existing literature on the incidence, severity and duration of withdrawal symptoms as well as examined the relationship between characteristics of use (such as dosage, duration of use and type of antidepressant) and withdrawal symptoms. Information in these domains is limited and more research is required to draw firmer conclusions about the determinants of withdrawal symptoms, particularly regarding severity and duration.

From existing data there appears to be a relationship between duration of antidepressant use and risk of withdrawal symptoms, consistent with the idea that greater duration of use will produce greater neurological adaptation. For SSRIs (excluding fluoxetine), the risk appears to be approximately one third after 6 months of use, increasing to one half at 12 months of use, with relevant values for paroxetine withdrawal being 40% and 60%, respectively. However, the heterogeneity between studies is high for both these evaluations and so caution is required in interpretation. There also appears to be a gradient between duration of use of antidepressants and severity of withdrawal symptoms, with about half of patients reporting moderately severe or severe withdrawal symptoms after 2-3 years of use, although this data is derived from survey data and so may represent a

						skewed sample. Information is sparse for duration of withdrawal symptoms, which may be increased with duration of treatment. We also reviewed data suggesting that greater dosage of antidepressant is associated with greater chance of withdrawal symptoms, but that there may be ceiling effects, consistent with the hyperbolic relationship between dose and effect of antidepressants resulting in target receptor saturation. There appears also to be variation based on which antidepressant is taken. Clinical experience suggests that past experience of withdrawal symptoms on reducing or stopping medication is a strong predictor of withdrawal symptoms on subsequent attempts to reduce or stop. From these risk factors we have derived a simple rubric for determining withdrawal risk for a given patient, which may be useful in clinical practice for stratifying people according to risk. We hope that future empirical work will be able to offer a refined version of this risk calculator. In an accompanying paper we will outline a logical method for tapering patients off antidepressants based on their risk of withdrawal symptoms as determined by this preliminary risk calculator. When prescribing antidepressants consideration should be given to the likelihood of withdrawal effects (which can be severe and long-lasting in some people) and that risk is related to dose and duration of use.(Davies and Read 2019; Royal College of Psychiatrists 2019) Although many current guidelines recommend that antidepressants should be prescribed for long periods, the evidence for this has been derived from antidepressant discontinuation studies in which withdrawal symptoms may have been misdiagnosed as relapse (as these were not specifically recorded), exaggerating the relapse prevention properties of antidepressants.(Hengartner 2020; Hengartner and Plöderl 2021)	

Current evidence indicates that the incidence and severity of antidepressant withdrawal effects increases with duration of use: that by 6 months of use, at least a quarter of patients will be at risk of experiencing withdrawal symptoms for many antidepressants, and that by 12 months up to a half of patients will be at risk for withdrawal. Care should therefore be taken both in starting antidepressants and in long-term continuation of antidepressants, setting the increased likelihood of difficulty in stopping medication against the dearth of clear evidence of long-term efficacy.

References

Figures

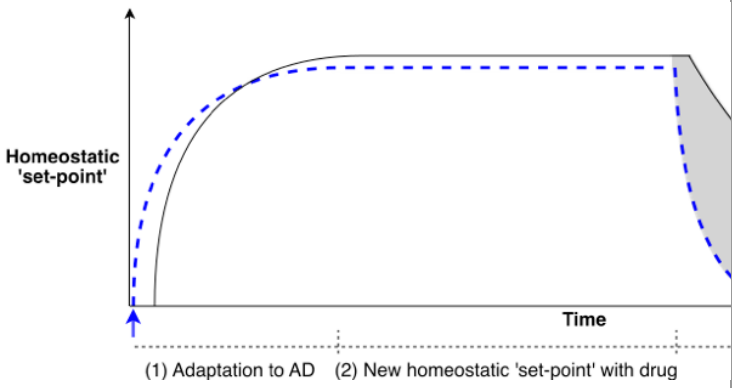


						Figure 1. The neurobiology of antidepressant withdrawal. In this diagram, the homeostatic 'set-point' is shown in black and antidepressant drug levels are shown in blue dotted lines. (1) The system is at baseline. At the blue arrow, an antidepressant is administered; drug plasma levels increase. Physiological adaptations of the system to the presence of the drug begin (which may be the period for which 'start-up side effects' are most pronounced). (2) At the plateau, drug plasma levels (and target receptor activation) have reached a steady state with a new homeostatic set-point of the system established ('start-up side effects' may reduce). (3) The antidepressant is abruptly ceased and plasma drug levels drop to zero (exponentially, according to the elimination half-life of the drug). This difference between the homeostatic set-point (the 'expectations' of the system) and the level of drug in the system (dotted blue line) is experienced as withdrawal symptoms. The duration of withdrawal symptoms is largely determined by the time required for adaptations to the drug to resolve. Hence, withdrawal symptoms may worsen or peak even long after the drug has been eliminated from the system. The shaded area under the curve, representing the difference between the homeostatic set-point and the level of the drug, indicates the degree of risk of withdrawal symptoms: the larger the area the greater the risk. The greater the departure of drug level from the homeostatic set-point, the greater the risk.	

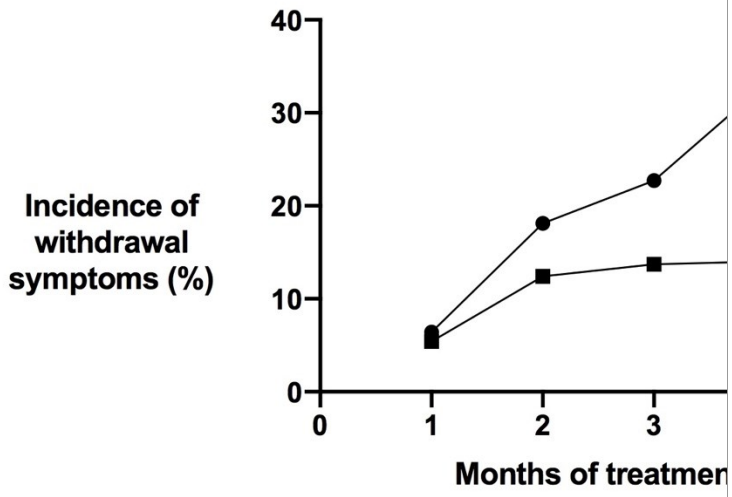
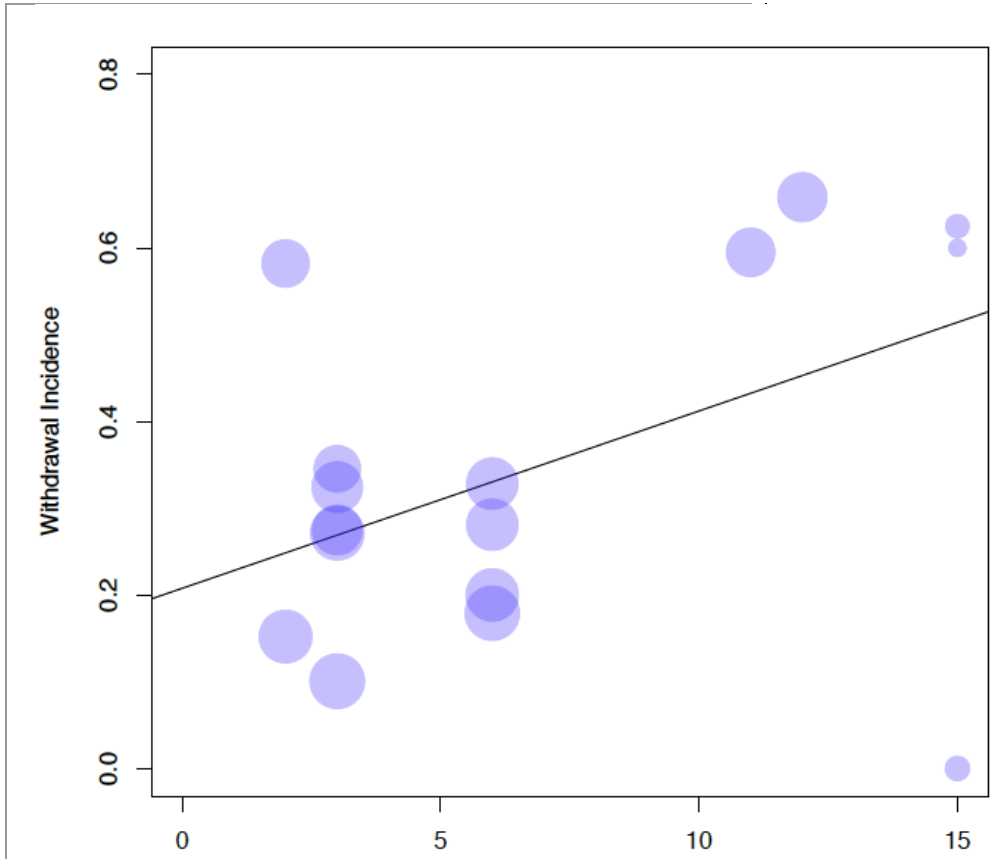


Figure 2. The relationship between duration of treatment and proportion of patients who experienced withdrawal effects on stopping either paroxetine or placebo.(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005)

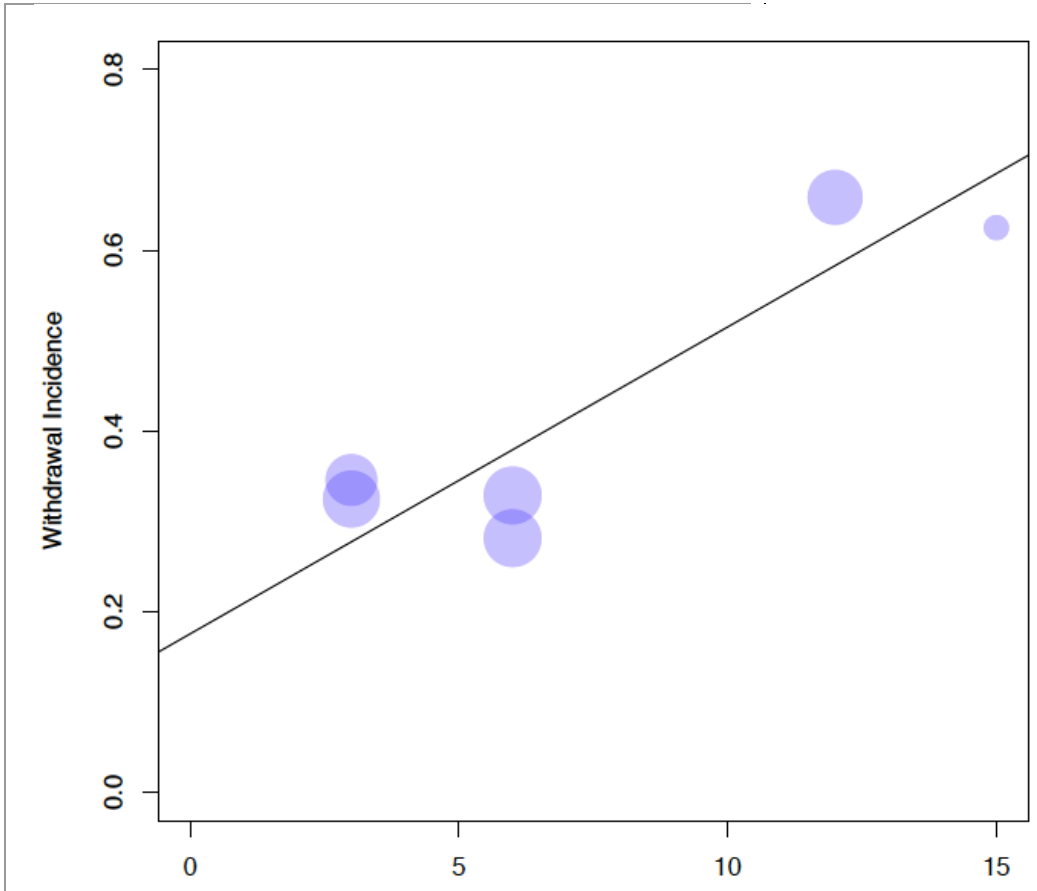
All SSRIs (except fluoxetine)

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

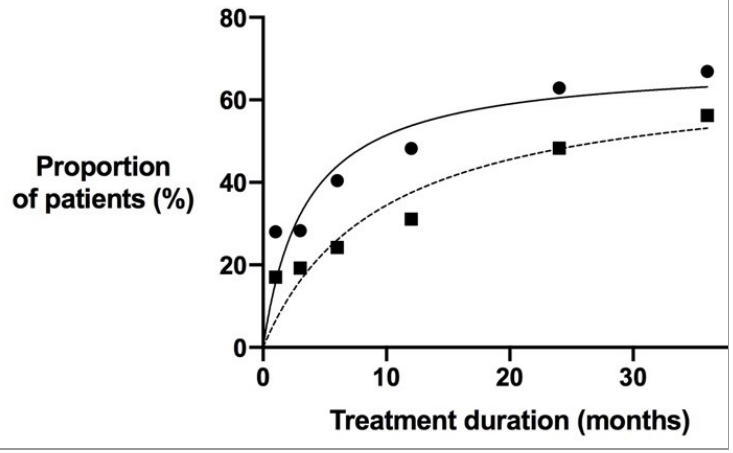


a
Paroxetine



b

Figure 3. Bubble plot of relationship between duration of use of antidepressant and incidence of withdrawal syndrome for a) SSRIs (excluding fluoxetine) and b) paroxetine, with treatment duration

						in months. Weighted lines of best fit are shown in the graphs. Areas of bubbles are proportional to the sample size of the studies. Data sources are double-blind RCTs derived from Davies and Read (2019) and Jauhar et al. (2019). In (a) withdrawal incidence increases by 2.0 percentage points per month treated and in (b) by 3.4 percentage points per month treated. a  	

b

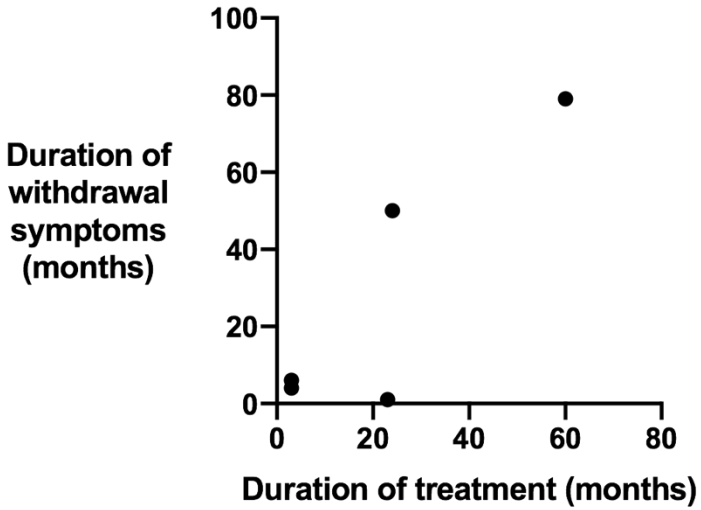


Figure 4. Relationship between duration of treatment and severity and duration of withdrawal symptoms from surveys of antidepressant users and observational studies. a) Relationship between duration of treatment of antidepressants and incidence of moderate or severe withdrawal symptoms. Graph is derived from data in Read et al. (2018)(Read, Cartwright, and Gibson 2018). b) Relationship between duration of use of antidepressants and duration of withdrawal symptoms in studies captured in the systematic review.(Davies and Read 2019)

Tables

Paroxetine treatment duration	% patients with withdrawal events (n/N)
1 – 28 days	6.4 (29/455)
29 – 56 days	18.1 (129/712)
57 – 84 days	22.7 (218/960)
≥ 85 days	33.1 (221/667)

Table 1a. Relationship of duration of use of paroxetine to incidence of withdrawal symptoms. (Source: CSM)

Fluoxetine treatment duration	% patients with withdrawal events (n/N)
12 weeks	75 (72/96)
28 weeks	89.7 (87/97)
50 weeks	82.0 (82/100)

Table 1b. Relationship of duration of use of fluoxetine to incidence of withdrawal symptoms. (Source: CSM)

Duration of antidepressant use	Withdrawal effects – any severity (%)	Withdrawal effects – moderate or severe (%)
<3 months	28.0	17.0
3-6 months	28.3	19.2
6-12 months	40.4	24.2
1-2 years	48.2	31.1
2-3 years	62.9	48.3
>3 years	66.9	56.2

Table 2a. The relationship between duration of treatment and severity of withdrawal symptoms from surveys of antidepressant users. Data is derived from Read et al. (2018).(Read, Cartwright, and Gibson 2018)

Duration of antidepressant use (months)	Duration of withdrawal symptoms (weeks)		Study
3	4		Zajecka et al., 1998
3	6		Narayan & Haddad, 2010
23	1		Bogetto et al., 2002
24	50		Davies et al., 2018
60	79		Stockmann et al., 2018

Table 2b. The relationship between duration of treatment and duration of withdrawal effects of studies included in the recent systematic review.(Davies and Read 2019)

Paroxetine Dosage	% patients with withdrawal effects (n/N)
10mg	9 (4/46)
20mg	16 (9/55)

30mg	18 (11/61)
40mg	17 (10/60)

Table 3a. The relationship between dosage of paroxetine and incidence of withdrawal effects.(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005)

Venlafaxine ER Dose	% patients with withdrawal effects (n/N)
Placebo	3 (2/77)
37.5mg	13 (11/92)
75mg	11 (9/92)
150mg	24 (20/98)

Table 3b. The relationship between dosage of venlafaxine and incidence of withdrawal effects.(Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D

Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R

2005)

ant withdrawal
ms

Antidepressant

sk

Nortriptyline, Tranylcypromine, Phenelzine, Paro
Duloxetine, Mirtazapine, Moclobe

risk

Citalopram, Escitalopram, Sertraline, Fluvoxan
Lofepramine, Trazadone, Reboxetine, Amitriptyl
Imipramine, Fluoxetine

sk

Bupropion, Agomelatine, Milnaci

Table 4. Common antidepressants stratified by risk of withdrawal symptoms, derived from Henssler et al. (2019), CSM report on antidepressants (Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R 2005) and calls to a withdrawal help-line, normalised to prescription numbers.(Taylor, Stewart, and Connolly 2006)

Determinant of withdrawal risk	Weighting

						Duration of use • Short term (1- 6 months) 0 points • Intermediate term (6 -12 months) 1 point • Long term (1-3 years) 2 points • Very long-term use (>3 years) 3 points Antidepressant type • Low risk (e.g. agomelatine) 0 points • Moderate risk (most SSRIs, imipramine, most TCAs) 2 points • High risk (e.g. SNRIs, paroxetine, MAO-Is, nortriptyline) 4 points Dosage • Minimum therapeutic dosage or lower 0 points • Greater than the minimum therapeutic dosage 1 point Past experience of withdrawal symptoms • Stopped antidepressant in past with no withdrawal symptoms/unknown 0 points • Mild to moderate withdrawal symptoms 1 point • Severe withdrawal symptoms 2 points • Very severe withdrawal symptoms 3 points Table 5a. Evaluation of risk of withdrawal for an individual patient. Note that very short term use (<4 weeks) is not normally assocated with significant risk of withdrawal. Evaluation of risk of withdrawal Low risk = 0 points	

						Medium risk = 1-3 points High risk = 4-6 points Very high risk = or > 7 points Table 5b. Summary of risk category for withdrawal effects based on characteristics of antidepressant use. END OF AUTHORS' DRAFT IN REVIEW Horowitz, M. A., Framer, A., Hengartner, M. P., Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs	

187	SH	Critical Psychiatry Network	Guideline	016-017	025-029, 001-011	A note on the sense of this guidance section (1.4.16) as a whole: It is essential that clinicians be advised not to attempt to taper any antidepressant other than possibly fluoxetine by alternating or skipping doses. While skipping doses may seem a convenient way to “average” dosage decreases in tapering, it is currently a huge problem in clinical practice, with many patients given this advice, leading to terrible problems for patients (often mis-diagnosed). (Framer, 2021; Lewis et al., 2021)There is no scientific basis for this common clinical practice -- it is contrary to what science knows about the dangers of inconsistent dosing, drug half-life, and the pharmacology of psychotropics (Kaplan, 1997; Osterberg et al., 2010; Reidenberg, 2011). As an outcome of neurobiological adaptation to and physiological dependence on a regular drug dosage, unpleasant symptoms of withdrawal are evoked when that “expected” dosage is not supplied (Peper, 2004), the body struggling to maintain homeostasis (Osterberg et al., 2010).While skipping doses to taper may seem to be a convenient recourse for doctors who have been advised to avoid liquid versions of medication, it is also causes great fluctuations in drug plasma levels that can lead to severe withdrawal symptoms. This can be easily visualized with antidepressants as an example: irregular dosing can cause fluctuations of receptor occupancy (Horowitz and Taylor, 2022) but, more immediately, drug plasma level, particularly with short half-life drugs (Sørensen et al., 2021) (meaning all but fluoxetine), which in fact are associated with more frequent reports of withdrawal syndrome (Quilichini et al., 2022). Moreover, in recommendation 1.4.11 (page 15, lines 7-	Thank you for your comment. The guideline does not suggest skipping doses as a method of tapering, except for fluoxetine, which is exactly what you suggest in your comment. The committee agreed that slow step-wise tapering was necessary and the recommendation has been amended to clarify this. They also agreed that in some cases it was necessary to use liquid preparations but were also aware that these were expensive and not available for all antidepressants. This recommendation has therefore been amended to clarify that liquid preparations should only be used when other methods (such as splitting or dispersing solid oral preparations) are not possible.

						19) of the draft for consultation, November 2021 of NICE Guideline Depression in adults correctly directs clinicians to "Advise people taking antidepressant medication that if they stop taking it abruptly, miss doses or do not take a full dose, they may have withdrawal symptoms…. (NICE, 2021)"Just as patients are at high risk of unpleasant withdrawal symptoms if they accidentally forget doses, skip them, or take them off-schedule (Demyttenaere & Haddad, 2000; Ho et al., 2016; Kaplan, 1997; Meijer et al., 2001; NICE, 2021), skipping doses or alternating dosages to taper causes withdrawal symptoms that can escalate to even worse symptoms if the irregular dosing continues. Like non-adherence, irregular dosing as a tapering method can lead to iatrogenic pseudo-resistance should a drug regimen be restored (Amsterdam et al., 2016; Fava et al., 2020; Howes et al., 2021).Psychiatrists, clinicians, and patient experts by experience have observed the adverse effects of skipping doses as a tapering technique (Framer, 2021; Gallagher et al., 2012; Stockmann, 2019). There is no reason for clinicians to put their patients at risk of withdrawal by recommending skipping doses to taper. Rather than irregular dosing, clinicians would better employ dosage ranges, tablet-splitting, liquid preparations, and custom compounded doses (such as tapering strips, described by Groot and van Os, 2021). A NICE recommendation for the use of liquid preparations for tapering is contained in 1.4.14 page 16, lines 11-12. This should be expanded for use of liquid preparations throughout the taper. Clinicians can use these to make up smaller lower doses so that the same amount is taken every day. (The exception to this is fluoxetine, which	

						has may have a long enough half-life to allow every other day dosing.)We urge NICE to specifically and emphatically advise clinicians not to recommend or employ skipping or alternating dosages to taper antidepressants other than, possibly, fluoxetine, the one with an exceptionally long half-life – and to closely monitor all tapering for withdrawal symptoms.Amsterdam, J. D., Lorenzo-Luaces, L., & DeRubeis, R. J. (2016). Step-wise loss of antidepressant effectiveness with repeated antidepressant trials in bipolar II depression. Bipolar Disorders, 18(7), 563–570. https://doi.org/10.1111/bdi.12442Demyttenaere, K., & Haddad, P. (2000). Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 101(s403), 50–56. https://doi.org/10.1111/j.1600-0447.2000.tb10948.xFava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The Deceptive Manifestations of Treatment Resistance in Depression: A New Look at the Problem. Psychotherapy and Psychosomatics, 1–9. https://doi.org/10.1159/000507227Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/20451253219912 74Gallagher JC, Strzinek RA, Cheng RJ, et al. The effect of dose titration and dose tapering on the tolerability of desvenlafaxine in women with vasomotor symptoms associated with menopause. J Womens Health 2002 2012; 21: 188–198.Groot, P. C., & van Os, J. (2021). Successful use of tapering strips for hyperbolic reduction of antidepressant dose: A cohort study. Therapeutic	

						Advances in Psychopharmacology, 11, 20451253211039330. https://doi.org/10.1177/20451253211039327Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029Horowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001Howes, O. D., Thase, M. E., & Pillinger, T. (2021). Treatment resistance in psychiatry: State of the art and new directions. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01200-3Kaplan EM. Antidepressant noncompliance as a factor in the discontinuation syndrome. J Clin Psychiatry 1997; 58 Suppl 7: 31–35; discussion 36.Lewis, G., Marston, L., Duffy, L., Freemantle, N., Gilbody, S., Hunter, R., Kendrick, T., Kessler, D., Mangin, D., King, M., Lanham, P., Moore, M., Nazareth, I., Wiles, N., Bacon, F., Bird, M., Brabyn, S., Burns, A., Clarke, C. S., … Lewis, G. (2021). Maintenance or Discontinuation of Antidepressants in Primary Care. New England Journal of Medicine, 385(14), 1257–1267. https://doi.org/10.1056/NEJMoa2106356Meijer WEE, Bouvy ML, Heerdink ER, et al. Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. Br J Psychiatry 2001; 179: 519–522.NICE. (2021). NICE Guideline Depression in adults Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care	

						Excellence. https://www.nice.org.uk/guidance/cg90Osterberg, L. G., Urquhart, J., & Blaschke, T. F. (2010). Understanding Forgiveness: Minding and Mining the Gaps Between Pharmacokinetics and Therapeutics. Clinical Pharmacology & Therapeutics, 88(4), 457–459. https://doi.org/10.1038/clpt.2010.171Peper, A. (2004). A theory of drug tolerance and dependence I: A conceptual analysis. Journal of Theoretical Biology, 229(4), 477–490. https://doi.org/10.1016/j.jtbi.2004.04.010Quilichini, J.-B., Revet, A., Garcia, P., Bouquié, R., Hamard, J., Yrondi, A., & Montastruc, F. (2022). Comparative effects of 15 antidepressants on the risk of withdrawal syndrome: A real-world study using the WHO pharmacovigilance database. Journal of Affective Disorders, 297, 189–193. https://doi.org/10.1016/j.jad.2021.10.041Reidenberg, M. M. (2011). Drug Discontinuation Effects Are Part of the Pharmacology of a Drug. The Journal of Pharmacology and Experimental Therapeutics, 339(2), 324–328. https://doi.org/10.1124/jpet.111.183285Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-wStockmann T. What it was like to stop an antidepressant. Ther Adv Psychopharmacol 2019; 9: 2045125319884834.	

188	SH	Critical Psychiatry Network	Guideline	17	003 - 005	In addition to paroxetine and venlafaxine, the commonly used antidepressants mirtazapine and duloxetine are particularly associated with withdrawal and these should be added to the list in 1.4.16. We would like to bring the committee's attention to the following proposed Tiers of risk based on drug type (Horowitz, et al., 2022, in review) A recent systematic review attempted to quantify the relative risks of different antidepressants based on controlled trials, cohort studies, retrospective analyses, and case reports.(Henssler et al., 2019) We have supplemented this review with data from the CSM (Weller, et al., 2005) and an analysis of calls to an English medication helpline for issues related to withdrawal, normalised to prescription numbers(Taylor, Stewart and Connolly, 2006), to provide a summary table of three levels of risk for antidepressants (Table 4). However, for some of the antidepressants outlined here, only case reports were available (Henssler et al., 2019), so this summary can only be considered preliminary.	Thank you for your comment. The committee agreed that paroxetine and venlafaxine stood out as the antidepressants most likely to lead to withdrawal symptoms and so it was important to highlight these, but that the guideline stated that withdrawal was possible with any antidepressant.

Tiers of risk based on drug type

ant withdrawal ms	Antidepressant
sk	Nortriptyline, Tranylcypromine, Phenelzine, Paro Duloxetine, Mirtazapine, Moclobe
risk	Citalopram, Escitalopram, Sertraline, Fluvoxam Lofepramine, Trazadone, Reboxetine, Amitriptyl Imipramine, Fluoxetine
sk	Bupropion, Agomelatine, Milnaci

Table 4. Common antidepressants stratified by risk of withdrawal symptoms, derived from Henssler et al. (2019), CSM report on antidepressants (Weller I, Ashby D, Chambers M, Chick J, Drummond C, Ebmeier K, Gunnell D, Hawking H, Mukaetova-Ladinska E, O'Tierney E, Taylor R, 2005) and calls to a withdrawal help-line, normalised to prescription numbers.(Taylor, Stewart and Connolly, 2006)

Henssler J, Heinz A, Brandt L, Bschor T. Antidepressant Withdrawal and Rebound Phenomena. Dtsch Arztebl Int. 2019 May 17;116(20):355–61.

						Horowitz, M. A., Framer, A., Hengartner, M. P., Sorensen, A., & Taylor, D. (2022). How to taper antidepressants in clinical practice—Part 1: Estimating risk of withdrawal from a review of published data. CNS Drugs (in Review).Taylor D, Stewart S, Connolly A. Antidepressant withdrawal symptoms-Telephone calls to a national medication helpline. J Affect Disord. 2006;95(1-3):129–33. Weller I Ashby D Chambers M Chick J Drummond C Ebmeier K Gunnell D Hawking H Mukaetova-Ladinska E O'Tierney E Taylor R YAAZM. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitors Antidepressants. 2005.	
189	SH	Critical Psychiatry Network	Guideline	17	006-007	This advice (1.4.16) about fluoxetine is misleading. The half-life of norfluoxetine, the active metabolite of fluoxetine, is 7-15 days. This will produce a washout period of 35-75 days considering 5 half-lives as an estimate period. As some patients require months or years to stop medications safely, this 'built in tapering' period is not long enough to greatly shorten tapering. As with other antidepressants, a gradual withdrawal schedule should be recommended for fluoxetine (although permitting greater reductions spread out at greater intervals – for example rather than recommending 10% reductions a month, 30% every 3 months might be permissible, performed in a proportional manner so that reductions become smaller as total dose gets lower). Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry, 6(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-XHorowitz, M. A., & Taylor, D. (2022). How to	Thank you for your comment. The committee have amended the details about the withdrawal of fluoxetine to provide more details and advise that step-wise dose reductions should be evaluated before making further reductions.

						reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001	

190	SH	Critical Psychiatry Network	Guideline	17	008-011	We agree that alternate day dosing can be a good strategy for dose reduction, however, we urge that this guidance explicitly recommend clinician caution in tapering fluoxetine by alternate day dosing, skipping doses, or otherwise irregular dosing schedules. Albeit at a lower rate than other antidepressants, fluoxetine has been associated with withdrawal symptoms ((Groot & van Os, 2021; Horowitz and Taylor, 2019; Stahl et al., 1997; Zajecka et al., 1997) even after brief exposure or for brief interruptions (Judge et al., 2002; Liston et al., 2002). Of the 69 subjects in a study of online reports of protracted antidepressant withdrawal syndrome, 10% had gone off fluoxetine. (Hengartner, et al., 2020) When withdrawal risk from the newer antidepressants became known in the mid-1990s (Coupland et al., 1996), Eli Lilly, Prozac's manufacturer, saw the opportunity to favorably position its product, with its lower recorded rate of withdrawal symptoms, in the antidepressant marketplace. Attributed to its exceptionally long half-life compared to other antidepressants, fluoxetine's low withdrawal risk was extolled in an influential suite of articles commissioned by Lilly as a supplement in the Journal of Clinical Psychiatry. (Schatzberg, 1997) Another representative of the manufacturer dubbed it "self-tapering". (Wernicke, 2004) Studies claimed fluoxetine has virtually no withdrawal syndrome (Demyttenaere & Haddad, 2000; Rosenbaum et al., 1998; Zajecka et al., 1998), but may have been too short to follow patients through the approximately 6 weeks required for discontinuation of fluoxetine to fully take effect.Due to these efforts, fluoxetine may have acquired an undeserved halo, appearing to be "self-	Thank you for your comment. The committee have amended the details about the withdrawal of fluoxetine to provide more details and advise that step-wise dose reductions should be evaluated before making further reductions.

						tapering" -- but withdrawal symptoms may emerge some weeks after a reduction.(Horowitz and Taylor, 2019) As the approved FDA package insert for fluoxetine points out: "Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment." (FDA, 2007)When SSRI intake is interrupted, there is evidence that drug plasma level falls faster than SERT occupancy. (Sorensen et al., 2021) With its non-linear pharmacokinetics, fluoxetine plasma level appears to fall precipitously within 20 hours of a missed dose. (Kondratenko et al., 2019) While fluoxetine's long half-life may be protective against withdrawal for some, it may be that those patients especially sensitive to fluctuation in drug plasma level will experience withdrawal symptoms from interruption of fluoxetine dosing sooner and more severely.Consequently, clinicans will need to monitor tapering of fluoxetine as carefully as any other antidepressant, as mild withdrawal symptoms may burgeon into severe as irregular dosing continues. This advice should be clarified so as to not misleadingly suggest that all that is required to taper fluoxetine is every second day dosing. Those patients who experience withdrawal may require more conventional gradual tapering, and whatever method is employed for dose reduction, patients will require access to liquid preparations for the small final doses. We suggest these points be added: "- Patients who display withdrawal symptoms may require more conventional gradual tapering.- for smaller final doses,	

						access to a liquid preparation of fluoxetine may be required.”Regarding these points in the guidance (1.4.16):“− in people taking 20 mg fluoxetine a day, a period of alternate day dosing can provide a suitable dose reduction − in people taking higher doses (40 mg to 60 mg fluoxetine a day), use a gradual withdrawal schedule. [2021]” It does not make great sense to more carefully taper higher doses of fluoxetine because there is little difference in between clinical effect (Figure 2 in Furukawa et al 2019) and receptor occupancy (Meyer et al 2004, Sorensen et al 2020). The reduction from 60mg to 20mg is relatively easy for most patients. In fact, it is the reductions from 20mg to 0mg that are most difficult and where gradual reductions are the most important, for reasons outlined in Horowitz and Taylor, 2019. Coupland, N. J., Bell, C. J., & Potokar, J. P. (1996). Serotonin reuptake inhibitor withdrawal. Journal of Clinical Psychopharmacology, 16(5), 356–362. https://doi.org/10.1097/00004714-199610000-00003Demyttenaere, K., & Haddad, P. (2000). Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 101(s403), 50–56. https://doi.org/10.1111/j.1600-0447.2000.tb10948.xFDA. (2017). Label for PROZAC (fluoxetine) (Approved Drug Label Reference ID: 4036401). US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018936s108lbl.pdfFurukawa TA, Cipriani A, Cowen PJ, Leucht S, Egger M, Salanti G. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major	

						depression: a systematic review and dose-response meta-analysis. The Lancet Psychiatry. 2019;6(7):601–9.Groot, P. C., & van Os, J. (2021). Successful use of tapering strips for hyperbolic reduction of antidepressant dose: A cohort study. Therapeutic Advances in Psychopharmacology, 11, 20451253211039330. https://doi.org/10.1177/20451253211039327Hengartner, M. P., Schulthess, L., Sorensen, A., & Framer, A. (2020). Protracted withdrawal syndrome after stopping antidepressants: A descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125320980573Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry, 6(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-XJudge, R., Parry, M. G., Quail, D., & Jacobson, J. G. (2002). Discontinuation symptoms: Comparison of brief interruption in fluoxetine and paroxetine treatment: International Clinical Psychopharmacology, 17(5), 217–225. https://doi.org/10.1097/00004850-200209000-00002 Kondratenko, S. N., Savelyeva, M. I., Kukes, V. G., Shikh, E. V., & Gneushev, E. T. (2019). Experimental and Clinical Pharmacokinetics of Fluoxetine and Amitriptyline: Comparative Analysis and Possible Methods of Extrapolation. Bulletin of Experimental Biology and Medicine, 167(3), 356–362. https://doi.org/10.1007/s10517-019-04526-9Liston, H. L., DeVane, C. L., Boulton, D. W., Risch, S. C., Markowitz, J. S., & Goldman, J. (2002). Differential Time Course of Cytochrome	

						P450 2D6 Enzyme Inhibition by Fluoxetine, Sertraline, and Paroxetine in Healthy Volunteers. Journal of Clinical Psychopharmacology, 22(2). https://doi.org/10.1097/00004714-200204000-00010Meijer WEE, Bouvy ML, Heerdink ER, et al. Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. Br J Psychiatry 2001; 179: 519–522.Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, et al. Serotonin Transporter Occupancy of Five Selective Serotonin Reuptake Inhibitors at Different Doses: An [11C]DASB Positron Emission Tomography Study. Am J Psychiatry. 2004;161(5):826–35.NICE. (2021). NICE Guideline Depression in adults Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90 Rosenbaum, J. F., Fava, M., Hoog, S. L., Ascroft, R. C., & Krebs, W. B. (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. Biological Psychiatry, 44(2), 77–87. https://doi.org/10.1016/s0006-3223(98)00126-7 Schatzberg, A. F. (1997). Introduction/Antidepressant Discontinuation Syndrome: An Update on Serotonin Reuptake Inhibitors. The Journal of Clinical Psychiatry, 58 Suppl 7, 3–4.Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-wStahl, M. M. S., Lindquist, M., Pettersson, M., Edwards, I. R., Sanderson, J. H., Taylor, N. F. A., Fletcher, A. P.,	

						& Schou, J. S. (1997). Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. European Journal of Clinical Pharmacology, 53(3–4), 163–169. https://doi.org/10.1007/s002280050357Wernicke, J. F. (2004). Safety and side effect profile of fluoxetine. Expert Opinion on Drug Safety, 3(5), 495–504. https://doi.org/10.1517/14740338.3.5.495 Zajecka, J., Tracy, K. A., & Mitchell, S. (1997). Discontinuation symptoms after treatment with serotonin reuptake inhibitors: A literature review. The Journal of Clinical Psychiatry, 291–297. https://doi.org/10.4088/jcp.v58n0702Zajecka, J., Fawcett, J., Amsterdam, J., Quitkin, F., Reimherr, F., Rosenbaum, J., Michelson, D., & Beasley, C. (1998). Safety of abrupt discontinuation of fluoxetine: A randomized, placebo-controlled study. Journal of Clinical Psychopharmacology, 18(3), 193–197. https://doi.org/10.1097/00004714-199806000-00003	

191	SH	NHS England and Improvement	Guideline	17	48	May we suggest using the term “oral antipsychotic” to avoid the unintended use of depot antipsychotics	Thank you for your comment. There is no mention of antipsychotics on page 17 or a line 48, so it is not clear what exactly the comment refers to. However, we have clarified at the beginning of the section on use of antipsychotics that this relates to oral antipsychotics.
192	SH	The College of Mental Health Pharmacy	Guideline	17	General	Line 15, withdrawal symptoms are described as “common”. In treatment terms “Common” means >1 in 10.Withdrawal effects do not happen to >1 in 10 patients. Please re word, or add a specific incidence.	Thank you for your comment. The committee agreed that withdrawal effects would occur in at least 1 in 10 people and so decided that the use of the term 'common' was appropriate.
193	SH	Critical Psychiatry Network	Guideline	017-018	029-030, 001-002	We commend the advice (1.4.19) for iterating instructions to clinicians regarding reinstatement of the antidepressant should withdrawal symptoms be significant. It should be noted that the reinstatement need not be at the original dosage, but at a partial dose, the patient’s nervous system having somewhat adapted to a lower dose in the process of tapering. (Framer, 2021) After reinstatement, cliniciians and patients are often determined to proceed with the taper, possibly prematurely. To make this advice even clearer, suggest this advice readIf a person has more severe withdrawal symptoms, consider reinstating the original antidepressant medication at the last dosage prior to emergence of withdrawal symptoms (which may be lower than the original dose), and attempt dose reduction at a slower rate with smaller decrements after symptoms have resolved for a month or more. Framer, A. (2021). What I have learnt from helping thousands of people to taper off	Thank you for your comment. The recommendation advises restarting the antidepressant at the 'previous dose' not the original dose, so just stepping back up one step in the withdrawal process, not back to the beginning again. The recommendation already advises that smaller decrements should be used, so the recommendation has not been amended.

						antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274	
194	SH	Anxiety UK	Guideline	18	15	We feel that 4 weeks is too long to wait – we would recommend this be changed to 2 weeks.	Thank you for your comment. The recommendation advises 'as often as needed but no later than 4 weeks' so the committee agreed that in many cases an earlier review could be arranged, but that 4 weeks would be the maximum time. This is in addition to the 1- week review which is advised in the bullet point above this one.
195	SH	The College of Mental Health Pharmacy	Guideline	18	15	"4 weeks" this is too long.This should be 2 weeks if it is to be meaningful and help avoid worsening of depression and suicides. Studies show that patients commonly stop new medications within 10 days therefore waiting for 4 weeks to re-assess whether an antidepressant is helping or not is far too late. It is likely that they will have stopped it and therefore will have been untreated for several weeks. Please revise this advice to 2 weeks, and 1 week for younger people and those at high risk or self harm and/or suicide, as per the previous guideline.	Thank you for your comment. The recommendation advises 'as often as needed but no later than 4 weeks' so the committee agreed that in many cases an earlier review could be arranged, but that 4 weeks would be the maximum time. This is in addition to the 1- week review which is advised in the bullet point above this one.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

196	SH	Anxiety UK	Guideline	19	8	We welcome this as it is our experience that often there is little co-ordination between mental health & physical health conditions.	Thank you for your comment and support of these recommendations.
197	SH	NHS England and Improvement	Guideline	19	6	Antidepressant medication for older people would suggest mentioning falls	Thank you for your comment. The committee has added advice about being alert to the increased risk of falls into their recommendation.
198	SH	The College of Mental Health Pharmacy	Guideline	19	1.4.23	Antidepressants in older peopleExample given re hyponatraemia – should more detail for monitoring of sodium levels when starting antidepressants in this patient group not be included e.g. U&Es after 1 month.	Thank you for your comment. The committee agreed that in practice routine monitoring of U&Es would not always be necessary after 1 month, but they strengthened the recommendations relating to the risks of hyponatraemia.
199	SH	The College of Mental Health Pharmacy	Guideline	19	1.4.24	LithiumShould monitoring recommendation not be every three months – not “3-6 months” – given evidence that closer monitoring of lithium reduces risk of longer renal effects?	Thank you for your comment. The manufacturer advises that renal function be monitored but does not specify how often, the BNF advises every 6 months, and therefore the committee agreed that suggesting at least every 6 months or more often if there is evidence of renal impairment provided a balance between safety and excessive monitoring
200	SH	The College of Mental Health Pharmacy	Guideline	19	General	Also should not routinely start MAOIs	Thank you for your comment. The committee agreed that it would be extremely unlikely for an MAOI to be started in a person at risk of suicide and by adding this in it would detract from the important message about TCAs, and so they did not amend this recommendation.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

201	SH	The College of Mental Health Pharmacy	Guideline	19	General	Please add that older people take longer to respond to antidepressants.	Thank you for your comment. The committee did not agree that older people took longer to respond to antidepressants and so did not amend this recommendation to state this.
202	SH	The College of Mental Health Pharmacy	Guideline	19	General	"Use of lithium" please add that this should never be used as monotherapy in unipolar depression. It is an augmentation strategy that should be used alongside an antidepressant.	Thank you for your comment. The committee has amended the title of this section on lithium to clarify that it should be used for augmentation.
203	SH	The College of Mental Health Pharmacy	Guideline	19	General	"Use of lithium" please add that this should only be newly started by secondary care services.	Thank you for your comment. The recommendation advises that lithium prescribing should be managed under shared arrangements. However, this does not preclude it being initiated in primary care, with advice from specialists so the amendment you suggest has not been made.
204	SH	The College of Mental Health Pharmacy	Guideline	19	General	Requiring calcium levels every 3-6 months is not necessary. plus, this section is contradicted by 1.4.25 which says levels can be done as infrequently as every 6 months. Yet all other tests still need to be done 3 monthly – this doesn't make sense. Everything should be decreased to 6 monthly in stable medically well individuals – as per the bipolar NICE Guidelines.	Thank you for your comment. Recommendation 1.4.25 relates to monitoring lithium levels, not calcium levels so the 2 recommendations do not contradict each other. However, the committee agree that monitoring 6 monthly is in accordance with the BNF so have amended this to at least 6 monthly.
205	SH	The College of Mental Health Pharmacy	Guideline	20	General	First take a CVD history before doing an ECG	Thank you for your comment. The recommendation advises ECG monitoring in people with a high risk of, or existing cardiovascular disease, so taking a

							cardiovascular history would be necessary in all people to determine if this is the case.
206	SH	The College of Mental Health Pharmacy	Guideline	21	General	This point is helpful. But it makes a very interesting comparison to the huge emphasis placed on stopping antidepressants. Those on lithium as an augmentation strategy will be the much more severely depressed. So to give only 2 lines of guidance to this seems disproportionate to the 3 pages on with drawing antidepressants. There's no advice about the importance of maintaining the antidepressant or reviewing for signs of relapse in depression or follow up care.	Thank you for your comment. The committee agreed that lithium withdrawal would need guidance from specialist mental health services and would not be carried out without advice in non-specialist services or primary care, and therefore it was not necessary to include such detailed information on its withdrawal as antidepressants which would commonly be started and stopped in primary care.
207	SH	The College of Mental Health Pharmacy	Guideline	21	General	"Use of antipsychotics" please add that this should never be used as monotherapy in unipolar depression. They are always an augmentation strategy that should be used alongside an antidepressant. Only one antipsychotic should be used at a time.	Thank you for your comment. The committee have amended the title of this section to clarify that antipsychotics should be used for augmentation only. The committee did not agree that it was necessary to specify that only 1 antipsychotic should be used at any time.
208	SH	The College of Mental Health Pharmacy	Guideline	21	General	"Use of antipsychotics" please add that this should only be newly started by secondary care services.	Thank you for your comment. The committee agreed that managing antipsychotic prescribing under shared care arrangements was best practice and this does not preclude primary care services from starting or stopping antipsychotics with specialist advice.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

209	SH	The College of Mental Health Pharmacy	Guideline	21	General	Please give advice about the preferred antipsychotic options to use, either as an augmentation strategy or for psychotic symptoms. There are different indications and therefore choices and this requires advice.	Thank you for your comment. This section of the guideline provides over-arching advice on the use of antipsychotics and their monitoring. More specific advice on choice of individual drugs (where this was available from the evidence) is contained in later sections of the guideline on treatment for different stages and types of depression.
210	SH	Diabetes UK	Guideline	22	004-005	The recommendations on what to do if there is rapid or excessive weight gain due to the use of anti-psychotic medications also need to be expanded with further recommendations and signposting to NICE's weight management guidance documents 'Obesity Prevention' [CG43] and 'Weight Management: preventing, assessing and managing overweight and obesity'.	Thank you for your comment. The recommendation advises that excessive weight gain should be investigated and managed, but the committee agreed it would over-complicate the guideline to list the mitigating actions for all possible side-effects.

211	SH	Association for Family Therapy and Systemic Practice	Guideline	22	20	Rec 1.5 – We do not understand the rationale for the use of the terms 'less severe' and 'more severe' depression. Researchers and providers have typically categorised depression into three broad categories of mild, moderate and severe. The usage of new terms in these guidelines makes it difficult to understand how these guidelines can be helpfully mapped onto existing guidance and service provision models and is likely to create confusion.	Thank you for your comment. The committee considered the current NICE classifications of mild to moderate and moderate to severe depression, and agreed that although these classifications have been adopted quite widely there is potential uncertainty with regards to the management of moderate depression. The committee agreed that a dichotomy of less and more severe depression was clearer, and the guideline includes definitions (that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression includes the traditional categories of moderate and severe depression) in order to improve practical utility. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line presentations of depression are managed in primary care).

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

212	SH	Anxiety UK	Guideline	22	022 - 023	We feel it would be helpful to make it clear whose responsibility it is to do the active monitoring	Thank you for your comment. The active monitoring would be carried out by the healthcare professional who had discussed with the person their decision to not start treatment. This would usually be the person's GP but this has not been specified as it may be another professional.
213	SH	The College of Mental Health Pharmacy	Guideline	22	General	Making shared care mandatory again seems unhelpful, and not consistent with other guidelines such as those for schizophrenia. Furthermore this is less relevant now with ICSs, and is commonly not relevant for this patient group for whom antipsychotic use may be relatively short term.	Thank you for your comment. The committee agreed that managing antipsychotic prescribing under shared care arrangements was best practice and so they have not amended this recommendation. However, this does not preclude primary care services from starting or stopping antipsychotics with specialist advice.
214	SH	The College of Mental Health Pharmacy	Guideline	22	General	Heading, confusingly this heading is virtually repeated on page 23 line 10.	Thank you for your comment. The repeated heading has been amended to 'treatment options'
215	SH	The College of Mental Health Pharmacy	Guideline	22	General	This section is hard to follow, doesn't flow well.Doesn't seem to cover the other health advice that needs to be provided concurrently eg about sleep hygiene, healthy eating and exercise, not over using alcohol, relationships and daily activities.	Thank you for your comment. Based on stakeholder feedback, a new recommendation has been added to the guideline that covers these other healthy-living topics.

216	SH	Critical Psychiatry Network	Guideline	022-030	General	Whilst we welcome the committee's approach of recommending a variety of psychosocial interventions, and not prioritising drug treatment in less severe depression, we suggest that the committee should clearly suggest that antidepressants are not indicated in this situation, based on the committee's own review and other data on adverse effects that was not taken into consideration which is detailed below. In brief, antidepressants did not demonstrate statistically significant differences from treatment as usual (TAU) in any analysis presented for less severe depression. The analysis of cost effectiveness was conducted for antidepressants on the suspect premise that they showed a difference from TAU despite this difference not being statistically significant – that is, a treatment that was not shown to be effective was evaluated for cost-effectiveness. The study upon which this cost-effectiveness analysis was based did not show a clinically important difference for sertraline over placebo, amongst numerous methodological flaws. The adverse effects of medication in particular were not adequately evaluated in terms of balance of harms and benefits (which were assumed to be weighted towards benefit) and cost effectiveness due to relying on an unrepresentative single paper. Furthermore a neglect of the full costs of stopping antidepressants was neglected, in terms of personal loss of health and healthcare costs, using an inadequate four weeks of linear tapering as the model.The committee seems to have been inclined to prioritise existing clinical practice over the evidence produced by their own review so that antidepressants, despite not demonstrating	Thank you for your comment. This comment repeats points you have already made in another related comment of yours, about antidepressants, evidence review B and recommendations on the treatment of a new episode of less severe depression. Please refer to the full response to your other related comment as it is directly relevant to this comment too.

						effectiveness in any analysis, were recommended. This present practice-bias also seems to have informed including treatments that patients would 'prefer' despite this preference being based not on sound evidence but on historical medical practice, not the usual basis for making evidence based recommendations. The inclusion of antidepressants as an alternative treatment to those who do not prefer other (evidence-based) treatment is likely to have ramifications to an outsized degree. As current clinical practice commonly includes giving antidepressants, the inclusion of antidepressants as an option is likely to mean that they are used more often than intended, with the perverse outcome that a treatment that did no demonstrate efficacy (or if relying on the short-term PANDA study, marginal efficacy beneath the considered clinically important) in an irrelevant time period, with a host of adverse effects, that have not been adequately accounted for, will end up being used in preference to other safe and effective treatments. These points are elaborated further below:Lack of effectiveness for antidepressants in less severe depression in any analysis conductedSpecifically for effectiveness there was no effect when looking at SMD of depression scores (Table 3, page 21, Evidence Summary B), in terms of response (Table 6, page 28, Evidence Summary B), there was no data on remission (Table 8, page 30, Evidence Summary B), in bias-adjusted analysis of depression score change (Table 9, page 32, Evidence Summary B), there was no data on long term follow up for important outcomes examining antidepressant versus a control (Table 12, page 38, Evidence Summary B) or for 'critical' outcomes	

						(Table 13, page 39, Evidence Summary B) and no evidence looking at pairwise effects (Table 14 and 15, page 40). Overall, therefore there was no analysis that found that antidepressants were more effective than TAU for less severe depression presented. Reliance on a methodologically flawed single study for evaluation of cost-effectiveness which did not demonstrate minimum clinically important differences for its primary outcomeThe committee evaluated the cost effectiveness of treatments that did not demonstrate clinical effectiveness in their own analysis or in the paper from which the cost effectiveness data was extracted. As above no analysis for less severe depression demonstrated a statistically significant or clinically important difference for antidepressants when compared to TAU. The committee seems to have used the PANDA study published as Lewis et al (2019) with economic analysis published as Hollingworth et al (2020) to derive cost-effectiveness for sertraline. However, this study suffers from more than the 'minor limitations' designated. This study found marginal differences of patients assigned to sertraline rather than placebo (13% reduction in PHQ-9 score, 95% CI 3% to 21%). The change in the primary outcome of depression score (PHQ-9) was 4.89 points in the sertraline group and 4.18 in the placebo group. The difference in change between the two groups was 0.8 points on the 27-point PHQ-9 scale. The minimum clinically important difference for PHQ-9 has been calculated as 3.0 (Lynch et al 2021) or 5.0 points (Lowe et al 2021). A change of 0.8 points does not meet the threshold for a minimally clinical important difference. This corresponds to an effect size of 0.18	

						(Hengartner et al 2020a), which is below the threshold NICE designated for minimum effect size of 0.5. Effects on anxiety were similarly small (effect size <0.25) (Hengartner et al 2020a). This was not evaluated by the committee because cost-effectiveness data was extracted from this study without first evaluating whether this was treatment produced a minimally clinically important difference. It is unclear why a single study was prioritised over the extensive analysis performed by NICE. Furthermore, unblinding was an issue in the PANDA study and may have exaggerated differences in the two groups due to expectation effects for those assigned to sertraline – 81% of patients correctly guessed they were assigned to placebo and 46% correctly guessed they were assigned to sertraline (Hengartner, 2020a). There was also a lack of power to detect adverse effects, such as suicidal behaviour, cardiovascular events or hepatotoxicity which are recognised for antidepressants, which was therefore not considered in cost-effectiveness data – and the difficulty and costs of stopping sertraline was not taken into account in this calculation (Hengartner, 2020a). Patients were also only excluded if they had used antidepressants in the previous 8 weeks so some participants may have had antidepressant withdrawal symptoms at baseline, artificially exaggerating the beneficial effect of commencing sertraline which would resolve these symptoms, likely to register on symptom scales for anxiety and depression. Prioritisation of short symptom changes over long term quality of life and functioning outcomesFurthermore, less useful data was prioritised by the committee – although the committee recognised that long-	

						term studies and quality of life and functioning were more important than short term or symptom score reductions, because there was more information for the latter evaluation of effectiveness was made on short term symptom scores; long-term outcomes, including quality of life and functioning scores (which found large effects for a number of treatments) were neglected. It does not seem reasonable to prioritise less relevant data simply because it exists in greater quantities. This risks extrapolating recommendations for long-term treatment based on short term studies with outcomes that may be irrelevant to long-term benefits to patients. We recommend that if the committee does nothing else that it at least include in its research recommendations that studies evaluating treatment for depression should be conducted over relevant time periods (e.g. 1-2 years or longer) and evaluating the most relevant outcomes for patients of quality of life and functional status. Derivation of long-term treatment recommendations from short term studiesShort term studies of antidepressants are particularly ill suited to extrapolate to long-term recommendations because long term studies find much less promising results than short term studies – for example 3.7% of patients in the STAR-D trial at one year were free of relapse and did not drop out of the study (Pigott et al, 2010). Some authors have suggested poorer long term outcomes may result from tolerance (Kinrys et al, 2019). Use of unsuitable data for evaluating harms If despite the lack of demonstrated effectiveness of antidepressants in less severe depression, the committee still chooses to consider their cost-effectiveness, there remains an	

						alarming lack of consideration for the full extent of the harms (and therefore the cost of the harms) of this medication class. A single study looking at just 5 adverse effects (Anderson et al 2012) was used to estimate adverse effects for antidepressants to estimate their costs. This study retrospectively evaluated a commercially available national database used for making claims for payments. In other words, this database relied on clinicians to enter side effects using an ICD-9-CM diagnostic code into the medical records of patients during antidepressant use to make a claim from a healthcare provider in the USA. This is a very high threshold to determine that an adverse effect is having a significant effect on a person. As the authors of the study says “data from medical claims are subject to a considerable degree of under-detection because fewer patients may actually go to a doctor for these particular symptoms” (p.119, Anderson et al 2012). The authors go on to say “More general estimates of the occurrence of side effects associated with SSRIs are higher: increased agitation in up to 20% of users, nausea in up to 20%, sedation in up to20%, and sexual dysfunction in up to 20% (Whooley and Simon, 2000)” The authors further emphasise the “relatively low sensitivity of medical claims data for detecting these side effects at their true rates in treatment settings” (p.122, Anderson et al 2012).Marked under-estimation is clearly evident when examining the results derived as in Table 80 on page 316 of Evidence Summary B. An estimation that 0.07% of people on SSRI, 0.09% of people on SNRIs and 0.06% of people on mirtazapine will develop more than one side effect is implausible. For instance, on the SPC	

						for citalopram, https://www.medicines.org.uk/emc/product/5737/smpc#gref the most commonly used antidepressant in England there are 8 adverse effects that are 'very common' (occur in more than 10% of patients), including sleep disorder, somnolence, insomnia, headache, increased sweating and asthenia, 33 adverse effects which are 'common' (occur in 1% -10% of patients), with many more rarer adverse effects. Studies find rates of treatment-emergent sexual dysfunction of 30-60% in patients on SSRIs (Gregorian et al 2002). These values do not seem at all consistent with the reported estimate of 0.07% of SSRI users will experience a side effect. It has also been found that adverse effects are more common in longer term users of antidepressants than in the short term RCTs from which the SPC data is partially derived (Bet et al. 2013), with further details of incidence rates from this study in the response to Evidence Summary B below (which are often more than two orders of magnitude greater than that derived from Anderson et al. 2012). Additional costs of withdrawal or not being able to stop antidepressants not take into accountWhile there is no cost associated with stopping many of the non-pharmacological treatments outlined in this guidance, there is considerable costs to stopping antidepressants as outline in this guidance, which is not included in the cost-analysis. There are costs to people's wellbeing and there are costs to the health care system. In the first category there are the costs of time off work, inability to perform social roles such as caring for children or elderly dependents, and in some people long-standing inability and suicide (Guy et al, 2020; Hengartner et	

						al 2020b). Additionally there are the costs to the health care system – which include increased visits to the doctor, the requirement to prescribe liquid versions of medication and increased monitoring throughout the process which can take months and in some patients years. For example the prescription of liquid mirtazapine for 2 years to help someone stop their medication (a common time period) can cost 24*80 = 1920 pounds. Other medications are cheaper than this but extra costs should be taken into account in the cost-effectiveness analysis. The overview of this process was given in Evidence Summary B, page 324 that: "Acute pharmacological treatment was administered over 12 weeks. At the end of this period, adults with less severe depression who achieved remission had their drug gradually discontinued (tapered); this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over the period of one month (according to routine clinical practice, as advised by the committee)."This is not an accurate summary of the process of stopping – the committee's own recommendation is that patients stay on antidepressant for several months for an episode so 12 weeks is an under-estimation of the costs. Consequently the time required for stopping drugs is also under-estimated as it might take several months for a patient to stop a drug tolerable and linear reduction over 4 weeks has never been demonstrated to be effective for patients on anything but extremely short term treatment. This section therefore under-estimates the time and resources required for stopping these medications. Furthermore, there will also be a group of people for whom coming off their	

						antidepressant will be too aversive because of the withdrawal effects and who will then continue to use this medication for several years or the rest of their lives, leading to unnecessary medication costs, as conservatively estimated in Davies et al, 2021. A study looking at stopping unnecessary antidepressants found that 93% of patients were unable to stop (Eveleigh et al., 2017). The REDUCE study in England is aiming to help 20% of patients stop unnecessary antidepressants, meaning that 80% of patients on unnecessary antidepressants will stay on their medication for years or perhaps life long. This will lead to considerable unnecessary costs to the health system and exposure to adverse effects to patients. The near certainty that a large proportion of people will continue their medication beyond what guidelines recommend should be taken into account. Given the potential for extensive harms from antidepressants we do not think that the conclusion of the committee on page 60, line 42-44 of Evidence Summary B “However, thecommittee agreed that the potential benefits of treating depression were likely to outweighthe potential harms” is warranted. As this section of the evaluation is concerned with mild depression, unlikely to have severe consequences for sufferers, and for which antidepressants have not been shown to have a clinically important difference, whilst the adverse effects of antidepressants, much more extensive than acknowledged by the committee will be the same for people with mild or severe conditions, we do not share the confidence of the committee that benefits will ‘likely’ outweigh harms, and implore the committee to more	

						carefully evaluate harms, weighting and costing them appropriately. Inclinations to support existing clinical practice over evidenceA bias to cultural inertia, whereby treatments currently given, would tend to be favoured seems to be evident in the deliberations of the committee. This seems to explain why antidepressants which did not demonstrate efficacy in any analysis for less severe depression were recommended. It also underpins the notion of the committee that treatments should be offered because patients 'prefer' them, discussed further below. An inclination of the committee to support currently existing practice seemed to play an unusually strong role in making decisions about what to include in the recommendations to the point that the NICE Technical Support Unit were unable "to identify a clear decision rule to link the recommendations directly to the NMA results" (lines 15-16, page 58, Evidence summary B) so that they were unable to conduct a threshold analysis to account for uncertainty. This indicates the degree to which the NICE committee introduced subjective judgements to make decisions about what to include. The evidence review is explicit that the judgement relied on the members 'clinical experience' and 'need for inclusivity' (line18-19, page 58, Evidence summary B). Given that NICE is supposed to present objective data it is concerning that objective data was over-ruled by a potential over-reliance on particular clinicians' experiences. It is also unclear how 'inclusivity' was utilised as a criterion in the provision of options for medical treatment when it seems to have been used primarily to include antidepressants despite a lack of evidence for their inclusion.	

						In Lines 24 -34 on page 62 of Evidence B, it says: "The committee also discussed the role of pharmacological therapy in the treatment of less severe depression – the clinical results for depression symptoms had been similar to those seen for the psychological therapies, and the cost-effectiveness results had shown that both SSRIs and TCAs were likely to be cost-effective (they were placed 3rd and 4th in the cost-effectiveness ranking respectively). In addition, there may be people who do not wish or are not able to participate in a psychological or physical therapy, may prefer a pharmacological treatment, or would like to commence pharmacological treatment if there is a wait before they can commence another treatment. Based on these discussions, the committee recommended SSRIs as an alternative treatment, as these were generally better tolerated and safer than TCAs (italics added)."This rationale for recommendations does not seem reasonable. SSRIs had not shown significant differences from TAU on depression scales (SMD), response rate and no remission data was found. For QoL and functioning there was no data. Yet it was considered by the committee that there was similarity in effectiveness to other treatments. Furthermore, the committee decided that people who would not be motivated to use effective and cost-effective treatments like CBT or BA should be offered an alternative. It does not seem possible that a treatment which is not effective can be a suitable alternative treatment to treatments which are. Additionally, the idea of patients preferring a pharmacological treatment as a rationale for offering this as an alternative is not a convincing reason for	

						including this recommendation. Any preference that a patient might have for an antidepressant is based on existing cultural practice (not to mention the cultural saturation with messages that antidepressants are effective from multiple sources). To include antidepressants as an alternative treatment based on the sentiment of the public seems contrary to the purpose of NICE's evidence reviews to provide treatments that are objectively effective. Whilst many patients may prefer opioids for pain the committee making recommendations on the management of primary pain did not recommend opioids just to satisfy public wishes, but objectively evaluated their benefits and harms. The same analogy might apply to the wish for patients to have upper respiratory symptoms treated with antibiotics. Furthermore, the consideration that people might want to take an antidepressant while they wait for therapy does not seem the purview of this committee whose stated purpose is recommend clinically effective and cost effective treatments for less severe depression. It does not seem reasonable to recommend an ineffective treatment simply because the waitlist for an effective treatment is too long. The inclusion of antidepressants as an alternative treatment is likely to have ramifications to an outsized degree. As practice commonly includes giving antidepressants, the inclusion of antidepressants as an option is likely to mean it is used more often than intended, with the perverse outcome that a treatment that did no demonstrate efficacy (or if relying on the short-term PANDA study, marginal efficacy beneath the considered clinically important) in an irrelevant time period, with a host of adverse effects that have not been adequately	

						accounted for, will end up being used in preference to other safe and effective treatments. Bet PM, Hugtenburg JG, Penninx BWJH, Hoogendijk WJG. Side effects of antidepressants during long-term use in a naturalistic setting. Eur Neuropsychopharmacol. 2013 Nov;23(11):1443–51.Davies J, Cooper RE, Moncrieff J, Montagu L, Rae T, Parhi M. The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications. Addict Behav. 2021;107143.Fornaro M, Anastasia A, Novello S, Fusco A, Pariano R, De Berardis D, et al. The emergence of loss of efficacy during antidepressant drug treatment for major depressive disorder: An integrative review of evidence, mechanisms, and clinical implications. Pharmacol Res. 2019 Jan;139:494–502.Gregorian RS, Golden KA, Bahce A, Goodman C, Kwong WJ, Khan ZM. Antidepressant-induced sexual dysfunction. Ann Pharmacother. 2002 Oct;36(10):1577–89.Guy A, Brown M, Lewis S, Horowitz MA. The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition. Therapeutic Advances in Psychopharmacology. 2020 Jan 9;10:204512532096718.Hengartner MP, Plöderl M, Braillon A, Jakobsen JC, Gluud C. Sertraline in primary care: comments on the PANDA trial. Lancet Psychiatry. 2020 Jan;7(1):17.Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan	

						1;10:2045125320980573.Kinrys, Gustavo, Alexandra K. Gold, Vincent D. Pisano, Marlene P. Freeman, George I. Papakostas, David Mischoulon, Andrew A. Nierenberg, and Maurizio Fava. 2019. "Tachyphylaxis in Major Depressive Disorder: A Review of the Current State of Research." Journal of Affective Disorders 245 (October 2018): 488–97.Lerner, Alicja, and Michael Klein. 2019. "Dependence, Withdrawal and Rebound of CNS Drugs: An Update and Regulatory Considerations for New Drugs Development." Brain Communications, no. 2019 (October). https://doi.org/10.1093/braincomms/fcz025.Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care. 2004 Dec;42(12):1194–201.Lynch CP, Cha EDK, Jenkins NW, Parrish JM, Mohan S, Jadczak CN, et al. The Minimum Clinically Important Difference for Patient Health Questionnaire-9 in Minimally Invasive Transforaminal Interbody Fusion. Spine. 2021 May 1;46(9):603–9.Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: Current status of research. Psychother Psychosom. 2010;79(5):267–79.Solomon, David A., Andrew C. Leon, Timothy I. Mueller, William Coryell, Jedediah J. Teres, Michael A. Posternak, Lewis L. Judd, Jean Endicott, and Martin B. Keller. 2005. "Tachyphylaxis in Unipolar Major Depressive Disorder." The Journal of Clinical Psychiatry 66 (3): 283–90.	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

217	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	23	18	We support the inclusion of a range of treatment options as first-line treatments for less severe depression.	Thank you for your comment and support of these recommendations
218	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	23	18	The inclusion of Mindfulness Based Cognitive Therapy (MBCT) in this section is welcome and rightly recognises the evidence that MBCT is effective for people experiencing a current episode of depression.	Thank you for your comment and support of these recommendations

219	SH	NHS England and Improvement	Guideline	23	21	Add social prescribing (Treatment options for less severe depression listed)Wonder if there is capacity within SP services for this currently? Shared Decision Making and PHBs should also be recommended as part of the 'supported self-management' option.	Thank you for your comment. The committee did not have evidence for social prescribing so did not agree to include them in the table of suggested interventions, but considered they would be included in the references to 'other agencies' which are referenced from several places in the guideline. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental

							wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness). Shared decision making was not considered as a stand-alone intervention but the committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion.
220	SH	NHS England and Improvement	Guideline	23	23	Table 1 SSRI's (antidepressants) – key features- Change from the brain -to brain and the body – "these treatments may effect chemicals throughout the brain and body "(it is important to recognise the widespread impact of these drugs	Thank you for your comment. The mode of action of SSRIs is to modify neuronal transmission in the brain, so to keep the information in line with the information supplied for psychological interventions we

						in order to address concerns about side effect/unwanted effects)	have not added this detail. The 'other things to think about' column already provides information on potential side-effects and withdrawal.
221	SH	NHS England and Improvement	Guideline	23	23	Rec 'Table 1: Treatment Options for Less Severe Depression', for the 'self-help, with support' treatment, under the 'How is it delivered section', we recommend adding referral to a social prescribing link worker	Thank you for your comment. The committee did not have evidence for the role of social prescribing link workers so did not agree to include them in the table of suggested interventions, but considered they would be included in the references to 'other agencies' which are referenced from several places in the guideline.
222	SH	NHS England and Improvement	Guideline	23	23	Ref: 'Table 1: Treatment Options for Less Severe Depression', we recommend that 'nature-based activity' or 'green social prescribing' is offered as a treatment option beneath group exercise.Current review of evidence: 'Nature-based outdoor activities for mental and physical health: systemic review and meta-analysis', P Coventry et al, Oct 21 ********As stated in the guidance about referral to group physical exercise, the same reasonable adjustment considerations will apply, to ensure access.	Thank you for your comment. Nature-based interventions were not specified in any of the review protocols and thus specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, in response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not as a treatment for depression) and made a new recommendation to reflect this. The recommendation also emphasised the benefits of outdoors activities. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be

							physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).
223	SH	NHS England and Improvement	Guideline	23	23	Ref: 'Table 1: Treatment Options for Less Severe Depression', we recommend that 'arts based activity' or 'creative health social prescribing'' is offered as a treatment option beneath group exercise****Review of evidence: WHO Arts and Health Review	Thank you for your comment. Art therapy was listed as an intervention of interest for the treatment reviews. However, no eligible evidence was identified for art therapy as a first-line treatment. The only included study for art therapy (Nan 2017) was in the further-line treatment review. The committee considered the evidence too limited to make a recommendation for art therapy. Evidence for social prescribing was not sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might

							benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

224	SH	UK Council for Psychotherapy	Guideline	23	23	Table 1 Please include behavioural couples therapy in this table and the visual summary since it appears the decision to leave it out was in part based on an incorrect assumption that it is more or only appropriate for a subgroup of people with depression and studies were excluded from the research evaluation on this basis. This intervention is in the guidelines but, if excluded from the tables and visual summaries, is very unlikely to be considered as an option. Options such as counselling and STPP were included as the committee recognised that these treatments, although with less evidence of effectiveness, may be helpful for some people. This argument also applies to behavioural couples therapy. The committee agreed this treatment was available through the Improving Access to Psychological Therapy (IAPT) services and should be included as an option in the guideline but if listed in isolation and not in the table and visual summary there is a real risk it will be overlooked by commissioners and providers. Behavioural couples therapy is the only family-inclusive therapy option listed and may be of particular value to some minority ethnic and cultural groups who may find it harder to engage with services and do not all share individualistic Western values. Couple therapy by definition involves the partner of the person with depression. Carers often feel ignored by healthcare professionals in decisions about their loved ones and want to be involved in discussions about treatment options (Healthwatch, 2020). Couples therapy for depression should be more widely available to depressed people to help reduce the burden on partners and potentially prevent relationship breakdown (Priestley, J and McPherson,	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to include behavioural couples therapy in the tables or visual summaries of treatment options in the guideline as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with depression, unlike the other interventions listed in these tables/visual summaries. There is a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include: services delivered in culturally appropriate or culturally adapted language and formats; and procedures to

						SJ and Davies, F (2018) Couples Disease: The Experience of Living with a Partner with Chronic Depression. Journal of Couple and Relationship Therapy, 17 (2). 128 - 145. ISSN 1533-2683).If couples therapy is not included in the tables and visual summaries, it will be much less likely to be considered as an option for people with depression, and people from black, Asian and minority ethnic communities, and carers, will be negatively impacted in particular. It is very important that the choice of couples therapy alongside individual and group interventions is made more widely available within NHS services. The NHS constitution states that services should work in partnership with patients their families and carers.	support active involvement of families, partners, and carers. There are also recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend.

225	SH	Association for Family Therapy and Systemic Practice	Guideline	23	23	Table 1 – AFT members have noted the exclusion of systemic therapies and particularly behavioural couples therapy in this table, table 2 and the visual summary.It appears the decision to exclude behavioural couples therapy from the table despite being recommended in the guidelines is in part based on the incorrect assumption that this treatment is more or only appropriate for a subgroup of people with depression (who have relationship difficulties) and studies were excluded from the research evaluation on this basis. If excluded from the tables and visual summaries, behavioural couples therapy is unlikely to be considered as an option despite being available through the Improving Access to Psychological Therapy (IAPT) services. Furthermore, there is a real risk it will be overlooked by commissioners and providers. Treatment options such as counselling and STPP have been included in the visual map as the committee recognised that these treatments, although with less evidence of effectiveness, may be helpful for some people. If couples therapy is not included in the tables and visual summaries, it will be much less likely to be considered as an option for people with depression, and people from black, Asian and minority ethnic communities, and carers, will be negatively impacted in particular. It is very important that the choice of couples therapy alongside individual and group interventions is made more widely available within NHS services. The NHS constitution states that services should work in partnership with patients their families and carers.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to include behavioural couples therapy in the tables or visual summaries of treatment options in the guideline as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with depression, unlike the other interventions listed in these tables/visual summaries. There is a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include: services delivered in culturally appropriate or culturally adapted language and formats; and procedures to

							support active involvement of families, partners, and carers. There are also recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend.
226	SH	Talking Therapies	Guideline	23	General	Throughout the guidance, although more pertinent from this point forwards, there is not a clear differentiation between what are step 2 (low intensity) and step 3 (high intensity) treatments, which there was in the previous (2009) guidelines. Please can the stepped care model be clearly identified and implemented throughout depression guidelines.	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

227	SH	Care To Listen	Guideline	23	Table 1	We welcome the inclusion of counselling as a treatment for less severe depression. We feel the definition/description of counselling is reasonably accurate. We would like to see the timings reflect counselling practice in that counselling sessions tend towards 50 minutes rather than an hour and confusion around this might be felt by clients who read this guidance.	Thank you for your comment. The suggested duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of interventions.

228	SH	Stakeholder coalition	Guideline & Evidence Review B	23031	Table 1Table 2Visual summary 1 & 2	Service-user choice and shared decision-makingThe results of the NMAs and cost analysis for individuals with first episode of depression showed that the treatments included in this synthesis were all found to be clinically effective. Furthermore, the economic models overall show high levels of uncertainty related to the relative effectiveness and cost effectiveness of all the interventions, including a very high degree of uncertainty about estimates of cost. This is expressed in the relatively modest difference in overall quality of life gains, cost per QALY gains, and net monetary benefits between most interventions, and wide 95% credible intervals (CIs)around their mean rankings. In other words, all included interventions have been found to be cost effective. Notwithstanding the methodological concerns pertaining to these analyses, these findings stress the need to offer a menu (non-ranked) of treatment options to be made available.With respect to this, we suggest that the text, the tables within the document and the helpful visual summaries be amended accordingly. Interventions could be displayed in alphabetical order.Given the rising demand for mental health services, particularly in the wake of the wider impacts of the pandemic, and considerable waiting times for treatment in parts of the UK, it has never been more important to ensure that evidence-based support is available to whoever needs it. This guideline has a direct, real-world impact on centralised NHS workforce planning, as well as localised decision making by commissioners. Given NICE's assessment that all the listed treatments are clinically and cost-effective, removing the hierarchical ranking of treatments is a simple way to enable	Thank you for your comment. Although NMA and economic results were characterised by uncertainty, they did not suggest that all treatments were similarly clinically and cost-effective. For example, in less severe depression, the effect of group CT/CBT class vs TAU (based on an evidence base of N=480) was -1.01 (95%CrI -1.76 to -0.06), whereas the respective effect of counselling (based on a narrower evidence base of N=55) was -0.20 (95%CrI -2.82 to 2.50), i.e. one fifth of the effect of group CT/CBT class, although both treatments were recommended – see bias-adjusted results in Table 9, evidence report B. Similarly, in more severe depression, the effect of individual CT/CBT + AD class vs placebo (based on an evidence base of N=192) was -1.18 (95%CrI -2.07 to -0.44), whereas the respective effect of IPT (based on an evidence base of N=145) was -0.45 (95%CrI -1.36 to 0.47), i.e. almost a third of the effect of individual CT/CBT + AD class – see bias-adjusted results in Table 24, evidence report B. Regarding clinical effectiveness derived from the NMAs, the committee considered not only the mean effects of treatment classes vs the reference treatment, but the uncertainty around them

						capacity-building in the NHS mental health workforce, which is required to meet rising demand, as well as offering commissioners' greater flexibility in assessing both the needs of a local population and the immediate local workforce capacity. This would not preclude the Guideline from commenting on the relative strength of evidence for different treatments.As pointed out above, we strongly welcome the stronger focus on individualised care and the emphasis on the importance of service user choice and shared decision-making throughout this third iteration of the treatment guideline. This could be a hugely positive step forward in patient care. We welcome the recognition in the guideline that any additional resource invested in longer consultations with service users to have a meaningful discussion around treatment options will be repaid through greater adherence and better outcomes. However, we remain concerned that through not addressing some of our key methodological concerns, this guideline will still be falling short of achieving that goal in practice. As pointed out by utilising very stringent inclusion criteria, many studies that have shown to provide an evidence base for many interventions were not considered. We notice, for example, the omission and therefore non-recommendation of family therapy, couple therapy for depression, and the creative therapies, which many service users may benefit from (e.g. Albornoz, Y., 2011; Baucom et al., 2018; Nan & Ho, 2017;), and may want to choose. We also notice the absence of longer-term psychological treatments. Research and clinical practice have shown that many individuals with chronic or complex forms of depression have tried the available and	(as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of pairwise meta-analysis of follow-up data and additional outcomes (functioning and quality of life). Regarding cost-effectiveness, highly ranked interventions in the guideline economic analysis were more cost-effective than interventions lower in ranking, although there was uncertainty in the results and differences might be small in some cases (especially for interventions in close ranking places). Some interventions were found to be less cost-effective than GP care (reference treatment) in less or more severe depression (or both). For example, counselling was found to be less cost-effective than GP care in less severe depression, IPT was found to be less cost-effective than GP care in more severe depression, and short-term psychodynamic psychotherapy was found to be less cost-effective than GP care in both less and more severe depression. Based on these findings,

						recommended first or second-line short-term treatments without success (e.g. Leichsenring & Rabung 2011; Maj et al. 2020). In complex mental disorders, longer-term psychotherapy proved to be superior to short-term psychotherapy (Leichsenring & Rabung, 2011, Leichsenring et al., 2013). However, in the guideline the recommendation for those classified as having treatment-resistant depression, chronic depression, and depression with PD defaults back to first or further-line treatment recommendation - i.e. once again to a short-term treatment, instead of recommending a longer-term treatment. This is particularly perplexing as there is evidence of the effectiveness of longer-term treatments, both for long-term CBT (e.g. Leuzinger-Bohleber et al., 2019) and long-term psychodynamic psychotherapy (e.g. Fonagy et al., 2015; Leuzinger-Bohleber et al., 2019; Knekt et al., 2008/2013/ 2016) for individuals diagnosed with treatment-resistant/chronic depression.Although the Leuzinger-Bohlehber et al (2019) study was excluded from the chronic depression review as >20% had previous treatments, it should have been included under the further-line treatment review. We also cannot find any reason as to why the Knekt study (2008, 2013, 2016) was also not included there. Although the Fonagy et al., 2015 study was included, their important findings that both depression severity and functioning improved over the long-term have been ignored. All three studies not only provide important evidence of the effectiveness of long-term treatment, but moreover that the effects sustained over a 2–3-year follow-up. Given the scarcity of studies on longer-term psychological treatments, the	the committee considered appropriate to rank recommended treatments taking into account clinical and cost-effectiveness as well as other issues such as side effects (antidepressants), applicability of the evidence (e.g. for individual problem solving), structure of IAPT services, but also taking account of patient clinical needs and preferences. Interventions are arranged in Tables 1 and 2 of the guideline in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice.

						omission of those is futile.As a consequence, all recommended treatment options are brief interventions (with an average of 8 sessions). As pointed out above, given that these have already been shown to be non-beneficial for many individuals who experience more persistent and complex depression, we are not only concerned that this guideline may exacerbate the existing revolving-door problem, but would also deny people the choice of longer-term treatments.	The committee expressed the view that listing interventions in alphabetical order would not reflect the evidence base nor serve as a guide to choose for those who do not have pre-existing preferences. Considering cost-effectiveness issues when making recommendations ensures most efficient use of NHS resources and maximum health gains for the whole population. Prioritisation of treatments according to cost-effectiveness benefits not only the patient receiving the selected treatment but other patients whose needs must be covered by existing NHS resources. Nevertheless, the guideline also recommends shared decision on treatment choice, based on patients' clinical needs and preferences. It is reassuring that you acknowledge and agree with the stronger focus of the guideline on individualised care and the emphasis on the importance of service user choice and shared decision making. The committee were aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were

							stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agreed that it would be more consistent to name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations. Albornoz 2011 is included in the network meta-analysis for the treatment of a new episode of more severe depression. However, this was the only included study for music therapy, and the committee considered the evidence too limited to make a recommendation. Nan 2017 is included in the further-line treatment review. However, this was the only included study for art therapy, and the committee considered the evidence too limited to make a recommendation.

							As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The Baucom et al. (2018) study was not appropriate for inclusion in the review as it was not a randomised controlled trial. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions. The further-line treatment recommendation

							that cross-refers to psychological treatment options for more severe depression is for people whose depression has had no or a limited response to treatment with antidepressant medication alone. There was no evidence that specifically examined switching to a psychological intervention for those who have not responded to initial antidepressant treatment, however, the committee drew on the evidence for first-line treatments in more severe depression. The committee agreed that the psychological interventions that had been identified as effective and cost-effective for first-line treatment of more severe depression could be used for people who had not responded to antidepressants and wished to try a psychological therapy instead. Leuzinger-Bohleber et al 2019 was considered for the chronic depression review and was excluded. This study also did not meet eligibility criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line treatment, participants were not randomised at the point of non-response,

							and it could not be regarded as an augmentation study following limited or no response to antidepressants as only 36% of participants were taking antidepressants at baseline. This study has now been added to the excluded studies list in supplement D. Knekt et al 2008/2013/2016 was considered under first-line treatment as detailed in your comment, and did not meet criteria. It also did not meet criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line treatment (in fact those receiving psychotherapy within the previous 2 years were excluded), participants were not randomised at the point of non-response, and it could not be regarded as an augmentation study following limited or no response to antidepressants as only 22% of participants were receiving psychotropic medication at baseline. This study has now been added to the excluded studies list in supplement D. There was only single-study evidence (Fonagy et al. 2015) for augmenting antidepressant treatment with long-term psychodynamic psychotherapy, and the

							committee considered the evidence too limited to make a recommendation for long-term psychodynamic psychotherapy specifically. However, a treatment option in the recommendation for people whose depression has had no or a limited response to treatment with antidepressant medication alone, includes changing to a combination of psychological therapy and medication, which could include long-term psychodynamic psychotherapy although it is not listed as an example due to the limited evidence.

229	SH	Society for Psychotherapy Research	Guideline	23031	Table 1Table 2Visual summary 1 & 2	We are concerned that the treatments in these Tables and in the accompanying text throughout this document, including the two visual summaries provided separately, are hierarchically ordered even though not a single treatment included in these analyses have been proven more clinically effective or indeed more cost-effective. We notice that some interventions are highlighted as “more effective” or “more cost effective” compared to other interventions in various places of the guideline documents and review evidence B, which is misleading given the findings reported and ask for this to be amended.We strongly advise that the hierarchy of treatment options for first-line and ‘more severe’ depression must be replaced with a menu (non-ranked) on the basis that (1) there is no evidence that the treatments are differentially effective in any clinically meaningful way on the basis of the NMA analyse; (2) the economic analyses are – by admission of the researchers who conducted the analyses - show high levels of uncertainty related to the relative effectiveness and cost effectiveness of all the interventions, including a very high degree of uncertainty about estimates of cost (see further comments about the cost analysis in point 22 below).The NMA and cost economic analysis do not suggest a clear hierarchy of treatments and highlight the need to offer a menu (non-ranked) of treatment options for new episodes of depression to be made available. We suggest an ordering in alphabetical order in the Tables and Visual Summaries might perhaps be most appropriate. Notwithstanding the serious critique highlighted below about the NMA, this is an important finding as it replicates and confirms what many	Thank you for your comment. Although NMA and economic results were characterised by uncertainty, they did not suggest that all treatments were similarly clinically and cost-effective. For example, in less severe depression, the effect of group CT/CBT class vs TAU (based on an evidence base of N=480) was -1.01 (95%CrI -1.76 to -0.06), whereas the respective effect of counselling (based on a narrower evidence base of N=55) was -0.20 (95%CrI -2.82 to 2.50), i.e. one fifth of the effect of group CT/CBT class, although both treatments were recommended – see bias-adjusted results in Table 9, evidence report B. Similarly, in more severe depression, the effect of individual CT/CBT + AD class vs placebo (based on an evidence base of N=192) was -1.18 (95%CrI -2.07 to -0.44), whereas the respective effect of IPT (based on an evidence base of N=145) was -0.45 (95%CrI -1.36 to 0.47), i.e. almost a third of the effect of individual CT/CBT + AD class – see bias-adjusted results in Table 24, evidence report B. Regarding clinical effectiveness derived from the NMAs, the committee considered not only the mean effects of treatment classes vs the reference treatment, but the uncertainty around them

						other studies and systematic reviews have found, mostly recently Cuijpers and colleagues in two systematic reviews (2020, 2021a).	(as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of the pairwise meta-analysis of follow-up data and additional outcomes (quality of life and functioning). Regarding cost-effectiveness, highly ranked interventions in the guideline economic analysis were more cost-effective than interventions lower in ranking, although there was uncertainty in the results and differences might be small in some cases (especially for interventions in close ranking places). Some interventions were found to be less cost-effective than GP care in less or more severe depression (or both). Based on these findings, the committee considered appropriate to rank recommended treatments taking into account clinical and cost-effectiveness as well as other issues such as the applicability of the evidence (e.g. for individual problem solving in more severe depression), but also taking account of patient clinical needs and preferences.

							Interventions are arranged in Tables 1 and 2 of the guideline in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee expressed the view that listing interventions in alphabetical order would not reflect the evidence base nor serve as a guide to choose for those who do not have pre-existing preferences. Statements that one intervention was found to be 'more effective' or 'more cost-effective' than another intervention referred to results and conclusions of published economic studies included in the systematic review of economic evidence,

							described under 'Summary of studies included in the economic evidence review'. Such statements were not made for the results of the NMA or the guideline economic analysis, where treatments may have been described as 'ranking more highly' than another in terms of clinical or cost-effectiveness.

230	SH	The College of Mental Health Pharmacy	Guideline	23	Table 1	This is a very unhelpful way of displaying this information as a portrait table over 8 pages.	Thank you for your comment. This is a long table, but the committee agreed it would be better included in the body of the guideline rather than as an appendix. The format of tables in NICE guidelines has to be very simple to ensure accessibility.

231	SH	Tavistock and Portman NHS Foundation Trust	Guideline	023 - 031	Table 1Table 2Visual summary 1 & 2	We are very concerned that the treatments in these tables and in the accompanying text throughout this document, including the two visual summaries provided separately, are hierarchically ordered with short-term psychodynamic therapy (STPP) appearing at the bottom (or appearing last in the visual summary) even though not a single treatment included in these analyses have been proven more clinically effective or indeed more cost-effective. As clearly stated in the summary of the cost-effectiveness, the differences in overall quality of life gains, cost-per-QALY gains, and net monetary benefits between most interventions are small and negligible.Notwithstanding the methodological concerns pertaining to these analyses (see points below), these findings from the NMA and cost economic analysis do not suggest a clear hierarchy of treatments and underscore the need to offer a menu of treatment options to be made available. We suggest an ordering in alphabetical order might perhaps be most appropriate. We notice that CBT appears to be highlighted as “more effective” or “more cost effective” compared to other interventions in various places of the guideline documents and review evidence B which is misleading given the findings reported and ask for this to be amended.	Thank you for your comment. Although NMA and economic results were characterised by uncertainty, they did not suggest that all treatments were similarly clinically and cost-effective and nowhere in the text is it stated that differences are 'negligible'. For example, in less severe depression, the effect of group CT/CBT class vs TAU (based on an evidence base of N=480) was -1.01 (95%CrI -1.76 to -0.06), whereas the respective effect of short-term psychodynamic psychotherapy (based on a narrower evidence base of N=49) was -0.48 (95%CrI -2.96 to 2.03), i.e. half the effect of group CT/CBT class – see bias-adjusted results in Table 9, evidence report B. Moreover, as seen in Table 10, results for most interventions within group CT/CBT class showed evidence of effect vs TAU, which was not the case for short-term psychodynamic psychotherapy at the intervention level. Similarly, in more severe depression, the effect of individual CT/CBT + AD class vs placebo (based on an evidence base of N=192) was -1.18 (95%CrI -2.07 to -0.44), whereas the respective effect of short-term psychodynamic psychotherapy (based on a somewhat larger evidence base of N=233) was -0.58 (95%CrI -1.35 to 0.10),

							i.e. again half the effect of individual CT/CBT + AD class – see bias-adjusted results in Table 24, evidence report B. As seen in Table 25, though, results for most or all interventions within both classes showed evidence of effect vs placebo, with interventions within the individual CT/CBT class showing overall higher effects compared with interventions within the short-term psychodynamic psychotherapy class. Regarding clinical effectiveness derived from the NMAs, the committee considered not only the mean effects of treatment classes vs the reference treatment, but the uncertainty around them (as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of pairwise meta-analysis. Regarding cost-effectiveness, short-term psychodynamic psychotherapy was found to be less cost-effective than GP care (reference treatment) in both less and more severe depression, and was one of the least cost-effective interventions in terms of

							ranking. Generally, highly ranked interventions in economic analysis were more cost-effective than interventions lower in ranking, although there was uncertainty in the results and differences might be small in some cases (especially for interventions in close ranking places). Therefore, the committee considered appropriate to rank recommended treatments taking into account clinical and cost-effectiveness as well as other issues such as side effects (antidepressants in less severe depression) and applicability of the evidence (e.g. for individual problem solving in more severe depression), but also taking account of patient clinical needs and preferences. Interventions are arranged in Tables 1 and 2 of the guideline in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table

							where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. Short-term psychodynamic psychotherapy was listed towards the bottom of the tables after considering its clinical and cost-effectiveness and its respective ranking relative to other treatments. Listing interventions in alphabetical order would not reflect the evidence base nor serve as a guide to choose for those who do not have pre-existing preferences. Statements that one intervention was found to be 'more effective' or 'more cost-effective' than another intervention referred to results and conclusions of published economic studies included in the systematic review of economic evidence, described under 'Summary of studies included in the economic evidence review'. Such statements were not made for the results of the NMA or the guideline economic analysis, where treatments may have been described as 'ranking more highly' than

							another in terms of clinical or cost-effectiveness.

232	SH	The Federation of Holistic Therapists	Guideline	023-030	General	p.23-30 of the draft guidance outlines “Table 1: Treatment options for less severe depression listed in order of recommended use, based on the committee’s interpretation of their clinical and cost effectiveness.” It is disappointing that such a limited number of physical treatments, and more specifically no massage, aromatherapy, reflexology or touch therapy options, are included in this section. Touch therapy refers to a type of therapeutic treatment in which the therapist physically touches the subject in a specific way and plays an important role within the services offered in the personal care sector. There is an increasing understanding that social touch plays a powerful role in human life, with important physical and mental health benefits in development and adulthood[1].The understanding of the link between mental health with physical and biochemical changes within the body has also developed in recent years. Levels of four key chemicals within the body have been shown to change significantly with physical/social touch:Oxytocin, a key hormone, is released by touch. Many of the positive effects caused during interaction, such a wellbeing, stress reduction and even health promotion, are linked to oxytocin released in response to activation of various types of sensory nerves[2].Cortisol levels can also be significantly reduced through a simple hug or massage[3]. High levels of cortisol are linked to type 2 diabetes, obesity, cholesterol and blood pressure and heart disease[4].Conversely, the reduction in cortisol from touch has been shown to lower blood pressure and heart rate.Serotonin and dopamine levels, key hormones associated with mental health and pain relief, are also	Thank you for your comment. The committee did not consider massage, aromatherapy, reflexology or touch therapy to be interventions that were in regular clinical use for the treatment of depression. Therefore these interventions were not specified in any of the review protocols and consequently the studies that you cite would not have met the inclusion criteria for the reviews. As such the evidence on massage, aromatherapy, reflexology and touch therapy has not been appraised and the committee were not able to make any recommendations on their use.

						stimulated by touch[5][6]. Research on increasing serotonin levels without drug intervention to address depression and other mental health symptoms has also proved successful[7].Recent research repeated by the BBC working with Prof Fulvio D'Acquisto, an immunologist from the University of Roehampton and the Bodyology Massage School, demonstrated a 70% boost in white blood cell count from massage[8].Massage Therapy (MT) is a service offered by a significant section of the Personal Care sector. It is broadly defined as the manual manipulation of muscles and certain other soft tissues in the body, including connective tissue, ligaments, and tendons, with the purpose of improving a person's health and wellbeing. MT can be a part of physical therapy or practiced on its own[9].The history of massage therapy dates back to approximately 3000 BCE in India, where it was considered a sacred system of natural healing. "Life health" medicine, massage therapy was a practice passed down through generations to heal injuries, relieve pain, and prevent and cure illnesses. In the early 1800s, Swedish doctor and gymnast, Per Henrik Ling created a massage method to help relieve chronic pain. Since then, the health service has focused more on drug (chemical) therapy for the management of pain and other ailments. It has only been since 1970's that massage moved out of the medical realm into being seen as part of a healthy lifestyle in the UK and US[10]. MT is now considered an alternative or complementary therapy rather than a medical discipline although it is still taught in physiotherapy courses.Mental illness has been a growing health crisis for some time. Mental ill-health is the single	

						largest cause of disability in the UK, contributing up to 22.8% of the total burden, compared to 15.9% for cancer and 16.2% for cardiovascular disease. The wider economic costs of mental illness in England have been estimated at £105.2 billion per annum[11]. Mental Health problems have increased by 8% during the pandemic[12]. It has been estimated that optimal treatment for mental disorders will only avert 28% of the burden of mental illness[13]. There is now significant global evidence that touch therapy, including massage, aromatherapy, reflexology can have a significant effect on reducing mental health problems. Whilst massage therapy (MT) has been seen as an important part of healthcare in mainland Europe and Asia, it has been less well supported in the UK. The National Institute for Health and Care Excellence reference a number of uses for MT including: back, neck and shoulder pain[14], osteoarthritis[15], cancer symptoms and treatment side effects, fibromyalgia, HIV/AIDs, premature infant care. As research has developed globally, the benefits of MT, aromatherapy and reflexology to mental health have become clearer. With the advent of improved technologies such as Magnetic Resonance Imaging (MRI), Electroencephalography (EEG) and chemical analysis, it has been possible to demonstrate not only the medical benefits of MT but the emotional and mental benefits[16]. This includes stimulation of the vagus nerve including the parasympathetic system[17]. A randomised controlled trial in Australia carried out by Most & Wallis, demonstrated the effectiveness of a 15-minute weekly massage in reducing physical and psychological stress in nurses[18]. Research by Moyer et al[19], supported	

						by the National Institute for Health Research (NIHR), cites that a course of massage therapy treatment provides similar benefits in magnitude to those of psychotherapy, with MT's greatest efforts being in reducing trait anxiety and depression. Further work by Moyer claimed cortisol levels were not significantly reduced by MT and as such, it cannot be the cause of MT's well-established and statistically larger beneficial effects on anxiety, depression, and pain. They conclude that other causal mechanisms, which are still to be identified, must be responsible for MT's clinical benefits[20]. History of Aromatherapy - Gattefossé coined the term aromatherapy in 1928 within an article where he supports the use of using essential oils in their whole without breaking them down into their primary constituents. Aromatherapy is highly respected early 20th century aromatherapists include Jean Valnet, Madam Marguerite Maury, and Robert B. Tisserand. Jean Valnet is most remembered for his work using essential oils to treat injured soldiers during the war and for his book, The Practice of Aromatherapy, originally entitled Aromathérapie in French. Austrian Madam Marguerite Maury is remembered as a biochemist who avidly studied, practiced and taught the use of aromatherapy for primarily cosmetic benefit. Robert B. Tisserand is an English aromatherapist who is responsible for being one of the first individuals to bring knowledge and education of aromatherapy to English speaking nations. He has written books and articles including the highly respected 1977 publication The Art of Aromatherapy. The Art of Aromatherapy was the first aromatherapy book published in English. From the late 20th	

						century and on into the 21st century, there is a growing resurgence to utilize more natural products including essential oils for therapeutic, and aromatic benefits.Research into Aromatherapy shows its effectiveness for depression, stress etc. The Effectiveness of Aromatherapy for Depressive Symptoms: A Systematic Review (nih.gov)****Effectiveness of Aromatherapy for Depression and Stress (nursinganswers.net)****History of reflexology in more modern form of reflexology was first pioneered by an ear, nose and throat surgeon by the name of Dr William Fitzgerald (1872-1942). Dr Fitzgerald was the founder of Zone Therapy, which was an earlier form of reflexology. He discovered that exerting pressure on the tips of the toes or fingers caused corresponding parts of the body to become anaesthetised. From this, Dr Fitzgerald divided the body into ten equal zones, which ran from the top of the head to the ends of the toes. By using tight elastic bands on the middle sections of the fingers or using small clamps on the tips of the fingers, minor surgery could be carried out with no further anaesthetic agents required.********However, reflexology as we know it today was pioneered by a woman called Eunice Ingham (1889 - 1974), or the mother of modern reflexology. Eunice Ingham was a physiotherapist working in a doctor's practise using the zone therapy developed by Dr Fitzgerald. Ms Ingham thought, however, that it would be more effective to be practised on the feet rather than the hands. After extensive research, she developed the map of the entire body on the feet - where one point on the foot corresponds to a certain part of the body. By using acupressure or massage techniques on these points, a	

						positive effect is created in the corresponding body part.********Eunice Ingham spent 30 years travelling around America teaching her reflexology first to medical staff, and then to non-medical practitioners. Modern Western reflexology uses the charts and theories developed by her and now called the Ingham Method. Ingham's work is carried on by the International Institute of Reflexology.Research into Reflexology shows its effectiveness for depression, anxiety etc. Effect of Foot Reflexology Intervention on Depression, Anxiety, and Sleep Quality in Adults: A Meta-Analysis and Metaregression of Randomized Controlled Trials - PubMed (nih.gov)The effects of foot reflexology on depression during menopause: A randomized controlled clinical trial - PubMedDespite the global evidence, NICE is yet to be satisfied that massage therapy, aromatherapy and reflexology can be used to address mental health issues. They have cited that their position is formed on the basis of further, more robust research being needed rather than because existing research has not shown evidence. We have therefore proposed the expansion of the recommendations for Research outlined from p.60 to include these treatment options.	

233	SH	University of Exeter Medical School	Guideline	023-030	Table 1	We support the inclusion of Behavioural Activation as a first line treatment for less severe depression. However, the order in which treatments are listed by clinical and cost effectiveness is inaccurate. Behavioural activation has been shown to be more cost-effective and no less clinically effective than individual CBT in a £2m head to head trial funded through NIHR HTA. We note that this trial (COBRA) alongside other NHS facing trials, has been excluded from the clinical effectiveness evidence synthesis. We will comment on the wisdom or not of this elsewhere. However, the decision to exclude this trial has removed the COBRA included health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world. Putting BA below CBT in table 1 is a mistake.	Thank you for your comment. The ranking of interventions recommended for less and more severe depression was based on evidence of clinical and cost-effectiveness as well as other clinical considerations, e.g. the risk of side effects for antidepressants, availability of treatments in the NHS and structure of IAPT services. Regarding clinical effectiveness derived from the NMAs, the committee considered not only the mean effects of treatment classes vs the reference treatment, but the uncertainty around them (as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of pairwise meta-analysis. Regarding cost-effectiveness evidence, this was primarily based on the guideline economic analysis, which allowed to simultaneously compare the relative cost-effectiveness of all relevant treatment options that were assessed in the guideline. This simultaneous comparison was practically impossible to be made by single studies. The COBRA trial was excluded from

							the NMA because it did not meet inclusion criteria for a new episode of depression. This is because <80% of the study sample received first-line treatment for a new episode of depression. This was a requirement of the review protocol in order to create a homogenous data set. Nevertheless, the committee used their knowledge of pragmatic trials such as the COBRA trial when interpreting the evidence from the NMAs and the economic analysis and making recommendations. The guideline economic analysis considered a wide range of evidence as it utilised clinical data from the guideline NMAs, which included 142 RCTs of treatments for less severe depression and 534 RCTs of treatments for more severe depression and was directly relevant to the NHS context as it utilised UK resource use data and unit costs, supplemented by the committee's expert opinion on the optimal delivery of interventions in UK routine care. In the economic analysis and the table of recommendations, behavioural activation is described and recommended as a high intensity intervention, delivered by Band 7 practitioners with therapy-specific training and competence. In contrast, in the COBRA

							trial, behavioural activation was delivered by junior mental health workers, and this was a parameter that highly contributed to the study conclusion that it was more cost-effective than CBT (which was delivered by high intensity therapists in the COBRA trial). Individual behavioural activation is placed just below individual CBT in both Tables 1 and 2 of the guideline, which reflects the fact that the two treatments have similar clinical and cost-effectiveness. Interventions are arranged in Tables 1 and 2 of the guideline in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice.

							. The treatment recommendations have now been updated to reflect more clearly the key principles of stepped care, which is the prevailing model of care in IAPT. In the updated recommendations, low-intensity behavioural activation, delivered by PWPs, has now been described as part of guided self-help.

234	SH	Talking Therapies	Guideline	24	General	Table 1 - Individual CBT (a step 3 treatment) is recommended ahead of 'self-help with support' (a step 2 treatment). Step 2 treatments require less resources than step 3 treatments (Bennet-Levy, 2010) and have excellent recovery rates for mild-moderate and first episode depression. To implement the draft guidelines and provide CBT prior to self-help with support would require a huge shift in the workforce, as more CBT therapists would need to be recruited. This would incur a significant cost and nationally the current staffing targets are already not being met (Royal College of Psychiatrists, 2021).It would therefore be prudent to for GSH/self-help with support to be recommended before individual CBT. It would also be in line with the explanatory paragraph 'Stepped Care Model' starting on page 59 line 26.	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice.
235	SH	Active Partnerships National Team	Guideline	24	Table 1	There is opportunity within the behavioural activation and self-help approaches to promote free national resources that support people living with mental health conditions to be more active. We recommend referencing and signposting patients to our We Are Undefeatable support tools. We recommend clinicians utilise the Moving Medicine programme. This is a free initiative by The Faculty of Sport and Exercise Medicine which supports healthcare professionals integrate physical activity conversations into routine clinical care. This includes evidence-based resources specifically for the treatment of depression.	Thank you for your comment. In response to stakeholder comments, the committee supported 'move more' advice for general wellbeing (although not as a treatment for depression) and made a new recommendation to reflect this. Thank you for telling us about the existing physical activity programmes and campaigns. These will be passed on to the NICE shared learning team.

236	SH	University of South Wales	Guideline	25	General	The draft NICE Guideline recommendations for Group mindfulness or meditation, would also benefit from specificity. Unfortunately, the words mindfulness and meditation are used interchangeably however there is a need for specificity. Meditation typically refers to formal meditation practices; some of which are secular, and others are within religious or spiritual practices. Which can come from very different origins and basis. There are many types of meditation for instance:Breath-awareness meditation (Tibetan, Zen, Tiantai and Theravada Buddhism)Loving-kindness meditation (Many Buddhist Denominations)Mantra-based meditation (Hinduism, Buddhism, Jainism, and Sikhism)More secular practicesWhich of these or other are the guidelines referring to?	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. The committee agreed that mindfulness based cognitive therapy (MBCT) should be given as an exemplar of this class and in Table 1 of the recommendations, in considering how to deliver group mindfulness or meditation it is recommended that 'a programme such as mindfulness-based cognitive therapy specifically designed for people with depression' is used.

237	SH	Talking Therapies	Guideline	26	General	Table 1 - Self-help with self-support – this appears to be an amalgamation of the current Guided Self Help (GSH) treatment and computerised CBT (cCBT) as materials can be provided in digital and non-digital ways. These are two separate treatment modalities, which serve different purposes, with cCBT requiring clients to tailor the materials to themselves with the help of a standardised computer programme, and GSH allowing for individualisation and more support for those clients who need it. To combine these two separate treatment options will remove patient choice and the ability to care for clients who lack motivation to engage with cCBT (a symptom of depression (APA. 2013) in a resourceful way, or who need greater tailoring of step 2 interventions due to learning difficulties, contextual/environmental factors. This would be against the Equality Act (2010) as IAPT services would not be able to make reasonable adjustments for protected characteristics, which we routinely do within GSH.	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. Self-help with support and self-help (with no or minimal support) formed classes and computerised CBT (CCBT) was a specific intervention within these classes. Different self-help approaches (with or without support) were searched for and were eligible for inclusion. In addition to computerised approaches, there are also

							RCTs of cognitive bibliotherapy, behavioural bibliotherapy, expressive writing, mindfulness meditation CD, relaxation training CD, and third-wave cognitive therapy CD, included in the network met-analyses (NMAs) for treatment of a new episode of depression. One intervention per class was used as an exemplar in the economic analysis, as it was not feasible to model all interventions included in the NMA. cCBT was selected as the exemplar from the class of self-help with support as it had a large evidence base and a high effect compared with other interventions in the same class. Thus, the clinical evidence and resource use data used to inform the economic analysis were specific to cCBT; consequently, the results of the economic analysis were specific to cCBT (but could also be extrapolated to any other intervention with similar acceptability, effectiveness and resource use). However, the treatment class effect size for self-help (with or without support) that was estimated from the NMA and reported in the clinical evidence sections of evidence review B, was informed by evidence from all interventions included in

							the treatment class. In addition, individual intervention effects have been reported in the evidence review B for all interventions within each class for the SMD outcome (for both less and more severe depression). In response to stakeholder comments, the self-help with support section has been relabelled as guided self-help, placed earlier in the treatment pathway, and the description of guided self-help has been amended to recommend that printed or digital materials that follow the principles of guided self-help are used including structured CBT, structured BA, problem solving or psychoeducation materials, delivered face-to-face or by telephone or online.

238	SH	University of South Wales	Guideline	26	General	The draft NICE Guidelines review evidence related to Mindfulness-based cognitive therapy(MBCT- n=76) and Mindfulness-based stress reduction (MBSR- n=70); therefore, theguidelines should specifically recommend these. Using the generic term“Mindfulness group” as that could lead to misinterpretation or delivery ofinterventions that do not have a specific theoretical framework and evidence.Likewise, the training and experience necessary to deliver these specific interventionsshould be specified.	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. The committee agreed that mindfulness based cognitive therapy (MBCT) should be given as an exemplar of this class and in Table 1 of the recommendations, in considering how to deliver group mindfulness or meditation it is recommended that 'a programme such as mindfulness-based cognitive therapy specifically designed for people with depression' is used. Table 1 includes the

							recommendation that this intervention should be delivered by trained practitioners, however, the committee did not consider it appropriate to further specify the training and experience necessary to deliver this intervention as this is a matter for implementation.
239	SH	Anxiety UK	Guideline	26	General	We welcome the addition of therapy groups, peer-support groups & exercise (Table 1) as we feel that choice is essential with regard to the treatment of depression.	Thank you for your comment and support of these recommendations
240	SH	Talking Therapies	Guideline	26	Table 1	Self-help with support – the draft guidelines suggest a 30 minute 1st appointment and 15 minute subsequent appointments, which is a change from the current session length, which on average is 30 minutes. Current competencies for an IAPT step 2 individual treatment session include a	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions

						review of risk, review of medication, symptom monitoring, homework review. This takes at least 10 minutes, more for clients who are not 'straight forward' and require risk or signposting support (which a great deal of clients across services do). This leaves no time for a clinician to support clients with the CBT techniques/strategies that comprise treatment. Therefore please can the 30 minute session length for all sessions remain.	has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions.

241	SH	Active Partnerships National Team	Guideline	26	Table 1	We support the inclusion of peer supportThere is strong evidence that peer-to-peer support is effective for improving mental health, and interactions with others with lived experience supports people to feel motivated (Kinnafick, Smith,Appleton,Tweed, Bayes & Tiler, 2017). Sport England's partnerships with Mind and Rethink take a peer support approach to physical activity as part of the treatment for mental health conditions. This has proven successful in supporting people with both mild and more severe mental health conditions.We are concerned about the frequency and duration information included within the exercise delivery information. We feel '60-minute sessions, usually 3 times a week for 10 weeks' could be unrealistic for people experiencing symptoms associated with mild depression i.e. low motivation and fatigue.Evidence demonstrates those living with diagnosed long term condition are more likely to be inactive - 42% of adults aged between 25 and 64 years of age with long - term health conditions (including mental health conditions are inactive (completing less than 30 minutes of physical activity a week).We surmise the duration conclusion has been drawn from reviewing only academic research from structured exercise programme interventions using RCT methodology. Setting or advising a 'dose' of physical activity is challenging given the broad spectrum of health outcomes and peoples varying starting points. Scientific evidence continues to support 150 minutes of MVPA per week spread across the week. However, there is also evidence that lower volumes (less than 150 minutes per week), lower intensities (i.e. light physical activity) and lower frequencies (one or two sessions	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. The committee considered RCTs as the most appropriate study design to assess clinical and cost effectiveness. This is consistent with the NICE guidelines manual which recognises RCTs as the most valid evidence of the effects of interventions. This was outlined a priori in the review protocols, and on this basis non-randomised trials and real-life research were not included. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this. The description of interventions in the tables is based on information from the

						per week) of physical activity may nevertheless confer health benefits (UK Chief Medical Officers' Physical Activity Guidelines, 2019). When considering the intensity, time, type, and frequency of physical activity improvements in health, it is important to tailor the intervention to the individual's needs (Review of Evidence Outcomes of Sport and Physical Activity, 2017). The inclusion of broader evidence to include non-randomised trials (NRTs) and informal, unstructured exercise approaches would surface a lower intensity and duration is also effective in combatting the symptoms associated with mild depression i.e. walking 30 minutes per day for 10 consecutive days or 20 minutes of running three times a week for 10 weeks (Review of Evidence on the Outcomes of Sport and Physical Activity, 2017) and Stubbs et al (2021) Movement for the Mind demonstrates clinically significant mental wellbeing benefits can be gained in two 30 minute sessions a week.We recommend the inclusion of behaviour change tools and techniques i.e. goal setting, chunking, self-monitoring, and planning are considered within intervention design. Interventions and resources which incorporate these principles have proven particularly successful in helping people to sustain activity levels and integrate into their daily lives beyond treatment pathways.QuestionsIt would be helpful to understand the NICE definition/interpretation of a 'trained practitioner' and 'a physical activity programme specifically designed for people with depression' which is referenced in the guidance. We are concerned that this recommendation may imply formal, structured physical activity or exercise only. We understand the table of	RCTs included in the network meta-analyses, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. The committee did not consider it appropriate to include the level of detail included in your comment about the content of the exercise intervention, in order to allow flexibility and tailoring based on individual clinical need. However, the committee did consider it important that the physical activity programme was specifically designed for people with depression, and included that in the recommendation. Treatment options were listed in order of recommended use in the tables based on the committee's interpretation of their clinical and cost effectiveness. In addition to the clinical and cost-effectiveness evidence, the committee also considered implementation issues, volume of the evidence base for each treatment, and applicability of the evidence to the UK context. These considerations and the rationale for recommendations are outlined in the committee's discussion of the evidence sections in Evidence review B.

						treatment options is listed in order of recommended use, based on the committee's interpretation of clinical and cost effectiveness. What is the weighting of clinical effectiveness to cost effectiveness to determine the ranking position?	

242	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	26	Table 1	As a provider of Increasing Access to Psychological Therapies (IAPT) services we have concerns that 15 minute supported self-help sessions would diminish the meaningfulness and face value of sessions for service users and Psychological Wellbeing Practitioner clinicians, and would seemingly reduce treatment dosage to a level that may not be helpful.	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

243	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	26	Table 1	Overall, there appears to be no mention of Guided Self Help nor Computerised Cognitive Behaviour Therapy (cCBT) specifically – as a practitioner this feels ambiguous regarding where step 2 fits in as nothing within the recommendations aligns with current ways of working (e.g., session length and number of them)	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice. The analyses utilised class models with each class consisting of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. Self-help with support and self-help (with no or minimal support) formed classes and computerised CBT (cCBT) was a specific intervention within these classes. In response to stakeholder comments, the self-help with support section has been relabelled as guided self-help, placed earlier in the treatment pathway, and the description of guided self-help has been amended. The recommended resource use for all

							interventions was based on relevant information reported in the RCTs that informed the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. This information has now been added in evidence review B, under Appendix N. The recommended 'usual' number of sessions serves only as guidance and can be modified depending on individual needs. This has now been clarified in the recommendations. The frequency and duration of sessions of psychological therapies has also now been removed from the recommendations, to allow more flexibility in the delivery of interventions.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

244	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	26	Table 1	Regarding self-help with support, we would like to raise concerns around:How much this strays from current teaching/ways of doing this within the Psychological Wellbeing Practitioner (PWP) remit. Having a 30-minute initial assessment, PWPs would struggle to cover all assessment areas within this time, the same can be said for the 15min sessions going forward. The client experience of sessions limited to 15 minutes, (especially if these were face to face), and what PWPs would be able to cover in that time. The session would be limited to some encouragement and reviewing progress which does not make full use of the PWP skill set and training. It may feel as though the PWP offer is being diminished to purely checking in on the client's ability to adhere to the workbooks. This is likely to have a negative impact on the client's experience and outcomes.	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions. No need to depart from current teaching/ways of currently delivering the intervention is anticipated.
245	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	26	Table 1	With contacts limited to 15 minutes we would envisage that a significant increase in caseload numbers would be needed to meet clinical expectations which would have a significant impact on Psychological Wellbeing Practitioner wellbeing, potential burnout and job satisfaction as they will not be able to spend any significant time with clients. They would probably also struggle to remember the clients if they are only seeing them once every 2 weeks for 15 minutes.Timescale of 16 weeks is also concerning, again straying significantly from the short-term intervention that PWPs usually work towards.	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions. For the same reason, the suggested length of the intervention (16 weeks) has also been removed, but it is indicated that regular sessions need to take place.

246	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	026-027-036	General	Group exercise and group mindfulness – peer support. The 'other things to consider' column on these three pages says, May allow peer support from others… Acknowledging the 'group' effect on an activity's outcomes is important. There are other physical group activities, most notably expressive dance, participatory music and nature-based approaches, that can fulfil mindfulness and physical exercise elements and also yield benefits from peer support.We suggest that these recommendations / options can encompass other suitable group activities such as those mentioned.	Thank you for your comment. The committee recognised that group interventions may allow peer support from others who may be having similar experiences. However, the specific group interventions (e.g. group CBT, group BA, group exercise, group mindfulness and meditation) were recommended based on their clinical and cost effectiveness, rather than the opportunity for peer support. There was limited evidence for the effectiveness of peer support interventions, and the committee made a research recommendation for peer support. The committee did not consider nature-based activities to be interventions that were in regular clinical use for the treatment of depression. Therefore these interventions were not specified in any of the review protocols. The committee also noted that the evidence reviewed for exercise was for a structured formal exercise programme. However, in response to stakeholder comments, the committee also supported less intense 'move more' exercise for general wellbeing (although not as a

							treatment for depression) and made a new recommendation to reflect this. This recommendation is to advise people that undertaking any form of physical activity on a regular basis may help improve their mood, and gives dance as an example. The recommendation also highlights the benefits of outdoors activities. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness). Music therapy was listed as an intervention of interest for the treatment reviews. However, only one study of music therapy (Albornoz 2011) is included in the network meta-analysis for the treatment of a new episode of more severe depression. The committee considered the evidence too limited to make a recommendation for music therapy as a treatment for depression.

247	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	27	General	Group mindfulness or meditation. Given that mindfulness and meditation can constitute a range of activities, including artistic activities (such as colouring in) and music (chanting), we would like to see a more precise definition of what mindfulness/meditation activities can include, or at least acknowledge the range of forms such activities might take. Again, this supports the core idea of patient choice, by offering sub-choices of specific activities within each broader choice as listed on the visual summary documents.	Thank you for your comment. The committee agreed that mindfulness based cognitive therapy (MBCT) should be given as an exemplar of the group mindfulness or meditation class and in Table 1 of the recommendations, in considering how to deliver group mindfulness or meditation it is recommended that 'a programme such as mindfulness-based cognitive therapy specifically designed for people with depression' is used. The committee did not consider it appropriate to further stipulate specific activities that might be involved as this will be variable and will depend on a number of factors including the patient, the clinician, and the specific intervention used.

248	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	27	Table 1	The row of table 1 on page 27 about group mindfulness / meditation requires considerable attention. Labelling this row 'group mindfulness or meditation' is problematic because that is very vague and broad heading. It could very easily be used to justify the provision of a variety of non-evidence-based interventions which may happen to include some elements of mindfulness / meditation. It would be preferable to label this row Mindfulness Based Cognitive Therapy (MBCT).Mindfulness Based Cognitive Therapy was designed specifically for people experiencing depression. It has a very substantial evidence base both for depressive relapse prevention and symptom reduction and has been in the NICE depression guidelines since 2004. MBCT is a very well-established and highly respected approach with an extensive literature, rigorous training pathways, a system for the accreditation of training, national good practice guidelines, rigorous methods for assessment of therapist competency, a register of trained therapists, etc, etc.MBCT is a mandated therapy within Increasing Access to Psychological Therapies (IAPT). There is a Health Education England funded national training (entering its 4th year) for High Intensity therapists in IAPT services and so there is steadily increasing availability of MBCT provision across the country.The details in this row of the table are misleading and appear to be written by someone who is not familiar with the approach. It would be best to involve an MBCT expert in re-writing it. For example: groups are sometimes delivered by just one practitioner rather than by two, as stated; 8 is often said to be the minimum group size but ideally there are 12-15 participants in a group; the	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. However, the committee did agree that MBCT should be given as an exemplar of the Group mindfulness or meditation class, and in Table 1 of the recommendations when considering how to deliver group mindfulness or meditation it is recommended that 'a programme such as mindfulness-based cognitive therapy specifically designed for people with

						sessions are quite often two and a quarter hours rather than two hours long; a full course of MBCT includes a day of practice, thus a total of 9 sessions rather than 8. The 'key features' and 'other things to think about' columns would also be better written by someone familiar with MBCT.	depression' is used. The recommended resource use was based on relevant information reported in the RCTs that informed the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. This information has now been added in evidence review B, under Appendix N. Few studies reported the number of participants in group interventions and even fewer made specific reference to the number of therapists per group. For MBCT, only one study on the treatment of a new episode of less severe depression reported the number of participants per group as 8-15. The committee expressed the view that group interventions should be optimally delivered by two therapists, one leading the delivery of the intervention and another one observing, and that the optimal number of participants is around 8. This has been reflected in the economic modelling and the respective recommendations. The committee has now modified the recommendation for MBCT, based on their clinical expertise and available evidence.

							The suggested delivery is now 'preferably by 2 practitioners at least one of whom has therapy-specific training and competence' with 'usually 8-15 participants per group'. The suggested number of sessions is 'usually' 8 sessions to allow flexibility around the number of sessions needed. This also covers programmes that involve 9 sessions. The duration of each session has now been removed from recommended resource use to allow flexibility in the delivery of interventions.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

249	SH	The College of Mental Health Pharmacy	Guideline	30	2	This title needs reviewing as there are many other things that would “NOT be recommended” eg ECT, MAOIs, carbamazepine, stimulants etc etcSuggest this section is just re-titled to “St Johns Wort”, as that is the focus of the message. SJW would not be recommended for “less severe depression” – as per the current heading, but equally it would not be recommended for more severe depression as well. So this needs adding.	Thank you for your comment. The section on St John's Wort has been retitled as you suggest and moved to the section of the guideline on delivery of treatments to clarify that it is not recommended for any depression.
250	SH	NHS England and Improvement	Guideline	30	13	Add social prescribing and PHBS (Treatment options for more severe depression listed)	Thank you for your comment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. Evidence for social prescribing was also not sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that

							maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

251	SH	Critical Psychiatry Network	Guideline	030-037	General	Feedback on more severe depressionWhilst we welcome the committee's approach of recommending a variety of psychosocial interventions for severe depression, we suggest that it has unduly prioritised antidepressant treatment in its recommendations, along with combination treatment of antidepressants and CBT. Although antidepressants alone demonstrate more effect in more severe depression than in less severe depression (although not entirely consistent with meta-analyses showing no gradient of effect based on baseline severity) their effects do not reach minimum clinically important effects and there are a number of biases unaccounted for in the studies that may lead even these small effects to be over-estimated. More importantly, there was an inadequate assessment of the harms of antidepressant, compared to the extensive analysis of benefits. This was also evident in the cost-effectiveness analysis, where reliance on an unrepresentative method for evaluating harms (claims made to insurer's for 5 specific adverse effects), which consequently over-estimated the cost-effectiveness of these drugs. Furthermore, there was an unwarranted reliance on dichotomisation of continuous data into categories with unclear relevance to clinical practice and evaluation of cost-effectiveness even for treatments that were not clinically effective. Additionally, there appeared to be evidence of an inclination to make recommendations consistent with current clinical practice rather than the evidence presented. There was also an inadequate assessment of the costs of stopping antidepressants both in terms of health related quality of life and disability as well as direct costs to the healthcare system	Thank you for your comment, and for providing references by way of context for the points raised. The response has been structured around the main themes raised in your comment. <u>Balance of harms (relative to benefits) of antidepressants in more severe depression</u> In response to your comment, the committee discussion of the evidence section of Evidence review B has been amended to make clearer that the committee considered side effects and withdrawal effects when making recommendations. In developing the recommendations, the committee were mindful of the negative consequences of prolonged depressive episodes including not only the impact on the mental health of the individual and their family but also on an individual's physical health (depression is associated with poorer physical health outcomes) and the impact on employment. The committee agreed that the benefits of improving the outcome of a depressive episode outweighed the potential harms. However, the guideline included detailed recommendations about starting and

						due to the use of inadequate data and unreasonably optimistic scenario for method of stopping medications (inconsistent with the recommendations of these very guidelines). Furthermore, there was inadequate attention paid to several methodological shortcomings of trials used to evaluate the effectiveness of medication (some applicable to non-drug treatments as well) as well as of a study relied on for cost-effectiveness evaluation. There was also an extrapolation of long-term recommendations from short term trials and an over-reliance on narrow measures of efficacy such as depression rating scales rather than the outcomes of most importance to patients such as quality of life and functional capacity. Overall this led to the committee recommending treatments such as antidepressants alone which did not demonstrate clinically important differences from pill placebo on the primary outcome of change in depression score (as measured by SMD), whether unadjusted or bias-adjusted, and prioritising treatments such as combination treatment with antidepressant and CBT over more cost-effective treatments like individual problem solving (likely to be associated with far less harm, though this was not adequately evaluated). We think a more accurate evaluation of the relative risks and harms of treatments would lead the committee to recommend safer and more effective non-pharmacological treatments.We also suggest that the committee include a recommendation for further research into effective treatments for depression at time points relevant to clinical practice (e.g. 1-2 years or more) looking particularly at outcomes that are most important to patients such as quality	stopping antidepressants, to enable people with depression and clinicians to make an individualised choice about the suitability of antidepressant treatment, and the choice of a specific antidepressant, based on patient preference and individual needs. <u>The suitability of data for evaluating harms</u> In order to estimate the rate of side effects for use in the economic analysis a review of studies was conducted. This has now been updated to include further studies reporting side effects of antidepressants. The committee reviewed the evidence and agreed that the rate of side effects used in the model should reflect side effects that resulted in a measurable reduction in health-related quality of life and led to additional healthcare resource use (e.g. additional GP visits and possibly medication for their management). The study by Anderson et al., which was used to inform the rate of side effects in the guideline economic analysis, reported prevalence data on 5 common side effects from a large USA managed care claims form that included 36,400 adults who were newly diagnosed with depression and were initiated on antidepressant monotherapy.

						of life and functional impairment to allow more informed choices for patients in the future. We outline the details of the limitations to the analysis below, with reference to relevant sections of Evidence Summary B. Inadequate assessment of harms in balancing benefits and harmsIn balancing benefits and harms there was only a cursory attempt to assess harms, which was assessed by drop outs from a studies as an indicator for tolerability. However, for example, antidepressants cause 30% of people to become overweight in years of use (Gafoor et al., 2018), a hugely impactful effect not present in an 8-week study, with similar reasoning applicable to sexual problems (treatment-emergent sexual dysfunction are found in 30-60% in patients on SSRIs (Gregorian et al 2002)), emotionally numbing, etc. These adverse effects may not cause a person to drop out of a trial, especially one in which they are paid to participate, but this effect over years or decades may have significant effects on social relationships, self-image and confidence, not to mention the physical health effects outlined below. Consequently the modelling does not adequately balance long term harms with benefits.In lines 33-39 of page 143 in Evidence B summary, the committee says: "The potential harms identified were attrition, with people not completing courses of treatment, issues with acceptability and the possibility of people deteriorating despite treatment (as data in clinical trials of all treatments estimated this could happen in 7-10% of people). However, the committee agreed that the potential benefits of treating depression were likely to outweigh the potential harms (italics added)." This categorical	Antidepressants assessed in the study included all classes of interest for the economic model. It is noted that the prevalence of side effects in the study, which was used in the guideline economic analysis, ranged from 4.7% (trazodone) to 9.2% (SNRIs). The figures of 0.07%, 0.09% etc. cited in the evidence review B as the prevalence of side effects of antidepressants were typos and have been corrected in the report (however, the economic analysis has used the correct figures reported in the Anderson et al. study). The committee reviewed evidence according to which, although side effects from antidepressants are often reported by patients, only a small proportion is considered 'bothersome' or is mentioned to the prescribing physician. The committee also expressed the view that studies asking specifically participants to self-report the presence of side effects, choosing from a list of potential side effects, tend to overestimate the prevalence of side effects in the study population, in particular as these studies use uncontrolled study designs and the causality between the antidepressant use and the reported side effects is not established; therefore, using

						assumption that the benefits of treatment will outweigh harms may be sensible for innocuous non-pharmacological treatments with few adverse effects but it is not a reasonable assumption for medications that can produce damage to the brain and the body. There is already recognition that half of patients will have trouble stopping their drugs because of withdrawal effects, and some may not be able to do so and for others the difficulties of stopping will be so great that they are disabled by the process (Guy et al 2020) and for others the consequences include suicide (Hengartner et al., 2020). The failure to consider these harms leads to the premature conclusion that benefits will outweigh harms for all treatments without thorough evaluation. A selection of some harms from antidepressants that were not considered by the committee is presented at the end of this document. Inadequate assessment of harms in economic analysisThere is a pronounced lack of consideration of the full extent of the cost of the harms of antidepressants. A single study looking at just 5 adverse effects (Anderson et al 2012) was used to estimate adverse effects for antidepressants to estimate their costs. This study retrospectively evaluated a commercially available national database used for making claims for payments. In other words, this database recorded adverse effects for which clinicians made claims to a healthcare provider in the USA. This is an unusually high threshold to determine that an adverse effect is having a significant effect on a person. Many patients will not report their symptoms, those that do may be told to tolerate them or clinicians may adopt a wait and see approach – so to reach the threshold	data from such studies would likely overestimate the impact of side effects on the relative cost-effectiveness between pharmacological and non-pharmacological treatments, especially as psychological treatments are assumed to have zero risks of side effects. In contrast, the committee expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, such as those reported in the study used to inform the guideline economic model, are more representative of the risk of side effects that have an impact on health-related quality of life and healthcare costs. The committee was also aware that apart from common side effects, there may be serious side effects from antidepressants, which are costly to treat and are likely to reduce the health-related quality of life of people who experience them more significantly. However, these side effects do not occur frequently, and their impact on the relative cost-effectiveness of antidepressants is expected to be very low. Discussion of the above points has now been added in Evidence review B, in Appendix J (Economic modelling methods -> Other clinical input parameters -> Probability of development

						that a clinician makes a claim for a side effect will only capture a tiny portion of the adverse experienced from being on medication. Harms do not need to result in an insurance claim to have a significant impact on people's quality of life and economic productivity so this cannot be considered an adequate basis for a health economics evaluation. As the authors of the study says "data from medical claims are subject to a considerable degree of under-detection because fewer patients may actually go to a doctor for these particular symptoms" (p.119, Anderson et al 2012). The authors go on to say "More general estimates of the occurrence of side effects associated with SSRIs are higher: increased agitation in up to 20% of users, nausea in up to 20%, sedation in up to 20%, and sexual dysfunction in up to 20% (Whooley and Simon, 2000)" The authors further emphasise the "relatively low sensitivity of medical claims data for detecting these side effects at their true rates in treatment settings" (p.122, Anderson et al 2012).Marked under-estimation is clearly evident when examining the results derived as in Table 80 on page 316 of Evidence Summary B. An estimation that 0.07% of people on SSRI, 0.09% of people on SNRIs and 0.06% of people on mirtazapine will develop more than one side effect is implausible. For instance, on the SPC for citalopram, https://www.medicines.org.uk/emc/product/5737/smpc#gref the most commonly used antidepressant in England there are 8 adverse effects that are 'very common' (occur in more than 10% of patients), including sleep disorder, somnolence, insomnia, headache, increased sweating and asthenia, 33 adverse effects which are 'common' (occur in 1% -10% of	of side effects from antidepressant treatment). In addition, the economic analysis has now included a sensitivity analysis that uses a 40% risk of side effects (assumed to cause a reduction in health-related quality of life and to trigger extra healthcare resource use), to explore the impact of a higher rate of side effects on the relative cost-effectiveness of antidepressants alone or combined with CBT. As expected, the position of these interventions in ranking fell, but their cost-effectiveness relative to psychological interventions did not materially change. Results (reduction in the relative cost-effectiveness of antidepressants) were more substantial for less severe depression, where, however, the recommendation was to not routinely offer antidepressants unless there was a preference for this type of therapy. For more severe depression, changes in the results were less substantial, and, again, they were consistent with the recommendations and the hierarchy for this population, according to which combined CBT+antidepressants was placed first, followed by individual CBT and BA, and then antidepressants.

						patients), with many more rare adverse effects. Studies find rates of treatment-emergent sexual dysfunction of 30-60% in patients on SSRIs (Gregorian et al 2002). These values do not seem at all consistent with the reported estimate of 0.07% of SSRI users will experience a side effect. It has also been found that adverse effects are more common in longer term users of antidepressants than in the short term RCTs from which the SPC data is partially derived (Bet et al. 2013), with further details of incidence rates from this study in the response to Evidence Summary B below (which are often more than two orders of magnitude greater than that derived from Anderson et al. 2012). These adverse effects, more of which are outlined at the end of this section should be taken into account when evaluating health related quality of life as well as incorporated into the economic model. Lack of evidence of clinical effectiveness for treatments recommended by the committee and evaluation of their cost-effectiveness despite lack of clinical effectivenessAntidepressants did not demonstrate clinically important differences in the primary outcome of change in depression score as measured by SMDs. In Table 24 on page 104-5 for bias adjusted results of the NMA all antidepressants showed statistically significant differences from pill placebo but failed to meet the threshold for minimally clinically important difference (MCID) set by the committee of 0.5 (albeit this is lower than the SMD of 0.875 established empirically (Leucht et al. 2013)):-SSRIs (-0.24, 95% CI -0.16 to -0.32)-TCAs (-0.29, 95% CI -0.05 to -0.50)-SNRIs (-0.32, 95% CI -0.22 to -0.43)-Mirtazapine (-0.35, 95% -0.22 to -0.49)These findings are consistent with other reviews of	It is noted that, based on the data reported in Anderson et al., the risks of side effects from antidepressants were applied over the majority or the whole period over which people received antidepressant treatment in the model (i.e. 1 year and 3 months at minimum and 2 years and 3 months at maximum in the updated model). In sensitivity analysis, the 40% risk of side effects from antidepressants is applied over the whole period people receive antidepressants. The economic analysis has now been amended, in line with relevant recommendations: antidepressants are assumed to be received for at least 1 year following successful treatment (or 2 years if relapse prevention with antidepressants is required), and linear tapering is assumed to happen over 3 months, based on the committee's expert opinion. During tapering, additional GP visits have been modelled. <u>Clinical effectiveness of antidepressants for more severe depression</u> The committee reviewed the results of the bias-adjusted NMA for more severe

						antidepressant research that also find that antidepressants fail to show clinically relevant differences from placebo (Munkholm et al, 2019). It is therefore not clear why these treatments were evaluated for cost-effectiveness and therefore considered as recommended treatments when they were not found to be clinically effective. The requirement specified on page 14 (line 5 to 7 of Evidence Review B) of an SMD >0.5 or <-0.5 to be designated an effective treatment seems to have been neglected when on page 122 in Evidence Summary B, in lines 34-35 only a "higher mean effect on the SMD outcome" required consideration for cost effectiveness. This does not seem reasonable given that this means that cost-effectiveness could be evaluated for treatments which did not produce a clinically important difference from placebo. This is not consistent with the committee's stated aim "to assess their [treatments'] clinical effectiveness prior to assessing cost-effectiveness" (lines 17-18, page 122, Evidence Summary B). In addition there are a number of reasons why studies may over-estimate the effectiveness of antidepressant medication compared to pill placebo including the use of placebo run-in in study design (whereby patients already on antidepressants are taken off their antidepressant for a week before randomisation to placebo or antidepressant, such that withdrawal effects present in the placebo group, but resolved by the antidepressant allocation will exaggerate the apparent effectiveness of antidepressants) (Munkholm et al 2019). The response rate illusion is particularly pertinent to antidepressant as the average effect of antidepressants and placebo lie on opposite sides of the	depression for the outcome of SMD, compared to pill placebo, and noted that pharmacological treatments (SSRIs, TCAs, SNRIs, mirtazapine), and combination therapy with individual CT/CBT plus antidepressants appeared to be effective. In reviewing the evidence, the committee noted that the point estimates for antidepressants did not meet the threshold for a clinically important effect. However, the committee also noted that the credible intervals for the pharmacological therapies were all very narrow, and that this was due to the fact that these results were based on large populations from multiple studies and therefore there was less uncertainty around these results. <u>Cost-effectiveness analysis</u> Treatments selected for the cost-effectiveness analysis were those that had shown a higher effect than pill placebo and had been tested on more than 50 participants in the trials included in the NMA on the SMD outcome, as well as the NMAs on discontinuation, response in completers and remission in completers, which were the outcomes that informed the economic analysis. This was the minimum

						50% reduction in score used to define 'response' (Kirsch and Moncrieff, 2007), and so it is not clear that response rate is a useful metric for evaluating the benefits of antidepressants. Unblinding leading to increased expectancy effects in the antidepressant arm is also likely to have a significant impact on results since expectancy effects have been shown to have substantial effects in numerous studies (Faria et al, 2017; Chen et al, 2011). Lastly it is not clear that publication bias was satisfactorily taken into account when it is recognised to be extensive for antidepressant trials, and that unpublished trials show half the effect size of published trials (Munkholm et al 2019). Present practice bias evident in support for existing treatments over evidence-based treatments We suggest there is evidence of an inclination towards recommending treatments used in current clinical practice over what the objective evidence in the review suggests because of the familiarity of those treatments to the clinicians involved in the review. Two major examples of this include the preference for recommending antidepressants alone, and in the choice to de-prioritise problem solving therapy and instead prioritise combination treatment with antidepressants CBT. As outlined above, despite failing to show clinically important differences from pill placebo antidepressants were recommended for more severe depression, suggestive of an inclination to recommend currently used treatments rather than based recommendations primarily on objective evidence. In all 12 health economics scenarios explored by the committee for cost-effectiveness (Table 99, Evidence Summary B), problem solving therapy emerged as the single	amount of evidence that a treatment class should have in order to be considered for a practice recommendation. The committee looked at the total size of the evidence base in this area (treatment of a new episode of depression) and the large volume of evidence for some treatment classes relative to others, and decided not to consider treatment classes with a small size of evidence base (tested on <50 participants) as there were several treatment classes with much larger volume of evidence. The cost-effectiveness of treatments was evaluated based on the guideline economic analysis. The PANDA study was included in the systematic review of economic evidence as it met inclusion criteria, but, like other studies included in the economic review, it was hardly considered when assessing the relative cost-effectiveness between interventions of interest and when making recommendations. As it is stated under 'The committee's discussion of the evidence -> Cost effectiveness and resource use': "Existing economic evaluations assessed a limited range of pharmacological, psychological and physical interventions in,

						most effective treatment. However, on page 144 of Evidence Summary B, lines 42 and 47 an unconvincing argument is put forward as to why antidepressant +CBT is elevated above problem solving, suggesting that there was 'high uncertainty' around problem solving therapy. However uncertainty around individual problem solving (a range of 8 ranks, 1 to 9) was less than the uncertainty concerning the treatment recommended in its place, CBT+ antidepressants, which has even higher uncertainty (a range of 15 ranks, 1 to 16), and a higher mean rank of 6.08 (for combination treatment) compared with 1.89 (for problem solving), with a lower rank indicating a more favourable treatment (Table 98, page 359, Evidence Summary B). A second rationale is provided for demotion of problem solving therapy on page 145 of Evidence Summary B in lines 21-25 which we believe to be equally unconvincing. Here the committee notes "that in some conceptualisations, it is only a variant of CBT" – again the conceptual relevance remains unclear when studies have demonstrated that this particular treatment is effective. Additionally it is not at all clear that problem solving and CBT are overlapping: CBT centres around re-appraisal of thinking patterns and does not necessarily have the same goal-directed behaviour that problem solving therapy entails. Overall, the rationale for de-prioritising problem solving does not seem convincing and we suggest that this treatment is retained as the first choice treatment. Overall, problem solving is likely to have significantly less harms associated with it than exposure to a medication, while it seems similarly effective. Reliance on a methodologically flawed single study for evaluation of cost-effectiveness which	mostly, pairwise comparisons, so it was difficult for the committee to draw any robust conclusions on the relative cost effectiveness of the full range of interventions that are available for the treatment of adults with a new episode of less severe depression." Hence, the committee relied heavily on the results of the guideline economic analysis, which was informed by the guideline NMAs, in order to make recommendations. No cost-effectiveness data were extracted from the PANDA study to inform the guideline economic analysis, nor was the PANDA study used to draw conclusions on the relative cost-effectiveness of sertraline versus other treatments, simply because the PANDA study compared sertraline to placebo and not to any other active intervention of interest. <u>Methodological flaws in the studies included in the clinical evidence review</u> The committee prioritised standardised mean difference (SMD) of depression symptom change scores at treatment endpoint as the primary critical outcome, as they recognised that continuous changes in scores on depression scales will show

						did not demonstrate minimum clinically important differences for its primary outcomeThe committee evaluated the cost effectiveness of antidepressants alone, despite them not demonstrating clinical effectiveness in NICE's own analysis or in the paper from which the cost effectiveness data was extracted (Lewis et al, 2019). As above no analysis for more severe depression demonstrated a clinically important difference for antidepressants when compared to pill placebo. The committee used the PANDA study published as Lewis et al (2019) with economic analysis published as Hollingworth et al (2020) to derive cost-effectiveness for sertraline. However, this study suffers from more than the 'minor limitations' designated. This study found marginal differences of patients assigned to sertraline rather than placebo (13% reduction in PHQ-9 score, 95% CI 3% to 21%). The change in the primary outcome of depression score (PHQ-9) was 4.89 points in the sertraline group and 4.18 in the placebo group. The difference in change between the two groups was 0.8 points on the 27-point PHQ-9 scale. The minimum clinically important difference for PHQ-9 has been calculated as 3.0 (Lynch et al 2021) or 5.0 points (Lowe et al 2021). A change of 0.8 points does not meet the threshold for a minimally clinical important difference. This corresponds to an effect size of 0.18 (Hengartner et al 2020a), which is below the threshold NICE designated for minimum effect size of 0.5. Effects on anxiety were similarly small (effect size <0.25) (Hengartner et al 2020a). This was not evaluated by the committee because cost-effectiveness data was extracted from this study without first evaluating whether this was treatment produced a	changes for people who have both fully and partially recovered and this was agreed by the committee to be the best measure of clinical effectiveness. However, dichotomous data was also extracted and analysed to examine consistency of effects, to use in the economic modelling, and to maximise the data available through transforming response data to change from baseline where continuous data were not available (see Appendix M of Evidence report B). Regarding economic modelling, use of dichotomous outcomes allowed defining model health states and linking to appropriate health state utility values and estimation of QALYs, which is the NICE preferred outcome measure and allows judgements on cost-effectiveness within the NICE decision-making context. Estimation of QALYs would not be possible had exclusively continuous outcomes, without any transformation, been used in modelling. The potential for bias introduced by short placebo run-ins and abrupt discontinuation of prior antidepressant treatment is not relevant to Evidence review B as the focus is on first-line treatment of a new episode of depression. For the relapse prevention

						minimally clinically important difference and therefore demonstrated clinical effectiveness. Furthermore, unblinding was an issue in the PANDA study and may have exaggerated differences in the two groups due to expectation effects for those assigned to sertraline – 81% of patients correctly guessed they were assigned to placebo and 46% correctly guessed they were assigned to sertraline (Hengartner, 2020a). There was also a lack of power to detect adverse effects, such as suicidal behaviour, cardiovascular events or hepatotoxicity which are recognised for antidepressants, which was therefore not considered in cost-effectiveness data – and the difficulty and costs of stopping sertraline was not taken into account in this calculation (Hengartner, 2020a). Patients were also only excluded if they had used antidepressants in the previous 8 weeks so some participants may have had antidepressant withdrawal symptoms at baseline, artificially exaggerating the beneficial effect of commencing sertraline which would resolve these symptoms, likely to register on symptom scales for anxiety and depression. Prioritisation of short term symptom changes over long term quality of life and functioning outcomesFurthermore, less useful data was prioritised by the committee – although the committee recognised that long-term studies and quality of life and functioning were more important than short term or symptom score reductions, because there was more information for the latter evaluation of effectiveness was made on short term symptom scores; long-term outcomes, including quality of life and functioning scores (which found large effects for a number of treatments) were neglected. It	review, the speed of tapering was considered in the risk of bias assessments, and in the committee's interpretation of the evidence. Publication bias was considered in the bias adjusted NMA models. Small sample size studies are associated with publication bias as small studies with positive results are more likely to be published compared with small studies with negative results, and may also be associated with lower study quality. As the NMAs included a significant number of small studies, sensitivity analyses were carried out on selected outcomes, which adjusted for bias associated with small study size effects. The analyses, which were based on the assumption that the smaller the study the greater the bias, attempted to estimate the "true" treatment effect that would be obtained in a study of infinite size. Data from unpublished studies were also included where they could be extracted from the previous 2009 NICE Depression guideline or from a systematic review (including the Cipriani 2018 NMA), and a considerable number of unpublished

						does not seem reasonable to prioritise less relevant data simply because it exists in greater quantities. This risks extrapolating recommendations for long-term treatment based on short term studies with outcomes that may be irrelevant to long-term benefits to patients. Indeed, short term studies of antidepressants are particularly ill suited to extrapolate to long-term recommendations because long term studies find much less promising results than short term studies – for example 3.7% of patients in the STAR-D trial at one year were free of relapse and did not drop out of the study (Pigott et al, 2010). Some authors have suggested poorer long term outcomes may result from tolerance to antidepressants (Kinrys et al, 2019), making the derivation of long-term outcomes from short term outcomes as fraught as for benzodiazepines and opioids. We recommend that if the committee should include in its research recommendations that studies evaluating treatment for depression should be conducted over relevant time periods (e.g. 1-2 years or longer) particularly evaluating the most relevant outcomes for patients of quality of life and functional status so that future evaluations can use the most relevant dataAdditional costs of withdrawal or not being able to stop antidepressants not taken into accountWhile there is no cost associated with stopping many of the non-pharmacological treatments outlined in this guidance, there is considerable costs to stopping antidepressants as outline in this guidance, which is not included in the cost-analysis. The overview of this process was given in Evidence Summary B, page 324 that: “Acute pharmacological treatment was administered over 12 weeks.	antidepressant trials were included in the NMAs. The committee were aware of the risk of non-blinding of participants due to adverse effects, and also considered the blinding of outcome assessors when making risk of bias judgements. <u>Interpreting the evidence, and existing clinical practice</u> The committee do not agree that they prioritised current clinical practice over evidence. Assessment and interpretation of the evidence to inform guideline recommendations is at the heart of the work of the committee. The committee did not place individual problem solving at the top of recommended treatments for more severe depression, despite of the results of the economic analysis which suggested it was the most cost-effective treatment option among those assessed, because they noted that relevant evidence was derived from US studies. The committee also noted that problem solving is not available as a stand-alone intervention in the UK and, in some

						At the end of this period, adults with less severe depression who achieved remission had their drug gradually discontinued (tapered); this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over the period of one month (according to routine clinical practice, as advised by the committee)."This is not an accurate summary of the process of stopping – the committee's own recommendation is that patients stay on antidepressant for several months for an episode so 12 weeks is an under-estimation of the costs. Consequently the time required for stopping drugs is also under-estimated as it might take several months for a patient to stop a drug tolerable and linear reduction over 4 weeks has never been demonstrated to be effective for patients on anything but extremely short term treatment. This section therefore under-estimates the time and resources required for stopping these medications. In practice, there are serious costs to people's wellbeing as well as costs to the health care system. In the first category there are the costs of time off work, inability to perform social roles such as caring for children or elderly dependents, and in some people long-standing inability and suicide (Guy et al, 2020; Hengartner et al 2020b). Additionally there are the costs to the health care system – which include increased visits to the doctor, the requirement to prescribe liquid versions of medication and increased monitoring throughout the process which can take months and in some patients years. For example the prescription of liquid mirtazapine for 2 years to help someone stop their medication (a common time period) can cost 24*80 = 1920 pounds. Other medications are cheaper than this but	conceptualisations, it is only a variant of CBT, with very similar efficacy with individual CBT but higher uncertainty around the mean effect, as demonstrated by the NMA on the SMD outcome. This further detail of committee's discussion has now been added under 'The committee's discussion of the Evidence' in Evidence review B. <u>Quality of life and functioning outcomes, and longer-term follow-up</u> The committee agree that quality of life and functioning outcomes, and long-term follow-up, are important. The committee noted the limited evidence for quality of life and functioning outcomes and for longer-term follow-up which made it difficult to compare these outcomes across interventions and inform new recommendations. These outcomes and follow-up time points were included for the research recommendations in the guideline. The guideline does not recommend long-term antidepressant treatment (except in the case of those at higher risk of relapse who have remitted with antidepressant treatment), and includes a recommendation

						extra costs should be taken into account in the cost-effectiveness analysis. Furthermore, there will also be a group of people for whom coming off their antidepressant will be too aversive because of the withdrawal effects and who will then continue to use this medication for several years or the rest of their lives, leading to unnecessary medication costs, as conservatively estimated in Davies et al, 2021. A study looking at stopping unnecessary antidepressants found that 93% of patients were unable to stop (Eveleigh et al., 2017). The REDUCE study in England is aiming to help 20% of patients stop unnecessary antidepressants, meaning that 80% of patients on unnecessary antidepressants will stay on their medication for years or perhaps life long. This will lead to considerable unnecessary costs to the health system and exposure to adverse effects to patients. The near certainty that a large proportion of people will continue their medication beyond what guidelines recommend should be taken into account. Unnecessary exclusion of options that did not involve medication for inadequate reasonsThe de-prioritisation of group exercise and self-help with support because of a lack of regular monitoring does not seem a reasonable rationale. On page 145 lines 28 to 33 of Evidence Summary B, the committee expresses uneasiness at the lack of development of a 'therapeutic relationship' if these treatments are encouraged. While we agree that a therapeutic relationship is important and that this might make psychological therapies more desirable, however we think that this is an unreasonable justification for prioritising medication over these treatments on the rationale that	(in the preventing relapse section of the guideline) that the potential risks of continuing with antidepressants long term, and how these balance against the risks of depression relapse, should be discussed with people with depression. <u>Costs of stopping antidepressants</u> Costs of time off work and inability to perform social roles were outside the scope of the economic analysis, which adopted a NHS and personal social services perspective, based on the NICE Guidelines Manual for interventions funded by the NHS. Additional visits to healthcare professionals over the period of tapering were considered in the analysis. Liquid preparations are not routinely required during tapering, and therefore they were not considered in the economic modelling. The related recommendation has been amended to say that these be considered once very small doses have been reached and slow tapering cannot be achieved using tablets or capsules. The recommendation involves a small sub-group of people who need to take very small doses of liquid preparations during last stages of tapering, over a short time period.

						people prescribed medication are monitored 'regularly'. Firstly, evidence suggests that patients are reviewed infrequently when on antidepressants with some simply having prescriptions automatically renewed and secondly if the intention is to have patients regularly monitored by doctors then this could be explicitly recommended without the need to prescribe antidepressants. A pre-requisite of a prescription to be monitored by a GP for depression does not seem a reasonable proposition. We suggest that it would be more reasonable to suggest treatments that are clinically effective and cost effective and if regular monitoring by a GP is thought to bring additional benefit (which might makes sense) then this is explicitly recommended. Equally, it might also be considered that self-help is personally empowering and reliance on a doctor fosters dependency. A selection of some adverse effects of antidepressants that were not considered by the evaluationThe adverse (or side) effects of antidepressants include numerous physical and psychological symptoms. Generally, adverse effects reported by surveys of long-term antidepressant users are greater than those reported by the manufacturers, which are derived from studies that are mostly of 6 to 12 weeks in duration.(Bet et al. 2013; Read and Williams 2018) One naturalistic study looking at adverse effects in 1,000 patients recruited from primary care and specialised mental healthcare settings with a median duration of antidepressant use of one year found that two-thirds had at least one side effect, with a third having three or more, with risk of side effects increasing with each year of use (Table 1).(Bet et al. 2013)	The impact of withdrawal symptoms has been taken into account by the committee. For this reason there are specific recommendations on how to stop antidepressant medication, and a key research recommendation on the incidence and severity of withdrawal symptoms for antidepressant medication. <u>Consideration of other non-pharmacological interventions</u> The committee included group exercise and self-help with support as treatment options for more severe depression but ranked these lower in Table 2 because of concerns about the suitability of these interventions for people with more severe depression, because (as acknowledged in your comment), they do not require the development of a therapeutic relationship in the same way that the more intensive psychological therapies do, or that would develop through more regular monitoring for antidepressant treatment. The recommendations suggest that routine outcome monitoring is considered for all treatments. However, the committee

							agreed that the evidence on whether routine outcome monitoring improves outcomes was equivocal, but noted that it may be valued by people with depression. On this basis, the committee agreed to recommend routine outcome monitoring as a 'consider' for all treatments. Whereas, for pharmacological interventions the regular monitoring recommendations are stronger due to the potential for side effects. <u>Adverse effects of antidepressants</u> Although the committee acknowledge that the outcome of discontinuation due to side effects in the context of short-term RCTs provides limited evidence for the potential of harms in the longer term, there is a recommendation about starting antidepressants that recommends discussing harms and includes as examples some of the harms you mention (the recommendation includes weight gain, sedation, and effects on sexual function, as examples). The guideline also includes a specific recommendation for prescribing antidepressant medication for older people. The list of potential harms is not exhaustive,

							but the committee agreed that, in their experience, the examples given were the side-effects that people were concerned about.

252	SH	NHS England and Improvement	Guideline	31	12	Table 2 – Please provide greater clarity over the decision/option to use antidepressant treatments alone – or in combination with any of the none- pharmacological treatment options listed in table 2	Thank you for your comment. The evidence of benefit was seen with antidepressants in combination with CBT so this is the only psychological therapy that is recommended with antidepressants, and this was more effective and appeared more cost-effective than antidepressants alone, which is why the combination is listed higher in the table.
253	SH	NHS England and Improvement	Guideline	31	12	Ref: 'Table 2: Treatment Options for More Severe Depression', we for the 'self-help with support' treatment, under the 'How is it delivered section', we recommend adding referral to a social prescribing link worker	Thank you for your comment. Evidence for social prescribing was not sought or reviewed, and on this basis the committee did not feel it appropriate to make the suggested change to the recommendation. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice.
254	SH	NHS England and Improvement	Guideline	31	12	Ref: 'Table 2: Treatment Options for More Severe Depression', we recommend that 'nature based activity' or 'green social prescribing' is offered as a treatment option beneath group exercise.Current review of evidence: 'Nature-based outdoor activities for mental and physical health: systemic review and meta-analysis', P Coventry et al, Oct 21 As stated in the guidance about referral to group physical exercise, the same reasonable adjustment considerations will apply, to ensure access.	Thank you for your comment. Nature-based interventions or green social prescribing were not specified in any of the review protocols and thus evidence for specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, in response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not as a

							treatment for depression) and made a new recommendation to reflect this. The recommendation also emphasised the benefits of outdoors activities. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).
255	SH	NHS England and Improvement	Guideline	31	12	Ref: 'Table 1: Treatment Options for More Severe Depression', we recommend that 'arts based activity' or 'creative health social prescribing'' is offered as a treatment option beneath group exercise****Review of evidence: https://www.euro.who.int/en/publications/abstracts/what-is-the-evidence-on-the-role-of-the-arts-in-improving-health-and-well-being-a-scoping-review-2019	Thank you for your comment. Art therapy was listed as an intervention of interest for the treatment reviews. However, no eligible evidence was identified for art therapy as a first-line treatment. The only included study for art therapy (Nan 2017) was in the further-line treatment review. The committee considered the evidence too limited to make a recommendation for art therapy. Evidence for social prescribing was not sought or reviewed, and on this basis the committee did not feel it appropriate to make the suggested change to the recommendation. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into

							account individual needs and allow patient choice.
256	SH	UK Council for Psychotherapy	Guideline	31	12	Table 2 Please include behavioural couples therapy in this table and the visual summary since it appears the decision to leave it out was in part based on an incorrect assumption that it is more or only appropriate for a subgroup of people with depression and studies were excluded from the research evaluation on this basis. This intervention is in the guidelines but, if excluded from the tables and visual summaries, is very unlikely to be considered as an option. Options such as IPT and STPP were included as the committee recognised that these treatments, although with less evidence of effectiveness, may be helpful for some people. This argument also applies to behavioural couples therapy. Please see additional points in Comment 6.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to include behavioural couples therapy in the tables or visual summaries of treatment options in the guideline as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with

							depression, unlike the other interventions listed in these tables/visual summaries.
257	SH	Association for Family Therapy and Systemic Practice	Guideline	31	12	Table 2 – It is also unclear why behavioural couples therapy has not been included in this table.It appears the decision to exclude behavioural couples therapy is in part based on an incorrect assumption that it is more or only appropriate for a subgroup of people with depression (who have relationship difficulties) and studies were excluded from the research evaluation on this basis. This intervention is in the guidelines but, if excluded from the tables and visual summaries, is very unlikely to be considered as an option. Options such as IPT and STPP were included as the committee recognised that these treatments, although with less evidence of effectiveness, may be helpful for some people. This argument also applies to behavioural couples therapy. Please see additional points in comment above.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to include behavioural couples therapy in the tables or visual summaries of treatment options in the guideline as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with

							depression, unlike the other interventions listed in these tables/visual summaries.
258	SH	University of South Wales	Guideline	31	Continuation Table 1	Outcome is being assessed for service delivery purposes in terms of a psychometric test, but this does not gauge what a patient cares about (the minimally important difference) e.g., back to normal or best functioning. It should be made clear that the outcome measure used is deficient. Examining service delivery may be premature unless it has first been established that therapy/medication makes a real-world difference in routine care	Thank you for your comment. As pre-specified in the review protocol, critical outcomes for the service delivery model review (Evidence review A) included depression symptoms, but also remission (usually defined as no longer meeting criteria for depression on a validated symptom severity scale) and response (usually defined as at least 50% improvement from the baseline score on a depression scale). A number of different care models did not have available data on the outcomes of remission and response. Therefore when considering the evidence the committee placed the greatest emphasis on depression symptomatology and antidepressant use, as these provided

							the best point of comparison across different interventions.
259	SH	The College of Mental Health Pharmacy	Guideline	31	Table 2	First line option is CBT plus “an antidepressant” – please add some advice in the boxes about choice eg try an SSRI first. Don’t put “see below” and leave this advice to the second page. Again this makes the message feel imbalanced, the reader needs everything in the first box.	Thank you for your comment. In order to keep the table to a manageable size, the committee agreed not to repeat the antidepressant and CBT information in multiple places.
260	SH	The College of Mental Health Pharmacy	Guideline	31	Table 2	First line option is “CBT plus an antidepressant” – how should clinician proceed if CBT is not immediately available?	Thank you for your comment. The delivery of treatments section of the guideline includes a recommendation that people are informed if there are waiting lists, and how long the wait is likely to be, are made aware of how to access help if their condition worsens, and the offer of self-help material in the interim is considered.

261	SH	The Federation of Holistic Therapists	Guideline	031-037	General	p.31-37 of the draft guidance outlines “Table 2: Treatment options for more severe depression listed in order of recommended use, based on the committee’s interpretation of their clinical and cost effectiveness.”Again, no massage, aromatherapy, reflexology or other touch therapy options are included in this section. Please refer to the comments made in ‘Comment 1'.	Thank you for your comment. The committee did not consider massage, aromatherapy, reflexology or touch therapy to be interventions that were in regular clinical use for the treatment of depression. Therefore these interventions were not specified in any of the review protocols and consequently the studies that you cite would not have met the inclusion criteria for the reviews. As such the evidence on massage, aromatherapy, reflexology and touch therapy has not been appraised and the committee were not able to make any recommendations on their use.

262	SH	University of Exeter Medical School	Guideline	031-037	Table 2	THIS COMMENT IS IDENTICAL TO THAT ON TABLE 1 SINCE THE SAME ERROR IS MADE BY THE GUIDELINE IN BOTH TABLES 1 AND 2. We support the inclusion of Behavioural Activation as a first line treatment for more severe depression. However, the order in which treatments are listed by clinical and cost effectiveness is inaccurate. Behavioural activation has been shown to be more cost-effective and no less clinically effective than individual CBT in a £2m head to head trial funded through NIHR HTA. We note that this trial (COBRA) alongside other NHS facing trials, has been excluded from the clinical effectiveness evidence synthesis. We will comment on the wisdom or not of this elsewhere. However, the decision to exclude this trial has removed the health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world. Putting BA below CBT in table 1 is a mistake.	Thank you for your comment. The ranking of interventions recommended for less and more severe depression was based on evidence of clinical and cost-effectiveness as well as other clinical considerations, e.g. the risk of side effects for antidepressants, availability of treatments in the NHS and structure of IAPT services. Regarding clinical effectiveness derived from the NMAs, the committee considered not only the mean effects of treatment classes vs the reference treatment, but the uncertainty around them (as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of the pairwise meta-analysis. Regarding cost-effectiveness evidence, this was primarily based on the guideline economic analysis, which allowed to simultaneously compare the relative cost-effectiveness of all relevant treatment options that were assessed in the guideline. This simultaneous comparison was practically impossible to be made by single studies. The COBRA trial was excluded from

							the NMA because it did not meet inclusion criteria for a new episode of depression. This is because <80% of the study sample received first-line treatment for a new episode of depression. This was a requirement of the review protocol in order to create a homogenous data set. Nevertheless, the committee used their knowledge of pragmatic trials such as the COBRA trial when interpreting the evidence from the NMAs and the economic analysis and making recommendations. The guideline economic analysis considered a wide range of evidence as it utilised clinical data from the guideline NMAs, which included 142 RCTs of treatments for less severe depression and 534 RCTs of treatments for more severe depression and was directly relevant to the NHS context as it utilised UK resource use data and unit costs, supplemented by the committee's expert opinion on the optimal delivery of interventions in UK routine care. In the economic analysis and the table of recommendations, behavioural activation is described and recommended as a high intensity intervention, delivered by Band 7 practitioners with therapy-specific training and competence. In contrast, in the COBRA

							trial, behavioural activation was delivered by junior mental health workers, and this was a parameter that highly contributed to the study conclusion that it was more cost-effective than CBT (which was delivered by high intensity therapists in the COBRA trial). Individual behavioural activation is placed just below individual CBT in both Tables 1 and 2 of the guideline, which reflects the fact that the two treatments have similar clinical and cost-effectiveness. Interventions are arranged in Tables 1 and 2 of the guideline in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice.

							The treatment recommendations have now been updated to reflect more clearly the key principles of stepped care, which is the prevailing model of care in IAPT. In the updated recommendations, low-intensity behavioural activation, delivered by PWPs, has now been described as part of guided self-help.

263	SH	The College of Mental Health Pharmacy	Guideline	32	Table 2	There doesn't appear to be a mention of augmentation drug treatments. Lithium and antipsychotics appear to have been omitted.	Thank you for your comment. This table only covers first-line therapy and even in severe depression this would not encompass lithium and antipsychotics, which are included in further-line treatment.
263	SH	Royal College of Psychiatrists	Guideline	033-034	Table 2	Section on "Counselling" in table 2. We note the comments on why the committee made the recommendations in table 2 for severe depression, and in particular p. 68, lines 9-10, that there was "some evidence" for counselling (i.e. less than for antidepressants and individual CBT). We would recommend that the weaker evidence base for counselling should be explicitly mentioned in table 2 in the column "Other things to think about".	Thank you for your comment. The committee considered it important to provide a wide range of interventions to take into account individual needs and allow patient choice. Non-directive counselling had also been demonstrated to be cost-effective in more severe depression and so the committee recommended this intervention as an alternative to the interventions listed higher in Table 2. The committee did not consider it appropriate to make the amendment suggested in your comment, but agreed that as the order in the table is based on the committee's interpretation of the clinical and cost-effectiveness, the position of counselling is consistent with this intervention being considered for use after taking into account the other treatments that appear higher in the table.

264	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	35	Table 2	As a provider of Increasing Access to Psychological Therapies (IAPT) services we have concerns that 15 minute supported self-help sessions would diminish the meaningfulness and value of sessions for service users and Psychological Wellbeing Practitioner clinicians, and from clinical experience and ongoing reviews of recovery data would seem to be a severely inadequate dosage of required treatment.	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions.

265	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	35	Table 2	Supported self-help for severe depression may make service users with high levels of depression feel unheard and their experience invalidated.	Thank you for your comment. The committee considered it important to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion. The committee noted that there was some evidence that guided self-help was both effective and cost-effective for more severe depression. It was also recognised by the committee that people who have had prior episodes of depression may have preferences for their treatment based on prior experience or insight into their own depression patterns. The committee were uneasy about recommending guided self-help for more severe depression, based on concerns that these interventions may not be suitable for people with more severe depression as they do not require the

							development of a therapeutic relationship in the same way that the more intensive psychological therapies do, or that would occur when people are monitored regularly if on antidepressants. However, the committee agreed that as the evidence had shown benefit and cost-effectiveness, guided self-help could be considered for use in people with more severe depression who had a preference for guided self-help, or who did not want to consider any other treatment options.

266	SH	Talking Therapies	Guideline	035-036	General	Table 2 – self-help with support is recommendation number 9. Again, as I have previously commented, this is not in line with the stepped care model, as it comes after more intensive step therapies. In line with the stepped care model, it should be one of the first recommended treatments, considered prior to CBT or other high intensity options. If for whatever reason it is not suitable for a client, then it can be 'stepped' over. Please can self-help with support be one of the first treatments to be recommended and considered for patients.	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice. The self-help with support section has been relabelled as guided self-help, placed earlier in the treatment pathway, and the description of guided self-help has been amended.

267	SH	Active Partnerships National Team	Guideline	36	Table – group exercise	We support the inclusion of exercise as an optional first line treatment for people experiencing more severe depression. Sport England's partnership with Rethink Mental Illness has embedded informal physical activity into community support groups across England to support individuals experiencing severe mental health challenges to be more active and better manage their symptoms. An unpublished report by Rethink 2021 showed improvements in resilience, psychological wellbeing, quality of life, health, and motivation to be active. We support the inclusion of peer supportThere is strong evidence that peer-to-peer support is effective for improving mental health, and interventions with others with lived experience supports people feel motivated (Kinnafick, Smith, Appleton, Tweed, Bayes &Tyler, 2017). Sport England's major investments with Mind and Rethink Mental Illness take a peer-to-peer support approach and this has proven successful in supporting people with mild and severe mental health conditions. Peer to peer support has been particularly effective in informal, less structured exercise within these partnerships and has helped integrate moving more generally into everyday life. We are concerned about the frequency and duration information included within the delivery information'60-minute sessions, usually 3 times a week for 10 weeks' could be unrealistic for people experiencing symptoms associated with severe depression i.e. low motivation and fatigue. We know that individuals with depression tend to be more sedentary and less physically fit than their non-depressed counterparts. Considering this and our experience of working with people with mental health conditions this	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. In response to stakeholder comments, the committee also supported less intense 'move more' exercise for general wellbeing (although not as a treatment for depression) and made a new recommendation to reflect this.

						would be very challenging for patients in practice and lead to high attrition rates and recruitment issues. We recommend assessing what patient's current activity levels are (utilising the Short Active Lives survey) as a helpful starting point. Taking a starting point into account, those who are currently'inactive' (taking part in less than 30 minutes of moderate intensity exercise per week) focus on building up to 30 minutes a week'fairly active' (taking part in 30-149 minutes of moderate intensity exercise per week) focus on building up to doing 150 minutes a weekalready 'active' (meeting the CMO guidelines of 150 minutes of moderate intensity per week) focus on maintaining 150 minutes or increasing.	

268	SH	Rethink Mental Illness	Guideline	036-037	General	We strongly recommend that the ranking system of treatment, placing 'group exercise as number 6, is reconsidered: The table displays treatment in order of recommended use, with group exercise as the 6th most clinically and cost effective. Physical activity can be done in conjunction with medicated treatment and has significant benefits beyond mental wellbeing, including reducing the risk of developing physical health conditions, such as coronary heart disease, stroke, type 2 diabetes and cancer, improves strength and flexibility, and supports weight management. Therefore, we suggest that rather than being ranked, a moderate level of physical activity is recommended alongside all other treatment options. Secondly, we urge more flexibility in the recommended timings for 'group exercise' of 60 minutes, 3 times a week: This may be an unrealistic expectation for those experiencing severe depression, particularly for those who are considered inactive according to the Chief Medical Officer's guidelines for physical activity (less than 30 minutes per week). The recommended duration and frequency are greater than the recommendation in the CMO guidelines, which suggests adults should aim to be active for at least 150 minutes per week spread across the course of seven days. Due to a number of social and medical factors, many of those with severe depression may be currently doing no physical activity – guidelines must recognise that for these people there is significant benefit in them starting with a smaller and more achievable amount physical activity to begin with.As stated in the CMO guidelines, "…there is now evidence that lower volumes (less than 150 minutes per	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this. In addition to the results of the network meta-analysis (NMA), the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee agreed that decisions on treatment should be made in discussion

						week), lower intensities (i.e. light physical activity) and lower frequencies (one or two sessions per week) of physical activity may nevertheless confer health benefits." This was reiterated in our physical activity peer support project, funded by Sport England, where participants were given autonomy over the quantity and duration of activity. This resulted in groups opting for a combination of 1 hour per week, 30 mins per week, and 3 x 10-minute bouts during a 2 hour peer support group meeting. This resulted in greater sustained participation and increases in motivation to be active:"…So, what the group have agreed is… we'll start off with 3 10-minute slots; the start, the middle and the end; all of them are different" (Peer support group lead).Proportionately, the greatest benefits of physical activity on health, including lower risk of obesity and all-cause mortality, and improved markers of lipid and glucose metabolism, come from progressing between being inactive and achieving moderate levels of physical activity, as stated in the CMO 2019 PA guidelines. We additionally urge that 'group exercise' is broadened to include other forms of physical activity, including individualised and person-centred activities which give people choice and encourage being active in everyday life. The We Are Undefeatable campaign (of which Rethink Mental Illness is an official partner) recognises that for those with severe depression, and other long term conditions, different approaches will work for different people."It is important to remember that everybody and how their condition affects them is different and finding the appropriate physical activity for you depends on your own personal circumstance."Suggested activities could also include	with the person with depression, and recommended that a shared decision should be made. Thank you for telling us about the existing physical activity programmes and campaigns. These will be passed onto the NICE shared learning team.

						walking, jogging, cycling and increased overall movement in everyday life, such as active travel.Personal Health Budgets can provide individuals affected by mental illness with a budget that can invest in support that will aid their recovery and help them achieve their goals. Rethink Mental Illness's recent guide to community mental health transformation details an individual who also lives with both a mental health and physical health condition who used a Personal Budget to employ a personal assistant who also acts as their personal trainer and pay for gym membership. (Keep thinking differently: continuing your journey of community mental health transformation. Rethink Mental Illness, 2021)"Having a personal budget and co-produced care plan focused on my future and my goals has helped me reconnect to the person I am. This is an organic approach that grows and changes with a person as their needs and aspirations change. Person -centred care should be a given, not a blessing." (Individual with lived experience of Severe Mental Illness)It has been found that if individuals are allowed choice over their activity it will result in longer term adoption (Self-Determination Theory. Basic Psychological Needs in Motivation, Development, and Wellness. Ryan and Deci, 2017). Our physical activity programme, funded by Sport England also showed people severely affected by mental illness benefitted from ability to choose the activities that were right for them:"…pay more attention to what people want rather than just planning and expecting them to fit in with what [we] think will work well. …go to them first and [ask] what they want rather than just planning and do it the other way around…especially with	

						groups of people that have got mental health problems, it's not going to be everybody's going to turn up every week and follow this lovely path, life isn't like that." (Peer support group lead)	

269	SH	UK Council for Psychotherapy	Guideline	37	5	Rec 1.7 It is welcomed that behavioural couples therapy is recommended for consideration for people with either less severe or more severe depression. However, it is incorrect to state that this intervention is only or more appropriate for people who have problems in the relationship with their partner. It is suitable for anyone with depression who has a regular partner willing to attend with them. This is supported in line 9 where it says: 'involving their partner may help in the treatment of their depression'. There is also evidence that it is effective for couples without relationship distress as well as those with relationship problems (Baucom, D., Fischer, M., Worrell, M., Corrie, S., Belus, J., Molyva, E. and Boeding, S. (2018) Couple-based intervention for depression: an effectiveness study in the national health service in England. Family Process, 57: 275–92. https://doi.org/10.1111/famp.12332).We strongly request deleting the words in line 5 'who have problems in the relationship with their partner' and the word 'the' in line 7 so it reads as follows: Consider behavioural couples therapy for people with either less severe or more severe depression if• relationship problem(s) could be contributing to their depression, or• involving their partner may help in the treatment of their depression.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to change the recommendation for behavioural couples therapy as the evidence considered was only for people with depression who also had problems in the relationship with their partner. There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. It is also recommended in the access to services section that commissioners and providers of mental health services should

							promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
270	SH	Association for Family Therapy and Systemic Practice	Guideline	37	5	Rec 1.7 - We suggest removing the words in line 5: 'who have problems in the relationship with their partner'.AFT members welcome the inclusion of behavioural couples therapy in the guidelines for people with either less severe or more severe depression. Couples therapy by definition involves the partner of the person with depression. However, our clinical experience and the family therapy literature offer a rationale for working with people with depression and others in their family or network even where relationship distress is not a factor. Our members who hold extensive expertise in behavioural couples therapy have noted the intervention is suitable for anyone with depression who has a regular partner willing to attend with them, not just those who have problems in the relationship with their partner. There is also evidence that it is effective for couples without relationship distress as well as those with relationship problems (Baucom, D., Fischer, M., Worrell, M., Corrie, S., Belus, J., Molyva, E. and Boeding, S. (2018) Couple-based intervention for depression: an	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to change the recommendation for behavioural couples therapy as the evidence considered was only for people with depression who also had problems in the relationship with their partner.

						effectiveness study in the national health service in England. Family Process, 57: 275–92. https://doi.org/10.1111/famp.12332).Couples therapy for depression should be more widely available to depressed people to help reduce the burden on partners and potentially prevent relationship breakdown (Priestley, J and McPherson, SJ and Davies, F (2018) Couples Disease: The Experience of Living with a Partner with Chronic Depression. Journal of Couple and Relationship Therapy, 17 (2). 128 - 145. ISSN 1533-2683) rather than being seen as an option where relationships have already become problematic.	There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. It is also recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
271	SH	Association for Family Therapy and Systemic Practice	Guideline	37	7	We strongly request deleting the word 'the' in line 7 so it reads as follows: Consider behavioural couples therapy for people with either less severe or more severe depression if• relationship problem(s) could be contributing to their depression, or• involving their partner may help in the treatment of their depression.	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered only in pairwise comparisons (and not included in the NMA). The committee did not consider it appropriate to change the recommendation for behavioural couples

							therapy as the evidence considered was only for people with depression who also had problems in the relationship with their partner.
272	SH	Association for Family Therapy and Systemic Practice	Guideline	37	9	Rec 1.7.1 - AFT welcomes the decision of the committee to recognise the inclusion of partners as helpful in the treatment of depression. We would suggest involving other family members or significant people in the network of the person with depression is also helpful.	Thank you for your comment. In the access section of the guideline there is a recommendation that commissioners and providers of mental health services should ensure that there are procedures in place to support active involvement of families, partners and carers. In the choice of treatments section of the guideline there is also a recommendation that family members, carers, or other supporters should be involved in discussions about treatment options if this is requested by the person with depression.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

273	SH	The College of Mental Health Pharmacy	Guideline	37	General	Re flow of the document. This section doesn't seem to sit comfortably here.	Thank you for your comment. The committee considered the section on Behavioural couples therapy for depression to be best placed after the general first-line treatment options and before the preventing relapse or further-line treatment options, as behavioural couples therapy is recommended as a first-line treatment for a new episode of depression. However, the committee did not consider it appropriate to include behavioural couples therapy in the sections above (1.5 or 1.6) as the evidence and recommendation for behavioural couples therapy was for a subgroup of people with depression (for people with problems in the relationship with their partner) , unlike the other interventions included in the previous sections.
274	SH	UK Council for Psychotherapy	Guideline	38	12	Rec 1.8.3. Suggest including in the list under 'Discuss with people that the likelihood of having a relapse may be increased if they have:' the words 'relationship problems'. Evidence exists showing relationship discord predicts the development of depression, depression predicts future relationship discord and relationship distress is associated with poorer outcomes from individual therapy (Baucom, Donald H., Whisman, Mark A. and Paprocki, C. (2012) Couple-based interventions for Psychopathology. Journal of Family Therapy, 34: 250–70).	Thank you for your comment. Relationship problems has been added to this list, as you suggest.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

275	SH	NHS England and Improvement	Guideline	38	22	Rec 1.8.3 – as with 1.2.7 recommendation does not cover a broad enough range of wider determinants, suggest using the same language as before.	Thank you for your comment. As this recommendation refers back to the determinants of depression, a hyperlinked cross-reference to recommendation 1.2.7 has been added.
276	SH	Association for Family Therapy and Systemic Practice	Guideline	38	24	Rec 1.8.3. – We would suggest adding a further point here to the final bullet point under 'Discuss with people that the likelihood of having a relapse may be increased if they have, so it reads as follows: "personal, social and environmental factors that contributed to their depression and that are still present (for example, ongoing stress, poverty, isolation, and/or relationship difficulties." This is because relationship discord predicts the development of depression, depression predicts future relationship discord, and relationship distress is associated with poorer outcomes from individual therapy (Baucom, Donald H., Whisman, Mark A. and Paprocki, C. (2012) Couple-based interventions for Psychopathology. Journal of Family Therapy, 34: 250–70).	Thank you for your comment. 'Relationship problems' has been added to this recommendation, but in order to keep the recommendations succinct, it is not usual to include the rationale or background information, so the additional information you suggest has not been added.
277	SH	The College of Mental Health Pharmacy	Guideline	38	General	Re flow of the document. Much of this section has been said before, but some hasn't. so partly feels repetitive and doesn't flow well. Please revise in order to ensure people can read the full message.	Thank you for your comment. This section has been reordered so that the general information is at the beginning of the section, then information about antidepressants, then psychological therapies, then monitoring at the end.
278	SH	The College of Mental Health Pharmacy	Guideline	38	General	And excess alcohol consumption.	Thank you for your comment. As this recommendation refers back to the determinants of depression, a hyperlinked cross-reference to recommendation 1.2.7 has been added, which includes alcohol use.

279	SH	Critical Psychiatry Network	Guideline	39	001-004	We are concerned that this cursory description of potential adverse effects from antidepressants will not equip people to make an informed decision about whether to continue or stop antidepressants. It is worth bearing in mind the small advantages of antidepressants found in short term and long term studies when addressing the importance of adverse effects. Using dichotomisation of data to generate response rates only 10-15% of people given antidepressants will benefit over and above those given placebo (when looking at short term outcomes). In relapse prevention trials (that are highly confounded by withdrawal effects mis-classified as relapse) only 20% of people benefit over and above placebo (e.g. 41% relapse rate in discontinuation arm of the Geddes et al (2003) meta-analysis compared with the 18% relapse rate in the maintenance arm). In this context, the finding that a similar or sometimes greater proportion of patients will experience an adverse effect should be weighted appropriately. Low mood is not like a deadly cancer for which effective treatment might justify common serious adverse effects. In the context of small effects for antidepressants (over-stated by the methodologies chosen by product manufacturers) adverse effects ('side effects') should be explained to the patient in detail so that they can make an informed choice. Antidepressants have more adverse effects in longer term use. In one study which involved evaluating people recruited for a study the following adverse effects occurring in more than 10% of people were noted (Bet et al., 2013). It is also worth noting that because people are on these drugs long term they do not attribute these effects to the antidepressant (and may therefore	Thank you for your comment and for this information on the potential side-effects of antidepressants. People who have already taken antidepressants will be aware of the side-effects they have experienced, and therefore will be able to use their own personal knowledge of these to weigh up whether the side-effects are more or less of a concern to them, than the possibility of their depression relapsing. The list of side effects is not exhaustive and increased bleeding risk and effects on sexual function are given as examples of two effects which may be of more concern to people taking antidepressants for longer.

						require prompting to recognise the relationship). Sexual dysfunction (23%)Sleepiness (21%)Dry mouth (22%)Profuse sweating (20%)Nausea (10%)Weight gain (19%)Dizziness (12%)In surveys of a convenience sample of people who were on antidepressants for longer (most on for more than three years) rates of adverse effects were even higher: • emotional numbness (71%), • 'feeling foggy or detached' (70%), • feeling not like myself (66%), • drowsiness (63%), • reduction in positive feelings (60%).(Read and Williams, 2018) Although this self-selected sample may not be a representative sample of all antidepressant users, 50% of this group reported suicidality that they attributed to the antidepressant.(Read and Williams, 2018)One survey found about 46% of patients reported emotional blunting.(Goodwin et al., 2017) This emotional numbing is described as "feeling emotionally detached" and "reduced sympathy and empathy".(Price, Cole and Goodwin, 2009).Weight gain Long-term use of antidepressants may cause a greater degree of weight gain than established in short-term trials. In one case-control observational study with almost 2 million patient years of follow up, in England, with patients taking SSRIs, SNRIs, and other commonly used antidepressants such as mirtazapine and tricyclics there was a 30% increased chance of people of normal weight becoming overweight or obese in 10 years of follow up, compared to people not taking antidepressants.(Gafoor, Booth and Gulliford, 2018) There was also a 30% increased chance of overweight people taking antidepressants becoming obese in 10 years compared to overweight people not taking antidepressants.(Gafoor, Booth	

						and Gulliford, 2018) It is possible that residual confounding might contribute to these associations. The effects were most marked for mirtazapine (50% increased chance of greater than 5% weight gain) and, notably, citalopram had greater effects than other SSRIs.(Gafoor, Booth and Gulliford, 2018) Cognitive effectsMeta-analysis has also found that antidepressants produce cognitive impairment in healthy controls, on tests of information processing, memory, hand-eye co-ordination, concentration, as well as higher order functions.(Hindmarch, 2009) There was variation between different antidepressants with SSRIs producing between 1 and 16% impairments (where proportions referred to the number of test points where impairment was found), while venlafaxine produced 9% impairment, mirtazapine produced 35% impairment, and older tricyclics producing between 19% and 47% impairment (highest for amitriptyline).(Hindmarch, 2009) These studies are useful in that they exclude confounding by an underlying disorder by studying the effects of antidepressants in healthy controls. Small studies find that MMSE scores (a crude measure of cognition that detects coarse changes in cognitive ability) decreased over consecutive weeks of follow-up in people with OCD given antidepressants.(Sayyah et al., 2016) The long-term consequences of these cognitive impairments have not been investigated. Risks in older peopleFor older people adverse effects can be more overt. A retrospective cohort study of over 61,000 patients found that the absolute risks over 1 year of exposure to SSRIs (adjusted for comorbidities and a range of potential confounding variables) of:• 5.7% for falls, • 2.6% for stoke/TIA, • 0.5% for upper	

						gastrointestinal bleeding, • 0.38% for seizures and • 0.44% for hyponatraemia.(Coupland et al., 2011)Absolute risks over 1 year for all-cause mortality were 7.04% for patients not taking antidepressants, 8.12% for those taking TCAs, 10.61% for SSRIs, and 11.43% for other antidepressants.(Coupland et al., 2011) This observational research is susceptible to confounding by indication, and residual confounding, so differences in characteristics between patients prescribed different antidepressants could account for some of the associations between them and the adverse outcomes.(Coupland et al., 2011)Potential increase in risk of dementiaThere is also evidence that antidepressants may increase risk of dementia. A large nested case-control study of 225 000 people found a dose-response relationship between total exposure to antidepressants and risk of diagnosis with dementia.(Coupland et al., 2019) Those patients with the highest exposure to antidepressants – more than 3 years of daily use of standard doses - had a 34% increased chance of dementia over those patients not exposed at all to antidepressants. Another nested case-control study of 40,000 people found similar results, with antidepressants with the strongest cholinergic properties (amitriptyline, dosulepin and paroxetine) producing a 10% increased risk of dementia.(Richardson et al., 2018) Other antidepressants (largely SSRIs), with lesser anticholinergic effects were also associated with dementia but associations were greater for prescriptions closer to dementia incidence suggesting reverse causation as a possible association.(Richardson et al., 2018) Although efforts were taken in both of these studies to	

						control for symptom score, diagnoses, there is the possibility that residual confounding may explain some of the associations. Sexual effectsSexual adverse effects can include a lack of desire as well as reduced sexual sensation, and can include failure to orgasm in both genders.(Rothmore, 2020) In one systematic review sexual dysfunction occurred in 25.8% to 80.3% of patients exposed to antidepressants (Serretti and Chiesa, 2009). It is now recognised that these sexual effects can persist even after cessation of antidepressants in a minority of patients, named post-SSRI sexual dysfunction (PSSD), and was recently recognised by the European Medicines Agency.(Bala, Nguyen and Hellstrom, 2018; Reisman, 2020) Sexual side effects can negatively affect a person's self-esteem, quality of life and relationships. Tardive dysphoriaAlthough not widely accepted there has been concern for some time that long-term use of antidepressants can itself induce dysphoria.(El-Mallakh, Gao and Jeannie Roberts, 2011; Fava, 2020) There are a number of different explanations for this phenomenon ranging from the effect of chronic numbing, lethargy, demotivation to non-specific brain changes caused by long term perturbation of neurotransmitter. It has been proposed to relate to the process of tolerance to these medications, involving serotonin receptor desensitisation, which can 'overshoot' leading to opposite effects to those originally produced by the medications.(Fava, 2020) This has been seen as analogous to opioid-induced hyperalgesia(Lee et al., 2011) and the increase in anxiety seen in long-term use of benzodiazepines.(Ashton, 1987) For example, one observation study found that	

						depressed people who used antidepressants long-term had poorer long-term outcomes compared to with non-users or those who used them short-term, even after controlling for baseline depressive severity.(Hengartner, Angst and Rössler, 2018) This is consistent with other prospective observational studies with 1-9 year follow-ups which also found poorer outcome in antidepressant users compared to non-users.(Goldberg et al., 1998; Bockting et al., 2007; Vittengl, 2017)Ashton, Heather. 1987. "Benzodiazepine Withdrawal: Outcome in 50 Patients." British Journal of Addiction 82 (6): 665–71.Bala, Areeg, Hoang Minh Tue Nguyen, and Wayne J. G. Hellstrom. 2018. "Post-SSRI Sexual Dysfunction: A Literature Review." Sexual Medicine Reviews 6 (1): 29–34.Bet, Pierre M., Jacqueline G. Hugtenburg, Brenda W. J. H. Penninx, and Witte J. G. Hoogendijk. 2013. "Side Effects of Antidepressants during Long-Term Use in a Naturalistic Setting." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 23 (11): 1443–51.Bockting, Claudi L. H., Mascha C. Ten Doesschate, Jan Spijker, Philip Spinhoven, Maarten W. J. Koeter, and Aart H. Schene. 2007. "Continuation and Maintenance Use of Antidepressants in Recurrent Depression." Psychotherapy and Psychosomatics 77 (1): 17–26.Coupland, Carol A. C., Trevor Hill, Tom Dening, Richard Morriss, Michael Moore, and Julia Hippisley-Cox. 2019. "Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study." JAMA Internal Medicine 179 (8): 1084–93.Coupland, Carol, Paula Dhiman, Richard Morriss, Antony Arthur, Garry Barton, and Julia Hippisley-Cox. 2011. "Antidepressant Use and Risk of	

						Adverse Outcomes in Older People: Population Based Cohort Study." BMJ (Clinical Research Ed.) 343 (aug02 1): d4551.Davies, James, and John Read. 2019. "A Systematic Review into the Incidence, Severity and Duration of Antidepressant Withdrawal Effects: Are Guidelines Evidence-Based?" Addictive Behaviors 97 (August): 111–21.El-Mallakh, Rif S., Yonglin Gao, and R. Jeannie Roberts. 2011. "Tardive Dysphoria: The Role of Long Term Antidepressant Use in-Inducing Chronic Depression." Medical Hypotheses 76 (6): 769–73.Fava, Giovanni A. 2020. "May Antidepressant Drugs Worsen the Conditions They Are Supposed to Treat? The Clinical Foundations of the Oppositional Model of Tolerance." Therapeutic Advances in Psychopharmacology 10 (January): 2045125320970325.Gafoor, Rafael, Helen P. Booth, and Martin C. Gulliford. 2018. "Antidepressant Utilisation and Incidence of Weight Gain during 10 Years' Follow-up: Population Based Cohort Study." BMJ (Clinical Research Ed.) 361 (May): k1951.Goldberg, David, Martin Privett, Bedirhan Ustun, Greg Simon, and Michael Linden. 1998. "The Effects of Detection and Treatment on the Outcome of Major Depression in Primary Care: A Naturalistic Study in 15 Cities." The British Journal of General Practice: The Journal of the Royal College of General Practitioners 48 (437): 1840–44.Goldsmith, Lucy, and Joanna Moncrieff. 2011. "The Psychoactive Effects of Antidepressants and Their Association with Suicidality." Current Drug Safety 6 (2): 115–21.Goodwin, G. M., J. Price, C. De Bodinat, and J. Laredo. 2017. "Emotional Blunting with Antidepressant Treatments: A Survey among Depressed Patients." Journal of Affective Disorders 221	

						(October): 31–35.Guy A, Brown M, Lewis S. The “patient voice”: patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. Therapeutic Advances in [Internet]. 2020; Available from: https://journals.sagepub.com/doi/abs/10.1177/2045125320967183Hengartner, Michael P., Jules Angst, and Wulf Rössler. 2018. “Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30 Years.” Psychotherapy and Psychosomatics 87 (3): 181–83.Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. 2020 Jan 1;10:2045125320980573.Hindmarch, I. 2009. “Cognitive Toxicity of Pharmacotherapeutic Agents Used in Social Anxiety Disorder.” International Journal of Clinical Practice 63 (7): 1085–94.Kendrick, Tony. 2021. “Strategies to Reduce Use of Antidepressants.” British Journal of Clinical Pharmacology 87 (1): 23–33.Lee, Marion, Sanford M. Silverman, Hans Hansen, Vikram B. Patel, and Laxmaiah Manchikanti. 2011. “A Comprehensive Review of Opioid-Induced Hyperalgesia.” Pain Physician 14 (2): 145–61.Price, Jonathan, Victoria Cole, and Guy M. Goodwin. 2009. “Emotional Side-Effects of Selective Serotonin Reuptake Inhibitors: Qualitative Study.” The British Journal of Psychiatry: The Journal of Mental Science 195 (3): 211–17.Read, John, and James Williams. 2018. “Adverse	

						Effects of Antidepressants Reported by a Large International Cohort: Emotional Blunting, Suicidality, and Withdrawal Effects." Current Drug Safety 13 (3): 176–86.Reisman, Yacov. 2020. "Post-SSRI Sexual Dysfunction." BMJ 368. https://doi.org/10.1136/bmj.m754.Richardson, Kathryn, Chris Fox, Ian Maidment, Nicholas Steel, Yoon K. Loke, Antony Arthur, Phyo K. Myint, et al. 2018. "Anticholinergic Drugs and Risk of Dementia: Case-Control Study." BMJ 361 (April): k1315.Rothmore, Jody. 2020. "Antidepressant-Induced Sexual Dysfunction." The Medical Journal of Australia 212 (7): 329–34.Sayyah, Mehdi, Kaveh Eslami, Shabnam AlaiShehni, and Leila Kouti. 2016. "Cognitive Function before and during Treatment with Selective Serotonin Reuptake Inhibitors in Patients with Depression or Obsessive-Compulsive Disorder." Psychiatry Journal 2016 (August): 5480391.Vittengl, Jeffrey R. 2017. "Poorer Long-Term Outcomes among Persons with Major Depressive Disorder Treated with Medication." Psychotherapy and Psychosomatics 86 (5): 302–4.	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

280	SH	The Challenging Behaviour Foundation	Guideline	39	5	Recs 1.8.5 – 1.8.7 Lived environment and support setting must also be considered for adults with learning disabilities, with involvement of family, support staff etc required to identify how aspects of the person's support setting may contribute to a risk of relapse.	Thank you for your comment. The recommendations on the possible determinants of relapse already include social and environmental factors, and have now been also been cross-linked back to the recommendations on the possible determinants of depression initially in recommendation 1.2.7 which includes more detail about possible determinants.

281	SH	Critical Psychiatry Network	Guideline	39	008-010	The evidence for continuation of antidepressant to prevent relapse is based on methodologically unsound studies. These studies are discontinuation studies in which a group of patients remitted on antidepressants (already a selected group, not representative of the entire population of people prescribed antidepressants at whom this guidance is aimed) in which half of patients are randomised to stop their antidepressant and half to maintain them. Following this depressive relapse is recorded by measurements on a standardised scale for several months or a year. In studies captured by the Geddes et al (2003) meta-analysis, and those captured by the NICE literature search, antidepressants are stopped very quickly, making withdrawal symptoms very likely, which would register on the depression scales used to detect depressive relapse, and therefore be likely to inflate the detected rate of relapse in the discontinuation group, inflating the apparent benefit of antidepressants at preventing relapse. Indeed, even when people withdraw slowly they can experience withdrawal symptoms if they have used the medications long-term. For example, in the 31 studies in the Geddes et al meta-analysis, the most common method of tapering patients from their antidepressants (which they had used for months or years) to placebo was abrupt cessation (22 of the 37 trials evaluated) and the weighted mean taper duration was 5 days (see Table below). It has been demonstrated that tapering over two weeks does not reduce the risk of withdrawal symptoms compared with abruptly stopping (Baldwin et al., 2006; Tint, Haddad and Anderson, 2008). The latest guidance suggests that for patients who	Thank you for your comment. The committee were aware of the limitations of the studies which used rapid withdrawal of antidepressants , and their discussion about this is included in the committee's discussion of the evidence section in Evidence review C. The section of the recommendations on stopping antidepressants (in those people who do not want to continue) also reflects the committee's knowledge on the necessity of tapering. However, despite this, the committee agreed that in people at a high risk of relapse, there was sufficient evidence that there may be benefits of continuation, compared to the risk of relapse.

						have been taking antidepressants for more than a few weeks, tapering should be at a rate that is tolerable to the patients, which can be months or years, likely depending on several factors including the duration of previous treatment (Horowitz and Taylor, 2019; Burn et al., 2020), so the tapering rate employed in the studies summarised in this meta-analysis are, by modern standards, rapid. In the current NICE draft guidance tapering is recommended to occur over weeks or months (although some people require years) in order to avoid severe withdrawal effects, although withdrawal symptoms may also occur with more gradual reductions. Reviews of the evidence suggest withdrawal is common with around 50% of people reporting the occurrence of withdrawal symptoms and up to half reporting symptoms as being severe (Davies & Read, 2019). The risk of withdrawal symptoms in studies which stop antidepressants this quickly is therefore considerable.	

282	SH	Mental Health Matters	Guideline	39	20	We are concerned that IAPT services could not offer a 4 x session follow up within 12 months, due to offering time limited interventions. Clients would then remain open on practitioner caseloads for over 12 months.	Thank you for your comment. This recommendation is for preventing relapse in those assessed as being at higher risk of relapse, and the recommended resource use was based on relevant information reported in the RCTs that informed the guideline NMA and economic analysis, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. In response to stakeholder comments, this recommendation has been amended to clarify that the recommended 'usual' number of sessions serves only as guidance and the additional follow-up sessions have been reworded to 'consider additional sessions in the next 12 months where there are concerns'.
283	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	39	20	This section talks about the number of sessions. Mindfulness Based Cognitive Therapy (MBCT) often involves 9 sessions. It would therefore be better for this to read ‘8 or 9 sessions’	Thank you for your comment. The advice has been changed to 'usually' consists of 8 sessions to allow flexibility around the number of sessions needed. This also covers programmes that involve 9 sessions.
284	SH	The College of Mental Health Pharmacy	Guideline	39	General	Please advise, what do is meant by continuing, at the same dose? And a gradually reduced dose?	Thank you for your comment. Continuing at the same dose has been clarified to state that this is the dose at which full or partial remission from depression was achieved. There is no reference on this page to gradually reducing the dose.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

285	SH	Association for Family Therapy and Systemic Practice	Guideline	40	6	We would suggest including here “and how the person with depression might access social support”	Thank you for your comment. The recommendation advises making contingency plans and planning for anticipated challenging events and this will need to be an individualised plan, so accessing social support has not been added here, as it might not apply to all people.

286	SH	Critical Psychiatry Network	Guideline	40	023-028	This advice (1.8.11) commendably counters the common prescriber tendency to “set and forget” after antidepressant initiation, often refilling prescriptions for years without even annual review (Sinclair et al., 2014). However, it is incomplete. It is the clinician’s responsibility to actively monitor the maintenance phase in antidepressant treatment, not simply at 6-month intervals, as well as throughout the high-risk periods during drug dosage increase, decrease, or change (Avery, 2013; GMC, 2021; Steinman, et al., 2011; Steinman; 2013).In the continuation phase, one extremely common drug adverse effect in particular may call for patient education. Within weeks, patients taking these drugs regularly will become neurobiologically adapted to them and physiologically dependent. Once a regular drug schedule is established and the person is adapted to the drug, irregular dosing – skipped or delayed doses, taking an incorrect dose – may evoke withdrawal symptoms (NICE, 2021) reported to the clinician as mysterious psychological or physiological symptoms, or even lack of drug efficacy or relapse. Estimates for patient non-adherence to antidepressants run as high as 50% (Ho et al., 2016). This type of patient behaviour is also common with other psychiatric drugs; lack of clinician follow-up is a key factor (Semahegn et al., 2020). In the absence of clinician recognition and appropriate action, non-adherence may be expected to continue, potentially bringing about the additional risk and expense of inappropriate medical care and prescription escalation. Another potential outcome of inconsistent dosing is treatment resistance or iatrogenic pseudo-resistance (Amsterdam et al., 2016; Fava et al., 2020;	Thank you for your comment. The committee agreed that the recommendation stated that monitoring should be 'at least every 6 months' so it was not necessary to suggest more frequent monitoring. The recommendations already state the aspects that should be included in regular monitoring including efficacy, side effects and any other factors that may affect the risk of relapse, so the committee did not agree that it was necessary to add any more detail to this recommendation.

						Howes et al., 2021). The neurobiological basis for the adverse effects of irregular dosing of psychotropics is explained in Horowitz & Taylor, 2022 and Sørensen et al., 2021 in their discussions of fluctuations in receptor occupancy and drug plasma saturation in relation to dosing changes.A formal validated rating scale applied at 6 month intervals will not discern a pattern of non-adherence. If a patient who has been taking an antidepressant for six months or more reports mysterious psychological or physiological symptoms, lack of drug efficacy, or relapse, the clinician should closely inquire about dosing schedules. If non-adherence seems likely, the clinician should carefully explain the circumstance of physiological dependence, and specifically advise patients to take their drugs on a consistent schedule (Demyttenaere & Haddad, 2000; Ho et al., 2016; Meijer et al., 2001), with follow-up to verify that the unusual symptom pattern has resolved.It may be that the patient avoids taking an antidepressant consistently because of persistent, annoying drug adverse effects. Drug adverse effects may often improve over time because of neurobiological adaptation to the presence of the drug (Cleare et al., 2015). However, they do not always resolve and are not always tolerable. Braund, et al., 2021 found that 8 weeks after initiating antidepressants, 11% of subjects suffered a burden of adverse effects such that they were moderately impaired to unable to function, and that this degree of burden interfered with treatment effectiveness. Further, this section does not advise the clinician to inquire about potential treatment-emergent drug adverse effects and take measures that might be taken to	

						address them, which may include reducing the dosage or discontinuing the drug. Some adverse drug effects such as anxiety, jitteriness, activation, insomnia, hypomania, akathisia, serotonin toxicity, suicidality or, conversely, excessive somnolence or disorientation indicate the antidepressant should be immediately reduced or discontinued (Carvalho et al., 2016; Fava & Rafanelli, 2019; Hawkins, et al., 2021; Jha, et al., 2017; Khalil & Huang, 2020; Luft, et al., 2018; Talton, 2020; Van Gestel, 2018; Zareifopoulos, et al., 2021). Clinicians should also be alert to physiological symptoms, such as gastrointestinal, genitourinary, sexual dysfunction, hyponatremia, skin rashes, bleeding, sweating, ophthalmic manifestations, and hyperprolactinemia, indicating serious systemic adverse effects, as well as such risks as liver damage (Carvalho et al., 2016).We urge NICE to remind clinicians to be actively alert to adverse effects of antidepressants throughout the course of treatment, rather than imply review at six month intervals is sufficient.Amsterdam, J. D., Lorenzo-Luaces, L., & DeRubeis, R. J. (2016). Step-wise loss of antidepressant effectiveness with repeated antidepressant trials in bipolar II depression. Bipolar Disorders, 18(7), 563–570. https://doi.org/10.1111/bdi.12442Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368Braund, T. A., Tillman, G., Palmer, D. M., Gordon, E., Rush, A. J., & Harris, A. W. F. (2021). Antidepressant side effects and their impact on	

						treatment outcome in people with major depressive disorder: An iSPOT-D report. Translational Psychiatry, 11(1), 417. https://doi.org/10.1038/s41398-021-01533-1Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychotherapy and Psychosomatics, 85(5), 270–288. https://doi.org/10.1159/000447034Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093Demyttenaere, K., & Haddad, P. (2000). Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 101(s403), 50–56. https://doi.org/10.1111/j.1600-0447.2000.tb10948.xFava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151Fava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The Deceptive Manifestations of Treatment Resistance in Depression: A New Look at the Problem. Psychotherapy and Psychosomatics, 1–9. https://doi.org/10.1159/000507227GMC. (2021). Good	

						practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdfGMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdfHawkins, E. M., Coryell, W., Leung, S., Parikh, S. V., Weston, C., Nestadt, P., Nurnberger, J. I., Kaplin, A., Kumar, A., Farooqui, A. A., El-Mallakh, R. S., & For the National Network of Depression Centers Suicide Prevention Task Group. (2021). Effects of somatic treatments on suicidal ideation and completed suicides. Brain and Behavior. https://doi.org/10.1002/brb3.2381Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029Horowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001Howes, O. D., Thase, M. E., & Pillinger, T. (2021). Treatment resistance in psychiatry: State of the art and new directions. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01200-3Jha, M. K., Minhajuddin, A., South, C., Rush, A. J., & Trivedi, M. H. (2017). Worsening Anxiety, Irritability, Insomnia, or Panic Predicts Poorer Antidepressant Treatment Outcomes: Clinical	

						Utility and Validation of the Concise Associated Symptom Tracking (CAST) Scale. International Journal of Neuropsychopharmacology, 21(4), 325–332. https://doi.org/10.1093/ijnp/pyx097Khalil, H., & Huang, C. (2020). Adverse drug reactions in primary care: A scoping review. BMC Health Services Research, 20. https://doi.org/10.1186/s12913-019-4651-7Luft, M. J., Lamy, M., DelBello, M. P., McNamara, R. K., & Strawn, J. R. (2018). Antidepressant-Induced Activation in Children and Adolescents: Risk, Recognition and Management. Current Problems in Pediatric and Adolescent Health Care, 48(2), 50–62. https://doi.org/10.1016/j.cppeds.2017.12.001Meijer, W. E. E., Bouvy, M. L., Heerdink, E. R., Urquhart, J., & Leufkens, H. G. M. (2001). Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. British Journal of Psychiatry, 179(6), 519–522. https://doi.org/10.1192/bjp.179.6.519NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020). Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: A systematic review and meta-analysis. Systematic Reviews, 9. https://doi.org/10.1186/s13643-020-1274-3Sinclair, J. E., Aucott, L. S., Lawton, K., Reid, I. C., & Cameron, I. M. (2014). The monitoring of longer term prescriptions of antidepressants: Observational study in a primary care	

						setting. Family Practice, 31(4), 419–426. https://doi.org/10.1093/fampra/cmu019Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-wSteinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.xSteinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965Talton, C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042Van Gastel, A. (2018). Drug-Induced Insomnia and Excessive Sleepiness. Sleep Medicine Clinics, 13(2), 147–159. https://doi.org/10.1016/j.jsmc.2018.02.001Zareifopoulos, N., Katsaraki, M., Stratos, P., Villiotou, V., Skaltsa, M., Dimitriou, A., Karveli, M., Efthimiou, P., Lagadinou, M., & Velissaris, D. (2021). Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic. European Review for Medical and Pharmacological Sciences, 25(14), 4746–4756. https://doi.org/10.26355/eurrev_202101_26386	

287	SH	The College of Mental Health Pharmacy	Guideline	40	General	Good that using a “formal validated rating scale” is suggested here, as this was avoided during this initial assessment in section 1.2.6.	Thank you for your comment. Monitoring outcomes with a formal validated rating scale is included in the section of the guideline on the delivery of treatments, as well as this section on relapse prevention.

288	SH	Society for Psychotherapy Research	Guideline	41	7	1.91.101.11Treatment recommendations for further-line treatment, chronic depression, and depression with PD Recommended psychological treatments for the above groups default for no clear reason to the 'more severe' first episode list. As studies that include more than 20% of PD or chronic depression were specifically excluded from the first episode analysis, this seems rather odd. In addition, there seems to be an error in Table 17 (Evidence review B, p.86) with regard to the effect size of the combined short-term psychodynamic therapy (SMD=-0.51) which is much smaller than the one reported in Figure 10 (SMD between -1 and -2). Furukawa et al. reported a large effect size for psychodynamic therapy combined with antidepressants, too, which was descriptively larger than those of other treatments (Furukawa et al., 2021, p. 394, Figure 6).We therefore suggest, that (a) as pointed out above the inclusion/exclusion criteria are amended accordingly, and (b) as pointed out above (see point 15) these three categories be combined in one analysis.	Thank you for your comment. The further-line treatment recommendation that cross-refers to psychological treatment options for more severe depression is for people whose depression has had no or a limited response to treatment with antidepressant medication alone. There was no evidence that specifically examined switching to a psychological intervention for those who have not responded to initial antidepressant treatment, however, the committee drew on the evidence for first-line treatments in more severe depression. The committee agreed that the psychological interventions that had been identified as effective and cost-effective for first-line treatment of more severe depression could be used for people who had not responded to antidepressants and wished to try a psychological therapy instead. For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of

							psychotic depression, depression with coexisting personality disorder and chronic depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered. The point estimates for short-term psychodynamic psychotherapy + antidepressant are consistent in Table 17 and Figure 10. However, the alignment of labels and bars in the forest plot may have been confusing. The pink line labelled 28 in Figure 10 shows a SMD point estimate of -0.51. The Furukawa et al. (2021) NMA that you

							cite in your response does not report a list of included studies and it is therefore not possible to speculate as to why a larger effect size was found for combined short-term psychodynamic psychotherapy + antidepressant than found for the evidence review for this guideline.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

289	SH	NHS England and Improvement	Guideline	41	8	Rec 1.9.1 – suggest "personal, social and environmental factors or physical or other mental health conditions"	Thank you for your comment. Envrionmental factors has been added to this recommendation as you suggest.
290	SH	NHS England and Improvement	Guideline	41	18	Rec 1.9.1 – reads make a shared decision with the person about the best way to try and address problems raised, but does not state what these routes may be.	Thank you for your comment. This recommendation has been expanded to suggest that addressing the problems may need the involvement of other agencies, but it would not be feasible to suggest solutions to all the possible individual issues that may be raised, and which will require an individualised approach to address.
291	SH	Association for Family Therapy and Systemic Practice	Guideline	41	18	We would suggest adding "including whether the person with depression would find it helpful to involve a partner or family member in the treatment"	Thank you for your comment. Involvement of others is covered in the choice section at the beginning of the guideline and so it has not been repeated here.
292	SH	The College of Mental Health Pharmacy	Guideline	41	1.9	Further-line treatment Should there be a clearer algorithm for next-step treatments, instead of relatively vague examples.	Thank you for your comment. The committee did not have sufficient evidence to divide the further-line treatment options into earlier and later steps, so have suggested the options for which there is evidence, and used the recommendations to provide some guidance on their place in therapy.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

293	SH	The College of Mental Health Pharmacy	Guideline	41	General	This section is titled “Further-line treatment” but a review at 4 weeks is not “further”. That would be common to review treatment at 4 weeks, and if an antidepressant is used there should be an assessment of adherence, and a review of the dose. This section of advice should be placed much earlier in the document as it is quite early in the treatment pathway. The treatment options outlined in the rest of section 1.9 should not be visited at 4 weeks. They are much later on in the treatment pathway. Many of which should be done in secondary care. This section needs careful revision and separating into second line drug treatment steps, and then “later” drug treatment steps.	Thank you for your comment. The recommendation states this section should be used if after 4 weeks (medication) or 8 weeks (psychological therapy) the depression has not 'responded at all'. If this is the case then further investigation and discussion is warranted as people should not be left on treatment that is not working at all indefinitely. The later recommendation includes advice to explore adherence and dose.
294	SH	Active Partnerships National Team	Guideline	42	15	We support the inclusion of exercise as an optional first line treatment for people experiencing severe depression. However, we feel there is significant opportunity for clinicians to promote a broader ‘move more’ message and integrate physical activity in adjunct to all treatment pathways for patients experiencing severe depression. This is because of the positive relationship between sport, physical activity and mental wellbeing. There are a broad range of beneficial outcomes within this relationship, including impacts on enjoyment and happiness, building confidence and self-esteem and reducing stress, anxiety and mild depression (Review of evidence on the outcomes of Sport and Physical Activity, 2017). Exercise is effective in the management of mental health conditions, with increased appetite for exercise as a support tool through the Covid pandemic. 67% of all adults and 72% of people with a mental condition or illness agree that they exercise to help manage their mental health	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this.

						during the outbreak (Source: Savanta ComRes, Attitudes and Behaviours. Wave 21, 05.11.2021 - 08.11.2021)There are many ways to be more physically active and a vast amount of national, free resources that support both clinicians and patients to move more and improve mental and physical wellbeing. We recommend referring and signposting to the following existing support resources within the document:We Are Undefeatable – we have developed the inspiring, inclusive, and empathetic 'We are Undefeatable' campaign (https://weareundefeatable.co.uk/about-us) alongside 16 leading health and social care charities. To support and encourage people with health conditions to find ways to be active. The campaign uses a behaviour change approach that reframes the message to recognise the motivations and barriers people face when living with a long term condition. Moving Medicine (https://movingmedicine.ac.uk) – a central hub to support healthcare professionals integrate physical activity conversations into routine clinical care (including depression consultation guides).	Thank you for telling us about the existing physical activity programmes and campaigns. These will be passed onto the NICE shared learning team.

295	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	42	20	Group exercise – connotations. 'Exercise' can mean different things to different people (for some, there may be an implication of gyms and/or school PE lessons, which might trigger negative memories). Given the overarching patient choice rhetoric, alternative group activities such as music or dance should be made more explicit as options. Dance in particular constitutes a popular form of aerobic exercise, is available in many community settings and includes a creative/cultural element. Many other creative interventions are inherently multisensory and include complex cognitive and physical tasks such as extensive upper body movement, hand-eye coordination, and precision grip. For these reasons, we suggest that the group exercise option is broadened to include other suitable group activities. This suggestion does not challenge or preclude more traditional forms of physical exercise; it aims to signpost the diversity of types of group exercise and the myriad potential benefits of involvement in group activities, which include peer support, cultural engagement and specific arts-therapeutic aspects.	Thank you for your comment. The committee noted that the evidence reviewed for exercise was for a structured formal exercise programme. However, in response to stakeholder comments, the committee also supported less intense 'move more' exercise for general wellbeing (although not as a treatment for depression) and made a new recommendation to reflect this. This recommendation is to advise people that undertaking any form of physical activity on a regular basis may help improve their mood, and gives dance as an example. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

296	SH	NHS England and Improvement	Guideline	42	5	Rec.1.9.4 – include non-medical psycho- social options including social prescribing. The new SNOMED reference set of codes in health records for social prescribing will give the option of social prescribing nature based activityarts based activity	Thank you for your comment. Nature-based interventions or social prescribing were not specified in any of the review protocols and thus evidence for specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. Art therapy was listed as an intervention of interest for the treatment reviews. However, no eligible evidence was identified for art therapy as a first-line treatment. The only included study for art therapy (Nan 2017) was in the further-line treatment review. The committee considered the evidence too limited to make a recommendation for art therapy. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that

							maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).
297	SH	The College of Mental Health Pharmacy	Guideline	43	3	Please change “medication” to “antidepressant” as that is what the sentence refers to. Please add some recommended timeframes form switching treatments	Thank you for your comment. The guideline uses both the terms antidepressant and medication throughout, if only to avoid using the same word multiple times in a sentence which can be onerous to read, but as the stem of this recommendation relates to antidepressants, it is clear that this is what is referred to in this recommendation so it has not been changed.

298	SH	The College of Mental Health Pharmacy	Guideline	43	4	Remove MAOIs form this list to emphasise that these are not equivalent choices, as in lines 8-9 say that MAOIs are not easily swapped and this should be done with great care (more so than with other antidepressants).	Thank you for your comment. The committee amended the recommendation to clarify that SSRIs and SNRIs were suitable switches in primary care and that TCAs or MAOIs would both be options in secondary care.
299	SH	The College of Mental Health Pharmacy	Guideline	43	9	MAOIs should only be started in secondary care.	Thank you for your comment. The committee amended the recommendation to clarify that SSRIs and SNRIs were suitable switches in primary care and that TCAs or MAOIs would both be options in secondary care.
300	SH	The College of Mental Health Pharmacy	Guideline	43	10	Prescribers should not be advised to switch TO dosulepin given the safety concerns.	Thank you for your comment. The warning relating to the use of tricyclics has been strengthened to advise about their potential danger in overdose and no longer refers to amitriptyline or dosulepin, so they no longer appear as named treatment options.

301	SH	University of Exeter Medical School	Guideline	43	012-013	BA should be added to this list. It is illogical of NICE to exclude trials like the NIHR HTA COBRA trial on grounds that <80% of participants were not receiving first line treatment, and then not use this data for further line treatment. Both CBT and BA were effective in this trial under these circumstances.	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

							estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

							used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations. There was some evidence for benefits associated with augmenting antidepressant treatment with CBT, IPT or STPP relative to continuing with the antidepressant only and on this basis the committee considered it appropriate to provide these psychological interventions as examples in the recommendation. There was no eligible evidence for augmenting antidepressants with BA relative to continuing with antidepressant treatment only and the committee did not consider it appropriate to make the suggested change to the recommendation.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

302	SH	The College of Mental Health Pharmacy	Guideline	43	General	Please rephrase to emphasise that the 3rd line placement for vortioxetine was due to the weak evidence to support efficacy, and therefore its use could not be justified earlier on. Not that it is reserved as a more effective third line option for treatment resistant cases – which is how this can currently be misunderstood. Otherwise people may choose vortioxetine when they should be stepping up care and adding in an augmentation strategy.	Thank you for your comment. The place of vortioxetine in therapy is defined by the results of the technology appraisal, and so this cannot be amended, but the committee have added the words 'only consider' to emphasise that its role in treatment is limited.
303	SH	NHS England and Improvement	Guideline	44	8	Given the uncertainties around the final mechanism(s) of action of antidepressants – please offer further clarification and/or guidance to support this statement.	Thank you for your comment. The recommendation has been clarified that this means an antidepressant from a different class (for example, not 2 SSRIs) and antidepressants are classified by their mode of action.
304	SH	The College of Mental Health Pharmacy	Guideline	44	13	Use the term “second generation antipsychotic” rather than “atypical”.	Thank you for your comment. This change has been made.
305	SH	The College of Mental Health Pharmacy	Guideline	44	013-017	Please add guidance around the choice of antipsychotic. Again this section feels that it is partly repetition of earlier sections, but also not fully address in either place. Please add advice around antipsychotic choice as an augmentation strategy and secondly for psychotic symptoms. These are different choices.	Thank you for your comment. Choice of 4 suitable antipsychotics is suggested here, and in the section of the guideline on psychotic depression, suitable antipsychotics are also suggested, so these recommendations have not been amended.
307	SH	The College of Mental Health Pharmacy	Guideline	44	018-020	Triiodothyronine is actively NOT recommended by NHSE making this inconsistent.	Thank you for your comment. There was some evidence for the use of triiodothyronine, and the committee were aware that the advice not to use it is based on current cost and lack of availability, but

							agreed that it should remain as an option for use if cost and supply problems resolve.
308	SH	The College of Mental Health Pharmacy	Guideline	44	General	This section needs careful revision and separating into second line drug treatment steps, and then "later" drug treatment steps.	Thank you for your comment. The committee did not have sufficient evidence to divide the further-line treatment options into earlier and later steps, so have suggested the options for which there is evidence, and used the recommendations to provide some guidance on their place in therapy.
309	SH	UK Council for Psychotherapy	Guideline	45	23	Rec 1.10.3 For people with chronic depressive symptoms and interpersonal difficulties, suggest that behavioural couples therapy may be useful alongside or instead of cognitive behavioural therapy since this directly addresses and treats the relational elements of the depression.	Thank you for your comment. Studies on couple interventions (including behavioural couples therapy) were sought for the reviews on first-line treatment but only for a subgroup of people with depression and problems in the relationship with their partner, and for the reviews on depression with coexisting personality disorder, and psychotic depression. For other review questions (including chronic depression), these interventions were not specified in the review protocols and consequently the evidence was not reviewed and the committee were not able to include behavioural couples therapy in this recommendation.

							There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. It is also recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
310	SH	Association for Family Therapy and Systemic Practice	Guideline	45	23	Rec 1.10.3 - For people with chronic depressive symptoms and interpersonal difficulties, our members have commented that behavioural couples therapy may be useful alongside or instead of cognitive behavioural therapy since it addresses and treats the relational factors which impact the person with depression.	Thank you for your comment. Studies on couple interventions (including behavioural couples therapy) were sought for the reviews on first-line treatment but only for a subgroup of people with depression and problems in the relationship with their partner, and for the reviews on depression with coexisting personality disorder, and psychotic depression. For other review questions (including chronic depression), these interventions

							were not specified in the review protocols and consequently the evidence was not reviewed and the committee were not able to include behavioural couples therapy in this recommendation.
311	SH	The College of Mental Health Pharmacy	Guideline	45	1.1	This section feels as though it should have the “third” or “later” choices.	Thank you for your comment. The systematic review for the treatment of chronic depression was for first-line and relapse prevention only, and provided evidence for the recommended treatments - CBT, SSRIs, TCAs and some additional pharmacological agents such as SNRIS, moclobemide, phenelzine and amisulpride so the committee recommended these based on their acceptability and tolerability, but no evidence was sought for further or identified to suggest a set of third or later choices.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

312	SH	The College of Mental Health Pharmacy	Guideline	45	1.1	Chronic depressive symptoms? recommending TCA before trial of SNRI e.g., venlafaxine(Dosulepin is not formulary in some CCGs? At least in Devon)Why specific recommendation of low dose amisulpride? is moclobemide available	Thank you for your comment. The guideline has been revised to add the option of using SNRIs before TCAs, and the warning relating to the use of tricyclics has been strengthened to advise about their potential danger in overdose and no longer refers to amitriptyline or dosulepin, so they no longer appear as named treatment options. There was evidence for the use of amisulpride and the advice to use a lower dose was based on the committee's knowledge and experience, and the fact that for the treatment of negative psychotic symptoms, a lower dose of amisulpride is advised by the manufacturer. The committee were aware that there had been some previous supply problems with moclobemide but that it was available for prescribing.
313	SH	The College of Mental Health Pharmacy	Guideline	45	1.10.2	Please add in advice about the place of lithium and antipsychotics in here.	Thank you for your comment. Lithium was not included in the review protocol for chronic depression so no evidence was identified for its use in chronic depression. However, for people who have already had treatment for depression and who present with chronicity, the treatment choices for further-line treatment are suggested and these include lithium. There was evidence for the antipsychotic amisulpride and this is included in the recommendations.

314	SH	NHS England and Improvement	Guideline	46	17	Rec 1.10.7 – suggests 'befriending' and 'rehabilitation'. Are there specific definitions being used that apply here, or are they broad terminology for a range of interventions where someone receives 1:1 support with their practical, social and emotional needs? E.g. would interaction with a social prescribing link worker over 6-12 contacts be included in this category? This has implications for mental health workforce as they may not have the local connections or quality assurance processes in place to refer people to befriending schemes or community services that meet their needs and may default to large national organisations; whereas social prescribing link workers funded through primary care infrastructure may be more able to connect people to appropriate local community assets. The coronavirus pandemic has impacted on the ability of the VCSE to deliver befriending and listening schemes; owing to high demand and ability to train sufficient volunteers.	Thank you for your comment. No evidence was available for psychosocial interventions for chronic depressive symptoms as a study on befriending that had been included by the 2009 guideline did not meet the revised inclusion criteria in the protocol for this update, as this study had defined chronic depression as greater than 1 year instead of 2 years, and did not report the mean duration of depression. However, the committee recognised the potential benefit of additional social or vocational support, particularly given the lack of long-term data on psychological or pharmacological interventions and the potential for poor prognosis and long-term functional impairment, and on this basis the committee agreed to retain the recommendation from the 2009 guideline.
315	SH	The College of Mental Health Pharmacy	Guideline	46	Dec-14	The evidence base to support a specific role for amisulpride is unclear and yet not giving any context for any other named antipsychotics. Suggest this section on amisulpride is deleted.	Thank you for your comment. The evidence review identified evidence showing the benefit of amisulpride in the treatment of chronic depression so the committee agreed it should be included as a treatment option in the recommendations.
316	SH	The Challenging Behaviour Foundation	Guideline	47	1	Rec 1.10.9 Treatment offered should also account for the increased risk which adults and adolescents with learning disabilities have to chronic depression, and the way this may	Thank you for your comment. The committee did not have any evidence that adults with learning disabilities may be at

						present in individuals with specific communication and behavioural needs.	increased risk of chronic depression and so did not make this change.
317	SH	Talking Therapies	Guideline	47	15	Not all psychological treatments in tables 1 and 2 are suitable for patients who have personality disorders, especially those that are currently seen as step 2. There is no evidence base for them and IAPT clinicians are not trained to work with personality disorders. Please can the advice be amended to be more specific, and exclude provision within IAPT services. There is evidence that CBT and other psychological treatments are beneficial for people with personality disorder, but this needs to be delivered by clinicians with specialist training and within specialist services.	Thank you for your comment. There was limited evidence for CBT, STPP, IPT and STPP in the treatment of depression for people with personality disorder which is why the committee suggested these as examples in the recommendation. The committee recognised that people with personality disorder would not be treated in IAPT services and so included in their recommendation that treatment should be delivered in a structured multidisciplinary setting or in a specialist personality disorder treatment programme.
318	SH	The College of Mental Health Pharmacy	Guideline	47	1.11	Please add some text around trying to set realistic expectations of drug treatment with people who have a personality disorder and depression.	Thank you for your comment. The committee agreed that the use of medication in people with a personality disorder and depression should be approached with a positive expectation, and so they did not amend the recommendations.
319	SH	The College of Mental Health Pharmacy	Guideline	48	20	“does not wish to take antipsychotic medication” please add in “does not wish to also take antipsychotic medication”	Thank you for your comment. This has been changed to clarify that the antipsychotic medication is in addition to an antidepressant.

320	SH	NHS England and Improvement	Guideline	48	General	The recommendations for psychotic depression is quite limited	Thank you for your comment. The evidence identified for psychotic depression was very limited. The committee made some recommendations based on the evidence that was available, and on their clinical knowledge and experience. However, the committee also made a research recommendation for future research to investigate the most effective and cost effective interventions for the treatment and management of psychotic depression (including consideration of pharmacological, psychological and psychosocial interventions).
321	SH	The Challenging Behaviour Foundation	Guideline	49	9	Rec 1.13.1 - While evidence has shown a potentially positive use of ECT for patients with learning disabilities, there remain difficulties regarding accurate initial diagnosis and safety concerns for this population, meaning ECT should only be employed when diagnosis and risks have been evaluated throughout.	Thank you for your comment. The committee were aware that explanation of risks and benefits, and consent and capacity to consent were all important issues relating to ECT so have included recommendations covering all these topics, which will apply to people with learning disabilities.
322	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	49	015-016	ECT for severe depression if other treatments have been unsuccessful. While there is some evidence in support of ECT, we find it worrying that so much space is devoted to this 'esoteric' (Naqvi, 2007) therapeutic approach, yet none is devoted to any arts or cultural approaches. ECT is likely to be less preferable to patients compared with the broad range of non-clinical interventions that could be offered but are not	Thank you for your comment. The committee agreed that ECT was only indicated for use in specific circumstances , but that there was evidence for its place in therapy. Art therapy was listed as an intervention of interest for the treatment reviews. However, only one eligible study

						mentioned in these guidelines.ECT is often prescribed for patients who have lost all motivation and who are unresponsive to other therapies. If creative arts-based interventions are not available, this restricts choice, has human rights implications and costs a lot of money. The continued use of ECT, even as a last resort, has been described as 'a stark example of a system failing people' (Clarke, 2021).	was identified for art therapy (Nan 2017) for further-line treatment. The committee considered the evidence too limited to make a recommendation for art therapy as a treatment for depression. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice, and the recommendations reflect this.
323	SH	The College of Mental Health Pharmacy	Guideline	49	1.12.5	"The decision when to stop" please rephrase to "if and when".	Thank you for your comment. This change to the wording has been made.
324	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	50	015-016	ECT – informed consent. The guidelines rightly discuss informed consent. However, we have serious concerns that while a person with severe depression may be deemed to have cognitive capacity to understand, they might not have the motivational capacity to decline ECT as an option. Advance Treatment Decisions. "If a person with depression cannot give informed consent, only give ECT if it does not conflict with an advance treatment decision the person made".In making Advance Treatment Decisions, the patient is likely to opt for less intrusive options. These options must include non-clinical approaches if available. In line with our previous suggestions, we would like to see a wider range of alternatives (including creative arts-based approaches) offered ahead of ECT, including in Advance Treatment Decisions.	Thank you for your comment. The committee were aware that explanation of risks and benefits, and consent and capacity to consent were all important issues relating to ECT so have included recommendations covering all these topics. Art therapy was listed as an intervention of interest for the treatment reviews. However, only one eligible study was identified for art therapy (Nan 2017) for further-line treatment. The committee considered the evidence too limited to make a recommendation for art therapy for the treatment of depression. The committee were aware of the need to provide a wide range of interventions to

							take into account individual needs and allow patient choice, and the recommendations reflect this.
325	SH	NHS England and Improvement	Guideline	51	20	Add Personalised care (Commissioners and providers of mental health services should consider using models such as stepped care or collaborative care….)	Thank you for your comment. The committee did not consider it appropriate to add personalised care to this recommendation as RCT evidence for personalised care as a service delivery model has not been reviewed, unlike for the examples that are provided (stepped care and collaborative care). However, there is a strong emphasis on patient choice throughout the guideline.
326	SH	Diabetes UK	Guideline	051-054	020-021	We welcome the new sections on collaborative care and active care planning for those with significant physical health problems and depression as research has shown that people with severe mental illness and diabetes often do not receive adequate support to help them manage their diabetes. Integrating diabetes action plans into care planning is required as well as providing psychological support and people with severe mental illness and diabetes should not be disadvantaged as a result of disjointed services.References: Mulligan, K. et al. (2018) “Barriers to Effective Diabetes Management – a Survey of People with Severe Mental	Thank you for your comment and your support.

						Illness", BMC Psychiatry, 18(1). Cohen, A. (2018) Diabetes and Severe Mental Illness.	
327	SH	NHS England and Improvement	Guideline	52	16	Rec 1.15.2 suggests 'community services' should be included in providing an integrated primary and secondary mental health service. Suggest this includes a broader range of community services in 'examples' e.g. "for example, social care, education, housing, statutory services and the voluntary and social enterprise sector". This point goes on to say that this should include "social interventions"; clarification needed as social interventions not defined elsewhere in document and not consistent with previous wording; suggest "interventions for personal, social and environmental factors"	Thank you for your comment. Statutory, social enterprise and voluntary sectors have been added as you suggest. The recommendation relating to social interventions has also been amended as you suggest.
328	SH	The Challenging Behaviour Foundation	Guideline	52	16	Recs 1.15.2-1.15.3 - There remains a great fragmentation in services, including specialist mental health services, commissioned for individuals with learning disabilities. For the function of a catchment-area-based community mental health service to be delivered upon, a greater collaborative framework must be created than exists in current commissioning or in proposals for integrated care systems.	Thank you for your comment. The committee were aware that services can be fragmented, and highlighted the need for services to be accessible and adapted where necessary in the subsequent recommendation

329	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	52	020-026	Social interventions. "…as well as community services (for example social care, education and housing). This should include: […] social interventions".'Social interventions' needs more attention throughout. While such interventions rely on a broader range of evidence types compared with more clinical interventions, which more often rely on RCT-type evidence, the fact that these are acknowledged here is positive and noteworthy.Social interventions may include community-based creative, cultural, nature- or heritage-related activities. An infrastructure is being developed to enable social prescribing to signpost these types of resource and this option should have more prominence in the guidelines.	Thank you for your comment. Social prescribing was not specified in any of the review protocols and thus evidence for specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee considered RCTs as the most appropriate study design to assess clinical and cost effectiveness. This is consistent with the NICE guidelines manual which recognises RCTs as the most valid evidence of the effects of interventions, and this was outlined a priori in the review protocols. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to

							the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

330	SH	Association for Family Therapy and Systemic Practice	Guideline	53	17	Rec 1.15.5 – AFT welcomes the decision of the committee to suggest commissioners and providers of mental health services promote access and uptake through structural changes to service systems and models or provision. For example, services delivered in culturally appropriate or culturally adapted language and formats, and, on the following page (54, line 2), procedures to support active involvement of families, partners and carers. An AFT member has asked whether these points be integrated since one way of delivering psychological therapy in a culturally appropriate format is to actively involve families, partners and carers? For some groups this is a central way of facilitating their access to services. We request that behavioural couples therapy is also mentioned here as one option. Suggested wording: "Commissioners and providers of mental health services should ensure pathways have the following in place for people with depression to promote access and increased uptake of services:services delivered in culturally appropriate or culturally adapted language and formats. This may include procedures to support active involvement of families, partners and carers. Behavioural couples therapy may be a useful option to actively involve partners."	Thank you for your comment. Given that both the bullet points referred to in your comment are from the same recommendation, the committee did not consider it appropriate to integrate these points as supporting the active involvement of families, partners and carers may be important for promoting access for people from black, Asian and minority ethnic communities and may be part of cultural adaptations made to treatment. However, active family involvement may also be important for the other groups that were highlighted as experiencing barriers to accessing services, including men, older people, and lesbian, gay, bisexual and trans people, and for this reason the committee agreed that keeping separate bullet points better captured this. The committee did not consider it appropriate to add behavioural couples therapy to this recommendation as there is already a separate recommendation based on the evidence reviewed made for behavioural couples therapy. There are also recommendations in the choice of treatment section of the guideline that people with depression should be given the

							option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend.
331	SH	The Challenging Behaviour Foundation	Guideline	53	17	Rec 1.15.5 - Active involvement of families, partners and carers must be facilitated in a way which does not burden these families, partners and carers with the responsibility for coordinating the delivery of treatments across services, which is too often the case.	Thank you for your comment. The committee agreed that families should be involved, if that is what the person with depression wanted and so have amended the recommendation to state that, but agreed that the recommendation did not place a burden on families to coordinate care.

332	SH	UK Council for Psychotherapy	Guideline	53	20	Rec 1.15.5 It is welcomed that the guidelines say: Commissioners and providers of mental health services should ensure pathways have the following in place for people with depression to promote access and increased uptake of services:services delivered in culturally appropriate or culturally adapted language and formats and, on the following page (54, line 2), procedures to support active involvement of families, partners and carers. Please can these points be integrated since one way of delivering psychological therapy in a culturally appropriate format is to actively involve families, partners and carers? For some groups this is a central way of facilitating their access to services. We request that behavioural couples therapy is also mentioned here as one option. Suggested wording: Commissioners and providers of mental health services should ensure pathways have the following in place for people with depression to promote access and increased uptake of services:services delivered in culturally appropriate or culturally adapted language and formats. This may include procedures to support active involvement of families, partners and carers. Behavioural couples therapy may be a useful option to actively involve partners.	Thank you for your comment. Given that both the bullet points referred to in your comment are from the same recommendation, the committee did not consider it appropriate to integrate these points as supporting the active involvement of families, partners and carers may be important for promoting access for people from black, Asian and minority ethnic communities and may be part of cultural adaptations made to treatment. However, active family involvement may also be important for the other groups that were highlighted as experiencing barriers to accessing services, including men, older people, and lesbian, gay, bisexual and trans people, and for this reason the committee agreed that keeping separate bullet points better captured this. The committee did not consider it appropriate to add behavioural couples therapy to this recommendation as there is already a separate recommendation based on the evidence reviewed made for behavioural couples therapy. There are also recommendations in the choice of treatment section of the guideline that people with depression should be given the

							option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend.
333	SH	Anxiety UK	Guideline	53	020-030	We welcome all these points which we believe will lead to increased access and uptake	Thank you for your comment and support of these recommendations.
334	SH	Anxiety UK	Guideline	53	31	We would suggest to change this to reflect that some third sector orgs are delivering services entirely i.e. no NHS partnership in place.	Thank you for your comment. This recommendation relates to the access requirements for services, but NICE guidelines do not have a mandate to advise charities or the voluntary sector how to deliver their services, so this recommendation can only apply to joint services (although NICE hope that charities and the voluntary sector would also take these factors in consideration when

							delivering services without NHS partnership).
335	SH	UK Council for Psychotherapy	Guideline	54	10	Rec 1.15.6 People from Black, Asian and minority ethnic communities may particularly welcome being able to attend with their partners and we request that behavioural couples therapy is mentioned here as one option for addressing their needs.	Thank you for your comment. The committee did not consider it appropriate to add behavioural couples therapy to this recommendation as there is already a separate recommendation based on the evidence reviewed made for behavioural couples therapy. There are also recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. There is also a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include:

							services delivered in culturally appropriate or culturally adapted language and formats; and procedures to support active involvement of families, partners, and carers.

336	SH	Association for Family Therapy and Systemic Practice	Guideline	54	19	Rec 1.15.6 - People from minoritised groups (such as lesbian, gay, bisexual and trans people, or black, Asian and minority ethnic communities) may particularly welcome being able to attend with their partners. We request that systemic interventions and behavioural couples therapy is mentioned here as one option for addressing their needs. Please also see general comment on diversity (Comment 3).	Thank you for your comment. The committee did not consider it appropriate to add behavioural couples therapy to this recommendation as there is already a separate recommendation based on the evidence reviewed made for behavioural couples therapy. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression. On this basis, the committee did not consider it appropriate to include family in the recommendation referred to in your comment. There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a

							family member or friend. There is also a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include: services delivered in culturally appropriate or culturally adapted language and formats; and procedures to support active involvement of families, partners, and carers.

337	SH	University of Exeter Medical School	Guideline	54	22	We support the inclusion of collaborative care to organise treatment for people with depression. However, a 2016 individual patient data (IPD) meta-analysis (Panagioti et al, 2016, JAMA Psychiatry. Sep 1;73(9):978-89) has shown that there is no difference between outcomes for people receiving collaborative care with a significant physical health problem and those without. Previous guidance that recommends limiting collaborative care to people with depression and physical comorbidities is not supported by this individual participant data meta-analysis, which is far more precise than the study-level meta-analyses which report the opposite and erroneous finding. This recommendation is not accurate, therefore, and should be amended to remove specific reference to those with physical health problems as collaborative care is effective for both groups.	Thank you for your comment. For collaborative care, the committee noted that there was evidence from a number of UK and international trials for clinical benefits associated with the use of collaborative care compared to standard care or enhanced standard care, with higher rates of response and remission at both 6 and 12 months. However, the committee noted that the heterogeneity was very high, and effect sizes for depression symptomatology were small compared to first-line acute treatments. Based on these factors, the committee made a 'consider' rather than 'offer' recommendation and identified groups where collaborative care may confer significant added value, for example, those with significant physical health problems or who are socially isolated. Older adults were also identified as a group that may particularly benefit from collaborative care. Subgroup analysis comparing outcomes for older (mean age ≥ 60 years) and younger (mean age <60 years) adults did not identify statistically significant subgroup differences. However, there was a consistent trend for larger benefits of

							collaborative care for older adults. Considered together with the committee knowledge and experience of difficulties with engagement in older adults particularly for those with physical health problems, and evidence for the cost-effectiveness of collaborative care in older people, the committee agreed to also recommend collaborative care for this group. There is also a more general recommendation in the access section of the guideline that commissioners and providers of mental health services should consider using models such as stepped care or collaborative care for organising the delivery of care and treatment of people with depression.

338	SH	The Challenging Behaviour Foundation	Guideline	57	6	Rec 1.5.13 - Consideration of inpatient care must be undertaken with regard to the risk which may be created by the inpatient setting to a potential worsening of condition, and for people with learning disabilities it must be understood in light of the widespread use of detention and inpatient services wherein no benefit is created for their treatment.	Thank you for your comment. The NICE guideline on Mental health problems in people with learning disabilities provides more detailed information on the delivery of care and care planning in people with learning disabilities and so a link to this guideline has been added to this recommendation.
339	SH	NHS England and Improvement	Guideline	60	8	Key recommendations: Given there is a research question on chronic depressive symptoms in older adults, can the other research questions also apply to older adults because research in treatment of depression is less in this population group than in working age adults? There is also no mention of the role of digital solutions	Thank you for your comment. The research recommendations on older people were because the committee had identified a lack of specific evidence for older people in these areas. However, all the other research recommendations relate to all adults, so older people would not be excluded from theses research recommendations. Evidence for digital solutions was not specifically included in the scope of this guideline, and the committee were aware of separate work at NICE to evaluate digital solutions for the treatment of depression (Digital therapies assessed and accepted by the Improving Access to Psychological Therapies Programme), so it was not possible for the committee to make a research recommendation.

340	SH	Critical Psychiatry Network	Guideline	60	009-011	We urge the committee to add to this research recommendation (1. Stopping antidepressants) this question: What is the most effective way for people to come off antidepressants, minimizing withdrawal symptoms and post-discontinuation syndromes?There is enough evidence in 35 years of clinical trials to show symptoms evoked by antidepressant discontinuation (Davies and Read 2019; Jauhar and Hayes, 2019) are substantially more than rare, with the debate now whether the rate of incidence is closer to 40% or SEP50%. In any event, it is clear that the incidence of antidepressant withdrawal is certainly not less than 10%, making it a common adverse effect. Given the many millions of people taking antidepressants, the number at risk for withdrawal syndrome is massive. By any measure of dimension, it is deserving of clinical concern.Likewise, the panorama of withdrawal symptoms has been surveyed since the days of tricyclic antidepressants with a special horror reserved for the outcomes of abrupt discontinuation, e.g. Kramer et al., 1961; Petti & Law, 1981; Benazzi, 1998; Bloch et al., 1995; Coupland et al., 1996; Haddad, 1997; Haddad et al., 1998; Black et al., 2000; Haddad & Qureshi, 2000; Rivas-Vazquez et al., 2000; Young & Haddad, 2000; Drug Ther Perspect., 2001; Einarson et al., 2001; Haddad et al., 2001; Bogetto et al., 2002; Tonks, 2002; Andrade, 2004; Maciag et al., 2006; Warner et al., 2006; Kotzalidis et al., 2007; Haddad & Anderson, 2007; Alehan et al., 2008; Valuck et al., 2009; Andrews et al., 2011; Renoir, 2013; Chouinard & Chouinard, 2015; Fava et al., 2015; Verbenko, 2015; Bainum et al., 2017; Reisman, 2017; Jha et al., 2018; Witt-Doerring et al., 2018;	Thank you for your comment. The recent NICE guideline on Safe prescribing has carried out quantitative and qualitative reviews on withdrawal of anridepressants, for which substantial evidence was identified. The recommendations on stopping antidepressants were based on the findings of these reviews. The committee did not therefore prioritise withdrawal techniques for a research recommendation.

						Davies & Read, 2019; Hengartner et al., 2019; Read, 2019; Cosci & Chouinard, 2020; Quilichini et al., 2022. Over several decades, every one of these papers urged more clinician training, that clinicians maintain a high index of suspicion for antidepressant withdrawal symptoms, more research into their incidence and severity, and research into ways to minimize their risk.It's possible that antidepressants have a similar degree of withdrawal risk as other psychotropics, prescribed and otherwise. They all share similar withdrawal syndromes. (Lerner & Klein, 2019)Given that millions of people are currently at risk of antidepressant withdrawal, it may be that to improve patient safety and outcomes, the medical community will need to cope with some uncertainty about the exact incidence in order to turn its attention to looking at ways to lessen whatever impact it does have. We call upon NICE to add a recommendation for research into tapering methods to this document.Alehan, F., Saygi, S., Tarcan, A., & Gürakan, B. (2008). Prolonged neonatal complications after in utero exposure to fluoxetine. The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 21(12), 921–923. https://doi.org/10.1080/14767050802266899Andrade, C. (2004). Antidepressant-withdrawal mania:a critical review and synthesis of the literature. The Journal of Clinical Psychiatry, 65(7), 987–993.Andrews, P. W., Kornstein, S. G., Halberstadt, L. J., Gardner, C. O., & Neale, M. C. (2011). Blue Again: Perturbational Effects of Antidepressants Suggest	

						Monoaminergic Homeostasis in Major Depression. Frontiers in Psychology, 2. https://doi.org/10.3389/fpsyg.2011.00159Bainum, T. B., Fike, D. S., Mechelay, D., & Haase, K. K. (2017). Effect of Abrupt Discontinuation of Antidepressants in Critically Ill Hospitalized Adults. Pharmacotherapy, 37(10), 1231–1240. https://doi.org/10.1002/phar.1992Benazzi, F. (1998). Sertraline Discontinuation Syndrome Presenting With Severe Depression and Compulsions. https://doi.org/10.1016/S0006-3223(97)00533-7Black, K., Shea, C., Dursun, S., & Kutcher, S. (2000). Selective serotonin reuptake inhibitor discontinuation syndrome: Proposed diagnostic criteria. Journal of Psychiatry & Neuroscience: JPN, 25(3), 255–261.Bloch, M., Stager, S. V., Braun, A. R., & Rubinow, D. R. (1995). Severe psychiatric symptoms associated with paroxetine withdrawal. Lancet (London, England), 346(8966), 57. https://doi.org/10.1016/s0140-6736(95)92691-7 Bogetto, F., Bellino, S., Revello, R. B., & Patria, L. (2002). Discontinuation Syndrome in Dysthymic Patients Treated with Selective Serotonin Reuptake Inhibitors. CNS Drugs, 16(4), 273–283. https://doi.org/10.2165/00023210-200216040-00006Chouinard, G., & Chouinard, V.-A. (2015). New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. Psychotherapy and Psychosomatics, 84(2), 63–71. https://doi.org/10.1159/000371865Cosci, F., & Chouinard, G. (2020). Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications. Psychotherapy and Psychosomatics, 1–24. https://doi.org/10.1159/000506868Coupland, N. J., Bell, C. J.,	

						& Potokar, J. P. (1996). Serotonin reuptake inhibitor withdrawal. Journal of Clinical Psychopharmacology, 16(5), 356–362. https://doi.org/10.1097/00004714-199610000-00003Davies, J., & Read, J. (2019). A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? Addictive Behaviors, S0306460318308347. https://doi.org/10.1016/j.addbeh.2018.08.027Drug Ther Perspect. (2001). Antidepressant discontinuation syndromes: Common, under-recognised and not always benign. Drugs & Therapy Perspectives, 17(20), 12–15. https://doi.org/10.2165/00042310-200117200-00004Einarson, A., Selby, P., & Koren, G. (2001). Abrupt discontinuation of psychotropic drugs during pregnancy: Fear of teratogenic risk and impact of counselling. Journal of Psychiatry and Neuroscience, 26(1), 44–48. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1408034/Fava, G. A., Gatti, A., Belaise, C., Guidi, J., & Offidani, E. (2015). Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. Psychotherapy and Psychosomatics, 84(2), 72–81. https://doi.org/10.1159/000370338Haddad, P. (1997). Newer antidepressants and the discontinuation syndrome. The Journal of Clinical Psychiatry, 58 Suppl 7, 17–21; discussion 22. mac.Haddad, P., Lejoyeux, M., & Young, A. (1998). Antidepressant discontinuation reactions. BMJ : British Medical Journal, 316(7138), 1105–1106. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1112935/Haddad, P. M., & Qureshi, M. (2000). Misdiagnosis of	

						antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 102(6), 466–467; discussion 467-468. https://doi.org/10.1034/j.1600-0447.2000.102006466.xHaddad, P. M., Devarajan, S., & Dursun, S. M. (2001). Antidepressant discontinuation (withdrawal) symptoms presenting as “stroke.” Journal of Psychopharmacology (Oxford, England), 15(2), 139–141. https://doi.org/10.1177/026988110101500210Haddad, P. M., & Anderson, I. M. (2007). Recognising and managing antidepressant discontinuation symptoms. Advances in Psychiatric Treatment, 13(6), 447–457. https://doi.org/10.1192/apt.bp.105.001966Hengartner, M. P., Davies, J., & Read, J. (2019). How Long Does Antidepressant Withdrawal Typically Last? The American Journal of Psychiatry, 176(6), 487. https://doi.org/10.1176/appi.ajp.2019.19020142Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692Jauhar, S., & Hayes, J. (2019). The war on antidepressants: What we can, and can’t conclude, from the systematic review of antidepressant withdrawal effects by Davies and Read. Addictive Behaviors, 97, 122–125. https://doi.org/10.1016/j.addbeh.2019.01.025Kotzalidis, G. D., Patrizi, B., Caltagirone, S. S., Koukopoulos, A., Savoja, V., Ruberto, G., Tatarelli, C., Pacchiarotti, I., Lazanio, S., Sani, G., Manfredi, G., Pisa, E. de, Tatarelli, R., & Girardi, P. (2007). The adult SSRI/SNRI withdrawal syndrome: A clinically	

						heterogeneous entity. Clinical Neuropsychiatry, 4(2), 61–75. https://moh-it.pure.elsevier.com/en/publications/the-adult-ssrisnri-withdrawal-syndrome-a-clinically-heterogeneousKramer, J. C., Klein, D. F., & Fink, M. (1961). Withdrawal symptoms following dicontinuation of imipramine therapy. The American Journal of Psychiatry, 118, 549–550. https://doi.org/10.1176/ajp.118.6.549Lejoyeux, M., & Adès, J. (1997). Antidepressant discontinuation: A review of the literature. The Journal of Clinical Psychiatry, 58 Suppl 7, 11–15; discussion 16.Lerner, A., & Klein, M. (2019). Dependence, withdrawal and rebound of CNS drugs: An update and regulatory considerations for new drugs development. Brain Communications, 1(1). https://doi.org/10.1093/braincomms/fcz025Maciag, D., Simpson, K. L., Coppinger, D., Lu, Y., Wang, Y., Lin, R. C. S., & Paul, I. A. (2006). Neonatal Antidepressant Exposure has Lasting Effects on Behavior and Serotonin Circuitry. Neuropsychopharmacology, 31(1), 47–57. https://doi.org/10.1038/sj.npp.1300823 Petti, T. A., & Law, W. (1981). Abrupt Cessation of High-Dose Imipramine Treatment in Children. JAMA, 246(7), 768–769. https://doi.org/10.1001/jama.1981.03320070052026 Quilichini, J.-B., Revet, A., Garcia, P., Bouquié, R., Hamard, J., Yrondi, A., & Montastruc, F. (2022). Comparative effects of 15 antidepressants on the risk of withdrawal syndrome: A real-world study using the WHO pharmacovigilance database. Journal of Affective Disorders, 297, 189–193. https://doi.org/10.1016/j.jad.2021.10.041Read, J. (2019). How common and severe are six withdrawal effects from, and	

						addiction to, antidepressants? The experiences of a large international sample of patients. Addictive Behaviors, 106157. https://doi.org/10.1016/j.addbeh.2019.106157Reisman, Y. (2017). Sexual Consequences of Post-SSRI Syndrome. Sexual Medicine Reviews, 5(4), 429–433. https://doi.org/10.1016/j.sxmr.2017.05.002Renoir, T. (2013). Selective Serotonin Reuptake Inhibitor Antidepressant Treatment Discontinuation Syndrome: A Review of the Clinical Evidence and the Possible Mechanisms Involved. Frontiers in Pharmacology, 4. https://doi.org/10.3389/fphar.2013.00045Rivas-Vazquez, R. A., Carrazana, E. J., Rey, G. J., & Wheeler, S. D. (2000). Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: Three Cases Presenting to a Neurologic Practice. The Neurologist, 6(6), 348–352. https://doi.org/10.1097/00127893-200006060-00005 Tonks, A. (2002). Withdrawal from paroxetine can be severe, warns FDA. BMJ, 324(7332), 260. https://doi.org/10.1136/bmj.324.7332.260Valuck, R. J., Orton, H. D., & Libby, A. M. (2009). Antidepressant Discontinuation and Risk of Suicide Attempt: A Retrospective, Nested Case-Control Study. The Journal of Clinical Psychiatry, 70(8), 1069–1077. https://doi.org/10.4088/JCP.08m04943Verbenko, V. (2015). Antidepressant Discontinuation Syndrome in Clinical Practice. European Psychiatry, 30, 1034. https://doi.org/10.1016/S0924-9338(15)30813-0Warner, C. H., Bobo, W., Warner, C., Reid, S., & Rachal, J. (2006). Antidepressant Discontinuation Syndrome. Am Fam Physician, 74(3), 449–456.	

						https://www.aafp.org/afp/2006/0801/p449.htmlWitt-Doerring, J., Shorter, D., & Kosten, T. (2018, April 18). Online Communities for Drug Withdrawal: What Can We Learn? Psychiatric Times. https://www.psychiatrictimes.com/article/online-communities-drug-withdrawal-what-can-we-learn Young, A., & Haddad, P. (2000). Discontinuation symptoms and psychotropic drugs. The Lancet, 355(9210), 1184. https://doi.org/10.1016/S0140-6736(05)72262-5	

341	SH	Critical Psychiatry Network	Guideline	60	General	Throughout Evidence Summary B repeated reference was made to the importance of long term outcome from studies of efficacy as well as the importance of quality of life outcomes and functional status (the outcomes most important to patients) and in almost all occasions the conclusion was that as there was a paucity of long term studies and a paucity of studies with outcomes looking at quality of life and functional outcomes that the more widely available studies looking at short term outcomes and symptom score changes were prioritised. It would therefore be helpful to include a research recommendation to evaluate the effectiveness of different treatments in both less severe depression and more severe depression over longer time frames (that are more relevant to the treatment of what can be a chronic condition for which treatments are often given for long periods and focusing on quality of life and functional outcomes so that future guidance can be based on studies which have most relevance to treatment in practice.	Thank you for your comment. The committee agree that quality of life and functioning outcomes, and long-term follow-up, are important. The committee noted the limited evidence for quality of life and functioning outcomes and for longer-term follow-up, and included these outcomes and follow-up timepoints for the research recommendations in the guideline. The number of research recommendations that the committee can develop is limited and unfortunately long-term treatments were not prioritised for a stand-alone research recommendation. However, the research recommendation on the mechanisms of action of effective psychological interventions includes the recommendation that psychological interventions should be analysed in terms of therapy structure (for example session duration, frequency), in addition to generic therapeutic components (for example therapeutic relationship, rationale; remoralization), and specific ingredients.

342	SH	University of Exeter Medical School	Guideline	61	001-005	This research recommendation is ironic to say the least. NICE has excluded several trials which would have answered this question. For example, the £2m NIHR HTA COBRA trial included participants with an average duration of antidepressant treatment of 329 weeks, people who were sufficiently symptomatic at study inclusion (by standardised diagnostic interview) to qualify as depressed. It is simply nonsense to exclude trials from the guideline using criteria which would have led to them being included to answer other questions, but then exclude them again. There is a very serious error of process that has led to these inaccurate recommendations and vital missing elements. Both CBT and BA are, by NICE's own logic, effective further-line treatments for depression.	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

							estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

							used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

343	SH	Association for Family Therapy and Systemic Practice	Guideline	62	1	We would welcome a suggestion for further research that addresses people from minoritised groups that are less likely to access standard treatments and believe this could helpfully be addressed in this section (see also Comment 3).	Thank you for your comment. Research recommendation 5 asks the question you have highlighted: 'What are the most effective and cost-effective methods to promote increased access to, and uptake of, treatments for people with depression who are under-served and under-represented in current services?'
344	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	62	3	Recommendations for research – peer support. Citing a lack of evidence (p.67, li.7), the guidelines recommend establishing if peer support is effective and cost-effective. We suggest extending this to recommend research into the efficacy/cost-effectiveness of peer support across clinical and non-clinical interventions.Most non-clinical creative approaches, such as singing or art classes, are conducted in groups, so have a strong peer support element (aligning with other NICE recommended activities including exercise and mindfulness). This would provide further opportunities for research into peer support.	Thank you for your comment. The research recommendation question about peer support is designed to guide future research and the actual nature of the interventions included would depend on the final protocol developed to answer this question.
345	SH	Anxiety UK	Guideline	62	3	We welcome the recommendation for research into peer support, but would like to see this extended specifically to focus on peer-led, online support groups.	Thank you for your comment. The research recommendation question about peer support is designed to guide future research and the actual nature of the interventions included would depend on the final protocol developed to answer this question.

346	SH	University of Exeter Medical School	Guideline	68	004-008	The statement: "In addition to the evidence reviewed, the committee were aware of large-scale and pragmatic trials of CBT and BA that were excluded from the network meta-analysis (because they involved patient populations that did not meet specific search criteria), but which were also consistent with this evidence and supported the recommendations" is genuinely perplexing. The trials referred to (and cited specifically elsewhere in the guideline's evidence reviews) are NHS facing trials of real world populations likely to be encountered by clinicians delivering treatments. They also represent the largest number of people with depression. Most of these trials were funded by public agencies supported by taxpayers' money (NIHR for example). Many hundreds of people with depression volunteered to suspend their right to treatment choice in order to participate randomised treatment allocation. It is simply not enough to cite these trials and the selfless efforts of these participant populations as 'consistent' evidence. These are the people who most need help and are the population who present daily to primary care. The £2m NIHR HTA COBRA trial of two psychological treatments, for example, included 440 patricipants with diagnosed depression. NICE has chosen to exclude these data (including 18m follow up) because most of the participants were also taking antidepressants as a so called 'first line' treatment (even though this treatment was not working). This is hardly surprising, given that they were people with multiple episodes of depression and histories of treatment lasting over 300 weeks prior to the trial. This is the usual behaviour of people struggling to overcome and manage their mood	Thank you for your comment. For the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading

						disorders. The evidence review criteria used by NICE has instead, derived evidence from an artificial cohort of participants that in no way represent the clinical and behavioural treatment seeking characteristics of the vast majority of people with depression. Had the COBRA trial excluded these people or asked them to halt their pharmacological treatment we would have a) struggled to find people who were not treating their depression, b) faced the accurate critique that the trial was not generalisable to the public at large c) faced real ethical difficulties in removing existing treatments from vulnerable adults. As noted in a previous comment, the decision to exclude this trial has removed the health economic data from NICE decision making. We face a post-pandemic mental health emergency and the decision to exclude vital health economic data on the relative cost-effectiveness of CBT and BA is a significant disservice to patients, their significant others, clinicians, funders and policy makers in the NHS. The COBRA trial demonstrated that 20% more people with depression could be treated using BA compared to CBT, vital information for a changed mental health context in the post-COVID world.In summary, the decision to exclude some of the largest, pragmatic health services research trials from this guideline cannot be assuaged by a side comment that they somehow back up the committee decisions. What would NICE have done, one wonders had these excluded trials NOT been consistent with the evidence reviews? Tax payers' money, patient volunteers and the efforts of hundreds of health services researchers cannot be dismissed in this cavalier	estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been

						manner. It also makes a mockery of the extensive peer review systems in place including at funder, trial governance and publication levels to treat this scientific endeavour with such disdain. The guideline has based its decision making on artificial criteria that do not represent the populations and the clinical situations faced by the NHS. We face a post-pandemic mental health emergency. These HSR pragmatic trials should be included as exactly the type of evidence that we are now so desperate to work with in order to advise our long-suffering and harassed clinical colleagues in their decision making. And of course, these data should be in the public domain so that patients and their closest significant others are enabled to make life changing decisions about their care.	used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. These exclusions were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to

							name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.

347	SH	Society for Psychotherapy Research	Guideline &Evidence review B	68058	5048	Related to the above point, we ask for the references to the pragmatic trails to be removed here.As pointed out above, we argue that these pragmatic trials should be included in the data analysis. Data from these studies cannot be used to justify or strengthen the higher priority and ranking of CBT and BA, AND not apply the same principle for other treatments where such data is available (even in the referred to pragmatic trial). As such	Thank you for your comment. The committee were aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to name all UK-based studies which were excluded on this basis but which the committee were aware of when making recommendations.
348	SH	UK Council for Psychotherapy	Guideline	69	16	Evidence was only considered for the effectiveness of behavioural couples therapy for people with depression who also had problems in their relationship. Couple therapy for depression is a psychological therapy for depression and is in fact appropriate for people with depression with and without relationship problems. The incorrect assumption that couple therapy for depression is only suitable for a subgroup of people with depression has resulted in several studies being excluded from the review. This is extremely concerning as this	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered

						presumably contributed to a significant reduction in the amount of evidence for couples therapy being considered. We request that the committee correct this error in the guidelines as a matter of urgency and include these studies in the evaluation of the evidence.	only in pairwise comparisons (and not included in the NMA). There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. It is also recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
349	SH	Association for Family Therapy and Systemic Practice	Guideline	69	16	In relation to the evidence for behavioural couples therapy, the only evidence considered by the committee was that which assessed the effectiveness of behavioural couples therapy for people with depression who also had problems in their relationship. Couple therapy for depression is a psychological therapy for depression and is in fact appropriate for people with depression with and without relationship problems. Please also see comment 17.The incorrect assumption that couple therapy for depression is only suitable for a subgroup of people with depression has resulted in	Thank you for your comment. As pre-specified in the review protocol, the committee identified couple interventions, including behavioural couples therapy, as interventions that would be more appropriate for subgroups of adults with depression (for people with problems in the relationship with their partner) and as such these interventions were considered

						several studies being excluded from the review. This is extremely concerning as this presumably contributed to a significant reduction in the amount of evidence for couples therapy being considered. We request that the committee correct this error in the guidelines as a matter of urgency and include these studies in the evaluation of the evidence.	only in pairwise comparisons (and not included in the NMA). There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. It is also recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

350	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	071-072	031-003	ECT – patient choice. “Based on their knowledge and experience, and to ensure better patient experience, the committee reinforced the recommendations about taking into account patient preferences when considering ECT as a treatment option, in line with their recommendations for other treatment options”.For this to be realistic, a wider range of therapeutic alternatives must be available, including arts and creative interventions, and other activities which, as we have noted, are not mentioned anywhere in this document.	Thank you for your comment. Art therapy was listed as an intervention of interest for the treatment reviews. However, only one eligible study was identified for art therapy (Nan 2017) for further-line treatment. The committee considered the evidence too limited to make a recommendation for art therapy for the treatment of depression. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The recommendations allow for a range of interventions that have found to be clinically and cost effective to be considered, in order to match the intervention to the person’s clinical needs and preferences.
351	SH	Critical Psychiatry Network	Guideline	17	12 to 20	This is a very useful section (1.4.17) and will be immensely helpful to patients and doctors. The addition of further information to lines 12-14 may make it even more useful, as below: If a person has withdrawal symptoms when they stop taking antidepressant medication or reduce their dose, reassure them that they are not having a relapse of their depression. As withdrawal symptoms can include low mood, anxiety and trouble sleeping, it is common for people to be alarmed their underlying condition has come back, but patients can be reassured that this is not commonly the case. Explain that:A point that distinguishes withdrawal symptoms from relapse could be added:- the accompaniment of low	Thank you for your comment. The committee agreed that this recommendation was to reassure people, and that it was not necessary to include details of all the possible symptoms in the recommendation.

						mood or anxiety by physical symptoms of withdrawal such as new-onset dizziness, headache, nausea, insomnia (more listed above in this guidance) further distinguishes withdrawal from relapse." (Chouinard & Chouinard, 2015; Framer, 2021)Chouinard, G., & Chouinard, V.-A. (2015). New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. Psychotherapy and Psychosomatics, 84(2), 63–71. https://doi.org/10.1159/000371865 Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/20451253219912 74Zwiebel, S. J., & Viguera, A. C. (2022). Discontinuing antidepressants: Pearls and pitfalls. Cleveland Clinic Journal of Medicine, 89(1), 18–26. https://doi.org/10.3949/ccjm.89a.21020	
352	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	38 - 41	general	Section 1.8 entitled Continuation of treatment for relapse prevention is confusing. It would be preferable to have a section Relapse Prevention that considers various options. One of the options would be to continue with an existing / previous treatment. Another option would be to introduce a new intervention purely for relapse prevention purposes. Mindfulness Based Cognitive Therapy was designed primarily for relapse prevention purposes and has a strong evidence base for its effectiveness in this regard. Many people have experienced multiple previous episodes of depression without coming to the attention of services. In the current draft of the guideline this sizeable group of people is excluded from consideration of relapse prevention because 'continuation of treatment' is not applicable to them.	Thank you for your comment. In response to your comment, this section has been renamed 'preventing relapse'

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

353	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	39	May-16	The guideline recommends that Mindfulness Based Cognitive Therapy (MBCT) should be considered as a relapse prevention intervention for people who have remitted from depression when treated with antidepressant medication alone and are at higher risk of relapse. In our view the link with previous antidepressant is not supported by theory or evidence and should be removed. It would be warranted and preferable to say that MBCT should be considered as a relapse prevention intervention for anybody who has remitted from depression and is at higher risk of relapse. This would be in keeping with recommendation in the 2009 NICE CG90 1.9.1.8 Psychological interventions for relapse prevention.	Thank you for your comment. The committee agreed that these recommendations should remain unchanged as there is a risk of moving people from one psychological treatment to another, so if people had remitted with a psychological intervention alone or a combined psychological and pharmacological intervention and were assessed as at higher risk of relapse it would be optimal for them to continue with the psychological intervention that they had achieved remission with.
354	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	40	Dec-16	The guideline recommends that people who have remitted from depression when treated with a combination of an antidepressant medication and psychological therapy (and are at higher risk of relapse) should have a discussion about whether they wish to continue 1 or both treatments. Whatever kind of treatment they have had, Mindfulness Based Cognitive Therapy should be considered as a relapse prevention intervention for these individuals. This would be in keeping with the recommendation in the 2009 NICE CG90 1.9.1.8 Psychological interventions for relapse prevention.	Thank you for your comment. The committee agreed that these recommendations should remain unchanged as there is a risk of moving people from one psychological treatment to another, so if people had remitted with a psychological intervention alone or a combined psychological and pharmacological intervention and were assessed as at higher risk of relapse it would be optimal for them to continue with the psychological intervention that they had achieved remission with.

355	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	40	07-Nov	The guideline recommends that people who have remitted from depression when treated with a psychological therapy alone (and are at higher risk of relapse) should have a discussion about whether they wish to continue with their psychological therapy for relapse prevention. Whatever kind of therapy they have had in the past, Mindfulness Based Cognitive Therapy should be considered as a relapse prevention intervention for these individuals. This would be in keeping with the recommendation in the 2009 NICE CG90 1.9.1.8 Psychological interventions for relapse prevention.	Thank you for your comment. The committee agreed that these recommendations should remain unchanged as there is a risk of moving people from one psychological treatment to another, so if people had remitted with a psychological intervention alone or a combined psychological and pharmacological intervention and were assessed as at higher risk of relapse it would be optimal for them to continue with the psychological intervention that they had achieved remission with.
356	SH	National Association for People Abused in Childhood (NAPAC)	Guideline	General	General	NAPAC is a signatory to the Guideline response by the coalition of organisations authored by Dr Felicitas Rost. NAPAC fully supports the seven headline points and other content in the coalition response prepared by Dr Rost.NAPAC takes just under 10,000 calls or emails per year from survivors of all types of childhood abuse and/or neglect. Depression is one of the most common and persistent problems we hear about. In some cases, the severity of depression described is very great and can be very long-lasting.NAPAC offers supportive listening and psychoeducation, all delivered in an anonymous and confidential way. This approach makes our service more accessible and trusted to people who have suffered abuse in childhood but also means that we cannot evidence what we learn in a verifiable way.We hear from some people who have had a range of diagnoses by different mental health professionals in different settings over many	Thank you for your comment. The guideline did not review evidence for a trauma-informed approach as an intervention or service delivery model, so the committee did not consider it appropriate to make a stand-alone recommendation. The committee were also aware of differing definitions and meanings of trauma-informed care. In response to your comment, a recommendation about initial assessment has been amended to include trauma as a factor to discuss with the person that may have affected the development, course and severity of their depression. This recommendation is also cross-referred to in a choice of treatment

						years. These people live with chronic depression that has been treatment resistant, some of those people come to NAPAC as last resort and with intense suicidal ideation.We have seen that our trauma-informed approach to offering support can be helpful to people who have not had their needs met elsewhere. This helps those people to believe that recovery is possible, if they are able to access the type of support that is right for them. This meets the headline requirement in the Guideline's Principles of Care in Section 1.1.1. in the second bullet point.	recommendation, so trauma should also be considered when making a shared decision about which intervention is right for the individual.

357	SH	National Association for People Abused in Childhood (NAPAC)	Guideline	General	General	There is no mention of a trauma-informed approach being considered in the recommended interventions for depression. Offering a choice of interventions is central to delivery of a trauma-informed approach to working with depression. There are public policy statements on this from the current Government, NHS England, and the Care Quality Commission. We urge NICE to consider these wider contextual policies as part of the revision of this guideline.Tackling Child Sexual Abuse Strategy 2021 by HM Government with foreword signed by Priti Patel https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/973236/Tackling_Child_Sexual_Abuse_Strategy_2021.pdf Paragraph 246 includes these lines:"…. victims and survivors of both recent and non-recent abuse will require different forms of care and support depending on their circumstances, how they wish to access help, the pace of their recovery and the level of support they receive when they disclose their abuse. There is no 'one-size fits all' approach. The support accessed by victims and survivors encompasses a broad range of statutory and non-statutory services funded by several different local commissioners (local authorities, Clinical Commissioning Groups, Police and Crime Commissioners (PCCs)) and national commissioners (NHSEI, the MoJ, the Home Office). Regardless of the type of support being accessed, victims and survivors stress the importance of being listened to, respected, believed and not judged."Paragraph 245 in the above document refers to the Strategic Direction for Sexual Assault and Abuse Services – Lifelong care for victims and survivors: 2018-2023	Thank you for your comment. The guideline did not review evidence for a trauma-informed approach as an intervention or service delivery model, so the committee did not consider it appropriate to make a stand-alone recommendation. The committee were also aware of differing definitions and meanings of trauma-informed care. In response to your comment, a recommendation about initial assessment has been amended to include trauma as a factor to discuss with the person that may have affected the development, course and severity of their depression. This recommendation is also cross-referred to in a choice of treatment recommendation, so trauma should also be considered when making a shared decision about which intervention is right for the individual.

						published by NHS England at https://www.england.nhs.uk/wp-content/uploads/2018/04/strategic-direction-sexual-assault-and-abuse-services.pdf Most of this document is about prevention but chapter 5 addresses recommendations for supporting recovery. Page 22 includes these lines:"Wherever disclosure takes place, many victims and survivors of sexual assault and abuse describe feeling let down and disappointed when seeking the help they need. They describe delays in being able to access initial help and support and suggest that, when they do, many professionals across the health and social care system have an inadequate understanding of and empathy for sexual assault and abuse and often fail to link behaviour and symptoms to the underlying trauma."The Care Quality Commission's Mental Health Inspectorate has for several years been saying that services must support recovery and not allow people to stay suffering for long periods. Excluding the 'difficult' cases of severe and/or long-term depression is counter to this requirement. For example, their The state of health care and adult social care in England 2016/17 – Mental Health report at https://www.cqc.org.uk/sites/default/files/20171010_stateofcare1617_mh.pdf which states on page 83 "care needs to be holistic and recovery focused".	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

358	SH	National Association for People Abused in Childhood (NAPAC)	Guideline	General	General	From 'cost-benefit analysis' perspective it would be helpful to note this recent Home Office document on the cost to society of child sexual abuse at https://www.gov.uk/government/publications/the-economic-and-social-cost-of-contact-child-sexual-abuse . The calculation of the total lifetime cost to society for a cohort of victims and survivors alive in the year up to 31/3/2019 (counting both children suffering abuse then and adult survivors) to be £10 billion. Much of that is made up of the mental health care needs of these individuals, including trauma-informed approaches in recommended ways of working with depression would speed recovery and reduce long-term costs.	Thank you for your comment. This is a very important cost-of-illness study that estimates the economic and social cost of contact child sexual abuse in England and Wales. This study does not meet criteria for inclusion in the Depression guideline review of economic evidence. For the Depression guideline only studies that assessed the comparative cost-effectiveness of specific interventions targeting depression were included in the review, according to the eligibility criteria listed in the Methods Supporting documentation (which are consistent with the NICE Guidelines Manual available here: https://www.nice.org.uk/process/pmg20/chapter/introduction)

359	SH	Rethink Mental Illness	Guideline	General	General	We welcome the inclusion of group exercise as a treatment option for severe depression. Rethink Mental Illness have seen the benefit of group exercise, particularly in peer support settings, within our own work: Rethink Mental Illness recently completed a project funded by Sport England to consider the impact of embedding physical activity into existing peer support groups. Our interim report found that participants:Scored higher in physical wellbeing questionnaires and improved psychological wellbeing scoresWere more physically active each week, with more autonomous motivation to take part in exerciseDemonstrated increased resilienceAnd reported improvements in health and a sense of better quality of life.We heard from participants that the peer-led element of the physical activity groups means they act as a safe space to take part in exercise with like-minded people who understand and share the same challenges.Those with a severe mental illness die 15 to 20 years earlier than the general population and, therefore, interventions to improve physical health must be a key consideration in treatment. People in contact with mental health services in England under 75 have death rates that are over 6 times higher for liver respiratory disease, over 4 times higher for cardiovascular disease, and 2 times higher for cancers, as per Public Health England data. Research shows that, on average, people severely affected by mental illness spend less of their time being active in comparison to the general population. (Sedentary behaviour and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this.

						meta-analysis. Vancampfort et al, 2017). Involvement in physical activity among those living with severe mental illness can not only pre-vent the development of physical health conditions and reduce the mortality gap, but can also play a significant role in improving mental wellbeing Recent research shows that physical activity can contribute to improvements in symptoms of mental illness, including mood, alertness, concentration, sleep patterns and psychosis. It can also improve quality of life through social interaction, meaningful use of time, purposeful activity and empowerment. (The impact of exercise on quality of life of people with severe mental illness: a critical review. Alexandratos, Barnett and Thomas, 2012) However, becoming more physically active can be a lot harder and present many more barriers for those living with SMI than those without.Therefore, we strongly emphasise the importance of treating physical and mental health together.	
360	SH	Tavistock and Portman NHS Foundation Trust	Guideline	General	General	Research Recommendations We would like to suggest for the committee add to their research recommendation the investigation of long-term treatments, especially for more complex forms of depression.We would also like to suggest for the committee to emphasise in that section that ALL future studies need to include a meaningful long-term follow-up and to report these outcomes as critical outcomes. Especially with	Thank you for your comment. The need to collect long-term follow-up data on outcomes has been added to the suggested protocols for each research recommendation suggested.

						regard to depression, we need to start to investigate whether effects can be sustained.	

361	SH	Big Health Ltd	Guideline	General	General	Background Sleep difficulties including insomnia are core features of depression (APA., 2014) and co-occur frequently (Stewart et al., 2006, SLEEP; 29(11): 1391-7; Nutt, Wilson & Paterson., 2008, Dialogues Clin Neurosci; 10(3): 329-336).Since DSM-5 insomnia should be coded as a disorder, whenever diagnostic criteria are met. This is echoed in ICSD-3 and in ICD-11. Consequently, insomnia should not be regarded as a secondary disorder just because depression is also presentIndeed, insomnia is a predictor of future depressive episodes (Baglioni et al., 2011; J Affect Disord; 135 (1-3):10-9; Hertenstein et al., 2019; Sleep Med Rev; 43:96-105), and therefore, residual sleep difficulties following depression treatment may also increase risk of depression relapse.Experiencing both depression and insomnia symptoms concurrently can be more challenging to treat and therefore may constitute a more severe clinical presentation than depression alone (Franzen & Buysse., 2008; Dialogues Clin Neurosci; 10(4):473-81). Moreover, the presence of both depression and concurrent sleep disturbances is associated with higher rates of suicidality (Soehner et al., 2014; J Affect Disord; 167(1):93-97). Although depression treatments often lead to remission of depression, many individuals continue to have complaints of poor sleep following depression treatment. Indeed, data shows that residual insomnia symptoms often persist following depression-specific treatment (e.g., CBT for depression and pharmacotherapy; Carney et al., 2007; J Clin Psychiatry; 68(2):254-60; Blom et al., 2015; SLEEP; 38(2): 267-277).Advances in our understanding in recent years indicate that insomnia should	Thank you for your comment. This guideline is about the treatment and management of depression in adults. People with depression and a chronic physical health problem, such as insomnia, are not within the scope of this guideline. Therefore it is not possible to make recommendations for the treatment of insomnia in this guideline. Although sleeping difficulties outcomes were included as a measure of functioning, where available. CG91 on 'Depression in adults with a chronic physical health problem' covers identifying, treating and managing depression in people aged 18 and over who also have a chronic physical health problem such as cancer, heart disease or diabetes. Your feedback will be passed on to the NICE surveillance team so that people with insomnia who are experiencing depression can be considered for inclusion in future updates of CG91.

						be actively managed as part of usual care for depression. Doing so may both improve depression outcomes and speed of outcomes, and prevent new onset depression or relapse into further episodes. Role of addressing sleep complaints and insomnia in depression using CBT for insomniaA substantial body of literature demonstrates the clinical benefits of addressing sleep in the context of depression using Cognitive Behavioural Therapy for insomnia (CBT-I).Indeed, CBT for insomnia is the treatment of first choice for insomnia (not medication) in all clinical guidelines (Edinger et al., 2021; J Clin Sleep Med; 17(2); Qaseem et al., 2016; Ann Intern Med; 165(2): 125-33; Riemann et al., 2017; Journal of Sleep Research; 26(6): 675-700; Wilson et al., 2019; J Psychopharmacol; 33(8): 923-947)RCT and synthesised systematic review data show that both therapist-delivered and digitally delivered CBT-I (web/ mobile) is an effective treatment for both insomnia and co-occurring depressive symptoms (Gebara et al., 2018; Depress Anxiety; 35(8):717-731). In-person CBTCBT for insomnia is effective at improving both insomnia and depressive symptoms when delivered as a sole treatment, or when adjunctive to usual care for depression (Gebara et al., 2018; Depress Anxiety; 35(8):717-731).CBT for insomnia is effective at improving insomnia and depressive symptoms in those with both low and high depressive symptom severity (Manber et al., 2011; J Clin Sleep Med; 7(6):645-52). The addition of CBT-I to pharmacotherapy for depression results in an augmented effect on sleep and depressive outcomes compared to pharmacotherapy and a quasi-desensitization control (Manber et al., 2008; 31(4):489-	

						95).Digital CBT for insomnia improves both insomnia and depression outcomes in individuals with both subclinical and clinically significant depressive symptomsFully-automated digital CBT (i.e. with no therapist involvement) for insomnia leads to significant reductions in depressive symptoms with a medium between-group effect (g=0.64) compared to sleep hygiene education in individuals with insomnia disorder (Cheng et al., 2019a; Psychol Med; 49(3):491-500). Importantly, treatment effects on depressive symptoms are not moderated by demographic or socio-economic variables, thereby supporting generalizability (Cheng et al., 2019a; Psychol Med; 49(3):491-500). In individuals with both insomnia disorder and MDD, guided digital CBT for insomnia was more effective than guided digital CBT for depression at improving sleep, and had equivalent effects on depressive symptoms (Blom et al., 2015; SLEEP; 38(2): 267-277). Both guided (van der Zweerde et al., 2019; Psychological Medicine; 49, 501-509) and fully-automated digital CBT (Christensen et al., 2016; Lancet Psychiatry; 3(4):333-341) is effective at improving both insomnia and depressive symptoms in individuals with subclinical depressive symptoms.The long-term effects of Sleepio were evaluated during the COVID-19 pandemic using participants who received Sleepio as part of a previously conducted RCT. Individuals who received Sleepio had significantly fewer insomnia and depressive symptoms, and lower COVID-related distress. Moreover, odds of moderate-to-severe depression during COVID-19 was 57% lower in those receiving Sleepio compared to Sleep Hygiene (Cheng et al., 2021; 44(4);zsaa258). Addressing insomnia as a	

						means of improve depression outcomesIn a sub-analysis comprising data from two large RCTs of 3,352 individuals with insomnia and clinically significant depressive symptoms (Freeman et al, 2017; Lancet Psychiatry; 4(10):749-758; Espie et al, 2019; JAMA Psychiatry; 76(1): 21-30: PHQ-9≥10 at baseline), those receiving fully-automated dCBT-I (Sleepio) experienced significantly greater reductions in both insomnia (g=0.76; p<0.001) and depressive symptoms (g=0.48; p<0.001) compared to control (waitlist or sleep hygiene) at post-intervention, which were maintained at follow-up (Henry et al., 2021; Journal of Sleep Research; 30(1):e13140). Importantly both the Freeman et al and Espie et al studies were designed specifically to employ causal mediation analysis and then demonstrated the causal role of insomnia reduction on the outcomes of interest. Improvements in sleep resulting from Sleepio intervention mediated improvements in depressive symptoms (Henry et al., 2021; Journal of Sleep Research; 30(1):e13140), Furthermore, treatment effects on insomnia and depressive symptoms were not moderated by demographic or baseline insomnia or depression severity. Participants receiving dCBT were 2.9 times more likely to achieve clinically significant improvement in depression (PHQ-9<10) compared with controls.Provision of Sleepio within IAPT services, as part of a UKRI-funded initiative, recently demonstrated that these effects are evident in real world data (Stott et al, 2021; Behav Res Ther; 144: 103922). IAPT remission rates for depression and anxiety increased from 58% to 64.7% when Sleepio was routinely added to IAPT treatment of depression and anxiety	

						as standard of care.All these data indicate that addressing sleep is a relevant and important clinical therapeutic target in individuals who experience both insomnia and depression, and that CBT-I improves clinical outcomes in depression Addressing insomnia as a means of preventing future depressionCompared to sleep hygiene (which is not an effective standalone treatment of insomnia), fully-automated digital CBT for insomnia reduces rates of incident depression by half at 1-year follow-up in those who had insomnia disorder but minimal to no depression at baseline (0.51, 95%CI [0.26 to 0.81, p<0.01; Cheng et al., 2019b; SLEEP: 42(10): zsz150).In pregnant women, the proportion of individuals experiencing depression 3-months postpartum is higher for those who received standard care (18%) compared to fully-automated digital CBT (4%; p=0.006; Felder et al., in press; SLEEP; zsab280).In older adults with insomnia disorder, those in the CBT-I group experienced significantly lower rates of incident or recurrent major depression compared to the sleep hygiene group (12.2% vs 25.9%; hazard ratio, 0.51; 95% CI: 0.29-0.88; p=0.02; Irwin et al., 2021; JAMA Psychiatry; 79(1): 33-41).A recent RCT showed that treatment with therapist-guided digital CBT for insomnia alone and when combined digital circadian rhythm support was effective at clinically meaningful improvement of depressive symptoms 1 year after treatment start, and that combined CBT and digital circadian rhythm support was effective at reducing the incidence of clinically meaningful depression worsening in individuals with insomnia who are at high risk for depression (Leerssen et al., in press; Psychother Psychosom).Summary	

						and recommendationsEvidence clearly demonstrates that addressing sleep disturbances and insomnia in the context of depression results in benefits to both insomnia and depressive symptoms.Intervention for insomnia using CBT or digital CBT is effective, whereas sleep hygiene measures are not.Clinical studies suggest that when a patient is experiencing both insomnia and depression the treatment plan should introduce CBT for insomnia alongside any active management of depressive symptoms (whether active management is drugs or CBT for depression).Doing so using Sleepio is feasible, and effective in real world implementation (Stott et al., 2021; Behav Res Ther; 144: 103922).Sleepio is recommended in both NICE-MIB (NICE., 2017 [MIB129]) and BAP guidelines (Wilson et al., 2019; J Psychopharmacol; 33(8): 923-947) as first line treatment for insomnia.In addition, in those with minimal or subclinical depressive symptoms who experience insomnia, treatment with CBT for insomnia may also prevent the development of future depression. Based on this, the current National Institute for Health and Care Excellence (NICE) treatment guidelines for depression needs to be updated.It currently recommends providing sleep hygiene to improve sleep. This is not evidence-based.The proposed guidelines do not include any recommendations for managing insomnia and sleep disturbance in the context of depression entirely, except when occurring in the context of antidepressant medication withdrawal (NICE., 2021). Even in these circumstances, sleep hygiene is not an effective treatment for sleep difficulties or insomnia symptoms (Edinger et al., 2021; J Clin Sleep Med; 17(2)).The available	

						evidence on insomnia in the context of depression has grown enormously in recent years and the new guideline needs to reflect contemporary science if patients are to benefit optimally.Fully-automated, evidence-based digital CBT, such as Sleepio, could be made available instantly to individuals presenting to primary care with depressive and insomnia symptoms.	

362	SH	Active Partnerships National Team	Guideline	General	General	We support the inclusion of exercise as an optional first line treatment for people experiencing mild depression. However, feel there is significant opportunity for clinicians to promote a broader 'move more' message and integrate physical activity in adjunct to all treatment pathways for patients experiencing mild or severe depression. This is because of the positive relationship that exists between sport, physical activity and mental wellbeing. There are a broad range of beneficial outcomes within this relationship, including positive impact on enjoyment and happiness, building confidence and self-esteem and reducing stress, anxiety and mild depression (Review of evidence on the outcomes of Sport and Physical Activity, 2017). Exercise is effective in the management of mental health conditions. Sport England have seen an increase in people using exercise as a support tool through the Covid pandemic '67% of all adults and 72% of people with a mental condition or illness agree that they exercise to help manage their mental health during the outbreak.' (Savanta ComRes, Attitudes and Behaviours. Wave 21, 05.11.2021 - 08.11.2021)There are many ways to be more physically active and a vast amount of national, free resources that support both clinicians and patients to move more and improve mental and physical health. We recommend referencing and signposting to the following existing support resources within the guideline:1. We Are Undefeatable – we have developed the inspiring, inclusive, and empathetic 'We are Undefeatable' campaign (https://weareundefeatable.co.uk/about-us) alongside 16 leading health and social care charities. This supports and encourages people with health conditions to	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this. Thank you for telling us about the existing physical activity programmes and campaigns. These will be passed onto the NICE shared learning team.

						find ways to be active. 2. Moving Medicine (https://movingmedicine.ac.uk) – a central hub developed with the Faculty of Sport and Exercise Medicine to support healthcare professionals integrate physical activity conversations into routine clinical care (includes depression consultation guides and resources).	

363	SH	Active Partnerships National Team	Guideline	General	General	We would welcome the consideration within the methodology of the inclusion of broader research (including real-life setting research, physical activity non-randomised trials and physical inactivity research) to enrich the guideline development. The current methodology only takes into account randomised control trials (RCTs) and structured exercise programmes which we feel is limiting. It excludes a vast amount of data and qualitative, practical research in relation to what is effective when supporting people with mental health conditions to become more physically active and improve their symptoms. When considering exercise as a treatment option, the inclusion of wider inactivity data and research sources would be beneficial, this is because people with a diagnosed mental health condition are more likely to be inactive. The national physical activity survey for England Active Lives demonstrates people with a diagnosed mental health condition are 1.6 times more likely to be inactive. Much of Sport England's work and expertise is focused on supporting people with long term conditions (including mental health conditions) to manage and improve the symptoms associated with their conditions and improve quality of life through being more physically active. Evidence from Sport England's inactivity investment portfolio, We Are Undefeatable campaign and our partnership with the Richmond Group of Charities suggests the most effective behaviour change principles and messages to apply in supporting people with long term conditions (including depression) to manage symptoms through moving more are; find something you enjoystart slowlybuild up graduallymake	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. The committee considered RCTs as the most appropriate study design to assess clinical and cost effectiveness. This is consistent with the NICE guidelines manual which recognises RCTs as the most valid evidence of the effects of interventions. This was outlined a priori in the review protocols, and on this basis non-randomised trials and real-life research were not included. In response to stakeholder comments, the committee supported less intense 'move more' exercise for general wellbeing (although not a treatment for depression) and made a new recommendation to reflect this. Thank you for telling us about the existing physical activity programmes and

						the most of good days. Enjoyment is an important consideration. Literature suggests that if people do not enjoy an activity to at least some extent then they are unlikely to persist and continue with it over a long period of time (Ryan. Frederick. Lepes, et all.; 1997). We would welcome the opportunity to share this insight to aid the development of the guidelines.	campaigns. These will be passed onto the NICE shared learning team.

364	SH	Active Partnerships National Team	Guideline	General	General	Whilst structured, group exercise may be appropriate for some individuals, broader options that are person-centred and individualised should be considered due to their proven effectiveness such as social prescribing, community provision and self-led activity for those experiencing mild or severe depression.Our portfolio of physical activity investments supporting people living with long term conditions (including mental health conditions) suggests a 'one size fits all' approach is unlikely to be effective.Whilst structured, supervised, group activity may be appropriate for some individuals i.e. those with multiple complex health conditions or unstable health conditions, in practice, many patients referred to exercise on referral style pathways fail to take up or complete the exercise offer. We also know from our latest IAPT physical activity interventions (unpublished 2021) many patients do not feel comfortable exercising as part of a group due to fear of judgement and lack of confidence exercising.Based on evidence (Moving for Mental Health: How physical activity, sport and sport for development can transform lives after Covid-19, Mind 2022) we recommend guidelines also incorporate broader self-led activity to include We Are Undefeatable, Active 10, 10 Today and Couch to 5k,plus widely accessible and affordable community based provision such as OurParks and Parkrun.Providing a range of activities and ways to be active will help patients find something they enjoy. Literature suggests enjoyment is a very important factor. If people do not enjoy an activity to at least some extent then they are unlikely to persist and continue with it over a long period of time (Ryan. Frederick. Lepes, et	Thank you for your comment. The committee noted that the evidence was for a structured formal exercise programme, with exercise of moderate to high intensity, but recognise there may be challenges to implement this. The committee has now removed the suggested duration of exercise sessions and modified the recommended frequency to allow more flexibility in the delivery of exercise programmes. In the 'Other things to think about' column of Tables 1 and 2 it is also highlighted that group exercise may need to be adapted to accommodate psychological aspects, for example anxiety or shame which may act as barriers to engagement. In response to stakeholder comments, the committee also supported less intense 'move more' exercise for general wellbeing (although not as a treatment for depression) and made a new recommendation to reflect this. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

						all.; 1997)Person centred approaches are most likely to lead to longer-term adoption of physical activity behaviours if choice about when and how people engage with exercise and opportunities for optimal challenge are provided (Self-Determination Theory. Basic Psychological Needs in Motivation, Development, and Wellness. Ryan and Deci, 2017).	
365	SH	Royal College of Psychiatrists	Guideline	General	General	Lack of recommendation around diagnosis and specifically which criteria to use. Section 1.2 refers to an assessment of a person answering "yes" to either of the Whooley questions (1.2.1) being made by a professional competent to perform a mental health assessment (1.2.3). We assume that NICE is therefore presuming that such an individual is aware of diagnostic criteria for depression. However, there are references through the guideline to "sub-threshold" depression. However, it is not possible to define what this is without knowing what the "threshold" is, with this differing between ICD and DSM criteria. We note that section 1.2.6 states that the assessment of a person with depression should not "reply simply on a symptom count" (p8, lines 2-3). We wonder whether this is a pointer away from ICD criteria where	Thank you for your comment. This guideline operates within a diagnostic/problem framework within ICD-11. However, the committee took into account a broad range of societal and contextual factors when making their recommendations. In response to stakeholder comments, definitions of depression, and less severe (including subthreshold symptoms) and more severe depression have been clarified and added to the beginning of the guideline.

						severity is determined by number of symptoms. The majority of, certainly pharmacological, treatment studies have been conducted in depression defined using DSM. Given this has a higher threshold for an episode of depression than ICD, and the concerns regarding over-medicalising distress and escalating use of antidepressants, DSM is arguably a more appropriate set of criteria than ICD. We would recommend NICE making explicit comments regarding ICD and DSM criteria to avoid this being a continued source of confusion amongst clinicians.	

366	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	General	General	Creative, cultural and nature-based approaches to addressing depression are not acknowledged anywhere in these draft guidelines (based on a keyword search: art, music, creative, cultural, nature). While the evidence of the effectiveness for those forms of intervention is diverse and less clinical / RCT-centric, this seems a needless oversight given that such approaches can correspond, enhance or be adapted to align with some of the main treatment options in these guidelines, and can provide support for patients experiencing significant waiting times for referrals and treatments.	Thank you for your comment. Art therapy and music therapy were listed as interventions of interest for the treatment reviews. However, only one study of music therapy (Albornoz 2011) is included in the network meta-analysis for the treatment of a new episode of more severe depression. There was also only one eligible study for art therapy (Nan 2017), in the further-line treatment review. The committee considered the evidence too limited to make a recommendation for art therapy or music therapy. Nature-based or cultural activities were not specified in any of the review protocols and thus evidence for specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee considered RCTs as the most appropriate study design to assess clinical and cost effectiveness. This is consistent with the NICE guidelines manual which

							recognises RCTs as the most valid evidence of the effects of interventions, and this was outlined a priori in the review protocols. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

367	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	General	General	Economics. The suggestions around group exercise and mindfulness potentially encompassing various creative and arts-based therapies, and the accompanying peer support benefits, are important. Broadening the range of choices may also have an economic benefit depending on the availability or proximity of such resources in the community.	Thank you for your comment. Art therapy and music therapy were listed as interventions of interest for the treatment reviews. However, only one study of music therapy (Albornoz 2011) is included in the network meta-analysis for the treatment of a new episode of more severe depression. There was also only one eligible study for art therapy (Nan 2017), in the further-line treatment review. The committee considered the evidence too limited to make a recommendation for art therapy or music therapy. Cultural activities or creative therapies (other than art and music therapy) were not specified in any of the review protocols and thus evidence for specific benefits of these interventions as a treatment for depression have not been sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice.

368	SH	Culture, Health and Wellbeing Alliance and University College London.	Guideline	General	General	Patient choice. Given NICE's commitment to patient choice we suggest that moving forward, better use could be made of qualitative evidence, as well as organisations such as the LENs (lived experience network), which exists to ensure that lived experience is central to the development of policy and practice in relation to culture, creativity and health. The LENs has champions in each English region, all with lived experience of mental health needs. Members' testimonials refer to the impacts of creativity on mental health:"Art making can enable us to listen to our inner thoughts and feelings, which we can quite often choose to hide away or ignore. Developing a sense of focus and understanding of these processes are as much challenges of understanding our true nature and questions of psychological wellbeing as they are of art making […] In addition to finding solutions, art can also help us to tell our stories, and this process can often provide us with a much needed healing. Perhaps some things that we experience just cannot put into words and are better told through drawing, painting, dancing or music?" https://www.culturehealthandwellbeing.org.uk/news/blog/sue-flowers-creative-perspective	Thank you for your comment. The guideline recommendations on choice were based on the results of a comprehensive qualitative review of people with depression and practitioner's views on barriers and facilitators to choose. The committee also included 3 members with lived experience of depression. Your comments on art are noted, and although no evidence for art therapy was identified that allowed its inclusion in the treatment recommendations, an additional recommendation on the role of art (and other activities) on wellbeing has been added to the guideline.

369	SH	Diabetes UK	Guideline	General	General	It is important to acknowledge the need for a system-wide integration of physical and mental health in this guidance and we welcome the principles of person-centred care as essential to any plan integrating the needs of all conditions.Diabetes is a complex, demanding and often progressive condition with potentially debilitating complications. At least four in ten people with diabetes experience emotional or psychological problems, such as depression, anxiety and diabetes-related emotional distress. The evidence suggests that treating emotional and psychological problems in isolation from an individual's diabetes does not always lead to improvements in physical health or self-management. References: (Peyrot M, Rubin RR, Lauritzen T et al.2005. Psychosocial problems and barriers to improved diabetes management: results of the Cross-National Diabetes Attitude, Wishes and Needs (DAWN) Study. Diabetic Medicine 22; 1379–1385).Gonzalez JS, Peyrot M, McCarl LA et al (2008). Depression and diabetes treatment non adherence: A Meta-Analysis. Diabetes Care 31 (12): 2398–2403 36 Fisher L, Gonzalez JS, Polonsky WH (2014). The confusing tale of depression and distress in patients with diabetes a call for greater precision and clarity. Diabetic Medicine 31; 764–772	Thank you for your comment and your support for the person-centred approach adopted in the guideline.
370	SH	Diabetes UK	Guideline	General	General	We are concerned that the guideline 'Depression in adults with a chronic physical health problem: recognition and management' [CG91] has not received a major update since its publication in 2009. As the identification, management and treatment of depression is greatly impacted by a chronic physical health condition like diabetes it is vital that full, up-to-date advice is available for people who live with the	Thank you for your comment. The committee are aware that the NICE guidance on Depression in adults with a chronic physical health problem (CG91) was published in 2009, and will bring this to the attention of the NICE surveillance team.

						condition and healthcare professionals who support them to manage both effectively. We would welcome clarification about how and when the guidelines focussing on depression in those with chronic physical health problems are due to be updated.	
371	SH	Diabetes UK	Guideline	General	General	There are key recommendations on joint decision-making, equity and consent which are proposed to be deleted as they are now also included in the NICE guideline on service user experience in adult mental health services which is been cross referenced. Whilst we appreciate it makes this document briefer and more accessible in some circumstances we think that in practice clinicians find it difficult to refer to two documents when reviewing a person with depression and it would be better to keep them within this guideline.	Thank you for your comment. The main reason for cross-referencing and hyperlinking from one guideline to another, is that if the linked guideline is revised or updated, the user will access the revised version.
372	SH	Diabetes UK	Guideline	General	General	It is important healthcare professionals are aware that people with severe mental illness are at increased risk of developing type 2 diabetes and some psychiatric medication is diabetogenic. We would therefore recommend that this information be included and feel that signposting to the guidance 'Type 2 diabetes: prevention in people at high risk' [PH38] is useful. This includes advice for identifying those who should be encouraged to undertake risk assessments and/or diagnostic tests and advises that healthcare systems particularly consider those experiencing problems with their mental health. Reference: https://www.nice.org.uk/guidance/ph38/resources/type-2-diabetes-prevention-in-people-at-high-risk-pdf-1996304192197	Thank you for your comment. NICE guideline CG91 on 'Depression in adults with a chronic physical health problem' covers identifying, treating and managing depression in people aged 18 and over who also have a chronic physical health problem including diabetes.

373	SH	NHS England and Improvement	Guideline	General	General	We are concerned that the draft guideline appears to have abandoned the stepped care model for the treatment of depression that NICE recommended in its previous guidelines without providing any clear justification for the change and without looking at data on the effectiveness of the model as currently implemented in the NHS through the Improving Access to Psychological Therapies (IAPT) programme. We ask the panel to think again. NICE's 2004 Depression Guideline recommended a stepped care model for the treatment of depression. Within that model, most patients with depression in the mild to moderate range would initially be offered a low intensity form of cognitive behaviour therapy such as guided self-help. It was expected that a substantial number would recover with low intensity intervention. For those who did not recover, prompt step up to a recognized high intensity psychological intervention was recommended. The NHS acted on NICE's guidance and built low intensity to high intensity stepped care into its Improving Access to Psychological Therapies (IAPT) programme when the national rollout started in 2008. A new workforce (Psychological Wellbeing Practitioners: PWPs) was recruited and trained to deliver the low intensity interventions. NICE affirmed its recommendation for Low to High intensity stepped care in its 2009 Depression Guideline and retained extensive sections on that treatment delivery system in the first (2017) and second (2019) drafts of the new revised guideline. However, the sections on low to high stepped care have been removed from the current (third) draft. A brief statement supporting some form of stepped care as a general principle does appear in the	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, the committee have re-structured treatment recommendations, guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent.

						draft guideline (Section 1.15.1) but the specific low to high intensity form of stepped care in previous guidelines no longer appears. Instead, Table 1 (third draft Guideline section 1.5.3) and the Supporting Document entitled "Depression in adults: choosing a first line treatment for less severe depression" both recommend that services first offer high intensity forms of CBT (group CBT, group BA, individual CBT, individual BA) before offering low intensity therapy (self-help with support). We would have expected NICE to look at the outcome data from IAPT before abandoning the NHS' implementation of its previously recommended service delivery model. Ensuring that limited NHS resources are used to give effective and timely therapy to the maximum number of people requires consideration of systems of delivery, not just the findings of RCTs comparing monotherapies. IAPT has been running for 13 years and has used its unprecedently complete dataset to refine the implementation of the low to high intensity stepped care model. Each year NHS Digital publishes detailed reports on the performance of IAPT. NHSD's most recent Annual Report covers April 2020 to March 2021. In that year, IAPT services saw just over 1 million patients for a standardized assessment. Some only required advice and /or signposting. However, 634,649 patients warranted and were offered a course of therapy (defined as attending at least two sessions, including the initial assessment). On average treatment started within 20 days of referral, which is a marked improvement from before the start of IAPT services, when average waits were over a year. NICE's previously recommended stepped care model was used, with	However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement. For each level of severity, for the class of Cognitive and cognitive behavioural therapies, both individual and group, the NMA classification system made a distinction between CBT ≥15 sessions and CBT<15 sessions, which were considered as separate interventions within the class, because there was great variation in the number of sessions reported across RCTs, and there was also a large evidence base that allowed formation of 2 separate groups of interventions according to the number of sessions offered. The committee wanted to explore if there was a difference in the effects of briefer vs longer CBT. For each level of severity, the economic analysis selected and analysed one intervention per effective class as an exemplar, as it was not feasible to model every single intervention considered in the NMA. The criteria for selection can be found in Appendix J, section 'Interventions assessed'. For less severe depression, CBT≥15 sessions and CBT<15 sessions had a similar SMD vs TAU,

						around 70% of patients having a low intensity intervention, either on its own or followed by high intensity therapy. Satisfaction with the service model was high with 92% of people saying they got the help that mattered to them "All or Most of the Time". Pre- and post-treatment measures of symptoms (PHQ-9 & GAD-7) and disability (WSAS) were collected from 99% of the treated cohort, a data completeness rate that is better than in most RCTs. 51.4% of treated patients met IAPT's strict recovery criterion (dropping below the clinical threshold for both depression and anxiety) and 68.3% showed reliable improvement. For 188,548 patients their primary problem was depression, with 180,165 meeting clinical caseness criteria at assessment. Of the latter group, 50.1% had recovered (IAPT joint criteria) by the end of their treatment in the stepped care system and 71.3% showed reliable improvement. Their means (and standard deviations) for the PHQ-9 were 17.2 (4.8) at pre-treatment and 9.9 (6.5) at post-treatment, giving a large pre-treatment to post-treatment effect size (cohen's d) of 1.5. We are aware that most of the RCTs considered by the NICE panel use a less strict measure of recovery (dropping below the clinical range on the depression measure alone, rather than on both depression and anxiety) and that the panel has issued separate recommendations for less severe and more severe depression. To help the panel relate the findings of IAPT to its own framework, we asked NHS Digital to break down the publicly reported data for 2020/21 by depression severity and to compute recovery / reliable improvement just based on PHQ-9 scores. We understand that NICE considers a PHQ	and CBT<15 sessions had a somewhat larger evidence base across RCTs on the SMD outcome - see Table 10, results of bias-adjusted analysis for less severe depression, in evidence review B. CBT<15 sessions individual was considered to have an appropriate intensity for a population with less severe depression by the committee, it had also a larger evidence base than CBT≥15 sessions, and given that they had similar effectiveness, CBT<15 sessions individual was selected for consideration as an exemplar of its class in the economic modelling (which ultimately informed guideline recommendations). This has now been explained in evidence review B, under 'The committee's discussion of the evidence'. The 'usually' 8 sessions in the respective recommendation for CBT were based on the resource use reported in the RCTs of individual CBT <15 sessions for less severe depression that informed the NMA and the guideline economic analysis. The vast majority of these studies reported 7-8 sessions (only one study reported 10 sessions). This means that the effect of individual CBT<15 sessions for less severe depression, which informed the guideline economic analysis and the respective

						score of 10-16 inclusive to represent “less severe depression” and a score of 17 or above to represent “more severe depression”. For NHS Digital’s additional analysis recovery was coded if a patient scored 10 or above on the PHQ-9 at pre-treatment and 9 or below at post-treatment and reliable improvement was coded if the PHQ-9 score dropped by 6 or more points. The findings are given below.All CASES (i.e. everyone with depression as the primary problem and an initial PHQ-9 of 10 or above)N = 172,762. Recovery = 55.3%. Reliable Improvement = 61.3%.PHQ-9 mean (and SD) = 17.6 (4.4) at pre-treatment and 10.1 (6.5) at post-treatment. Pre-post effect size (d) =1.7LESS SEVERE CASES (depression primary problem and initial PHQ-9 of 10-16 inclusive).N = 77,775. Recovery = 68.6%. Reliable Improvement = 53.7%.PHQ-9 mean (and SD) = 13.1 (2.0) at pre-treatment and 7.8 (5.1) at post-treatment. Pre-post effect size (d) =2.7MORE SEVERE CASES (depression primary problem and initial PHQ-9 of 17 or above).N = 100,987. Recovery = 45.9%. Reliable Improvement = 66.7%.PHQ-9 mean (and SD) = 20.6 (2.7) at pre-treatment and 11.7 (6.8) at post-treatment. Pre-post effect size (d) = 3.3We would contend that these clinical outcomes are good and, if one looks at the RCTs considered by the NICE panel, there is little evidence that better outcomes would be achieved by mass implementation of the revised model laid out in Table 1 of the draft guideline. We would also like to point out that implementation of the treatment delivery plan outlined in Table 1 and the Supporting Document on less severe depression would have a catastrophic effect on the availability of psychological	recommendations, was based on studies were individual CBT was offered in 8 sessions on average. Similarly the RCTs of BA for less severe depression reported 1-10 sessions, with larger studies reporting 8 sessions. The effect of BA in less severe depression was therefore based on studies where BA was offered in 8 sessions on average. The reported resource use in RCTs that informed the NMA, guideline economic analysis and, ultimately, guideline recommendations, is now provided in Evidence Review B, under Appendix N. The committee considered this information and agreed that 8 sessions of a high intensity intervention are usually adequate for a population with less severe depression. The recommended 'usual' number of sessions serves only as guidance and can be modified depending on individual needs. This has now been clarified in the recommendation. Regarding group CBT for less severe depression, as shown in evidence review B, under Appendix N, few studies made specific reference to the number of participants per group. Where this was reported, it ranged between 4-6. This reported use, combined with the committee’s considerations on optimal

						therapies for depression. PWPs treat more than twice as many patients each year as high intensity therapists. If we abandoned the low to high intensity stepped care model recommended in previous NICE guidelines, many fewer patients would be treated, and wait times to start treatment would greatly increase. We know that how long patients wait on average for the start of their treatment is negatively related to the outcomes a service achieves (Lancet 2018;391:679-86) so we would expect the increase in wait times to mean that a smaller proportion of treated patients recover. We would also be concerned that suicide rates would be likely to increase if therapy is delivered in a less timely fashion. Lastly, the cost of psychological therapy services would substantially increase as a much larger proportion of the staff would have to be high intensity therapists who are paid on a higher grade.Finally, we have concerns about the validity of some of the assumptions that underpin the monotherapy cost-effectiveness rankings that are shown in Table 1. For less severe depression it is assumed that individual CBT will involve just 8 sessions. Most of the RCTs in the NICE database that were used to calculate the effectiveness of individual CBT (or BA) involved considerably more sessions. We do not think it is reasonable to claim the outcomes of more than 8 sessions while costing treatment at only 8 sessions. Group CBT is considered the most cost-effective intervention. However, putting together a group of the recommended size (8 patients with 2 therapists) is very difficult in practice. It can take weeks or months to find 8 patients who are all willing to attend weekly at the same time,	delivery of group interventions, have been reflected in the economic modelling and the respective recommendation, which suggests the number of participants that groups should 'usually' have. This is not restrictive but allows flexibility around the number of participants per group. Also, it is noted that group high intensity psychological interventions, delivered by 2 therapists to 8 participants per group were found to be cost-effective for less severe depression according to the guideline economic analysis. The recommendations for treatments of a new episode of less severe depression have now been modified to suggest low intensity interventions as an earlier step in the care pathway, before group CBT.

						so there is usually a long delay in starting group treatment. To us it does not make sense to put a therapy that has a delayed start as one's first choice in a care pathway.	

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

374	SH	NHS England and Improvement	Guideline	General	General	Use of term 'patient is used on occasion, though there is some reference to 'person with depression' - can ‘person with depression’ be used throughout/replace any reference to the term ‘patient’?	Thank you for your comment. The use of the word 'patient' has been changed to 'person with depression' where this is appropriate (for example, in some places 'patient choice' has been left as that is a more succinct and well understood phrase)

375	SH	University of South Wales	Guideline	General	General	Evidence for a range of Low intensity CBT interventions currently delivered in the NHS and privately has not been reviewed and thus are not recommended (for example group psychoeducation); does this imply that these interventions should be de- commissioned?Moreover, the current recommendation describes these interventions as Self-help with support which undermines the importance and role of low intensity CBT. In addition, they suggest these interventions could be delivered in 15 minutes. Such a time scale may be possible for computerised CBT, but this is not the range of Low intensity CBT interventions currently delivered in the NHS and privately.	Thank you for your comment. Psychoeducation groups are not included in the recommendations for less severe depression as evidence from the network meta-analysis shows neither a clinically important nor statistically significant benefit of a psychoeducation group intervention relative to TAU on depression symptomatology for adults with less severe depression. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice. The self-help with support section has been relabelled as guided self-help, included earlier in the treatment pathway, and the description of guided self-help has been amended to recommend that printed or digital materials that follow the principles of guided self-help are used including structured CBT, structured BA, problem solving or psychoeducation materials, delivered face-

							to-face or by telephone or online. In response to stakeholder comments, the committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

376	SH	University of South Wales	Guideline	General	General	Much of the research evidence reviewed is not generalisable to mental health services in England, or reviews interventions that are out of date and no longer used in contemporary services (e.g., the computerised CBT programme Beating the Blues)	Thank you for your comment. When making recommendations, the committee interpreted the evidence in light of their knowledge of the clinical context, including applicability to the UK service setting, so that the 'reality' for people experiencing depression was taken into consideration and recommendations were made that were relevant to the populations that clinicians typically encounter. The committees' discussions on this are documented in 'The committee's discussion of the evidence' sections.
377	SH	University of South Wales	Guideline	General	General	For group interventions – it mentions that one of the things to think about is that "May allow peer support from others who may be having similar experiences". However, this could benefit from the specificity that such a group would be helpful as it allows an opportunity to normalise difficulties being experienced. And making clear this is not peer support or an expectation for participants to support each other.	Thank you for your comment. The committee agreed that the wording in the tables provided enough information about the purpose of peer support and did not place an undue expectation on participants as it used the phrase 'may allow'.
378	SH	Dorset Healthcare University NHS Foundation Trust	Guideline	General	General	Where there is limited evidence the committee has recommended further research. We are concerned that the research methodology should be expanded to include a full analysis of one and two-year follow-up data from trials. Treatment recommendations could then be prioritised on the basis of these data over and above data on short-term outcomes of less than one year.	Thank you for your comment. The need to collect long-term follow-up data on outcomes has been added to the suggested protocols for each research recommendation suggested.

379	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	General	General	The increased emphasis on involving patients in choices about treatment options is welcome.	Thank you for your comment and support for these recommendations.
380	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	General	General	Thank you for your comment. The committee were aware that there may be people who express a preference for 'talking therapy' compared to 'medication' and the table of interventions and the visual summary are designed to aid discussion, take into account people's preferences and facilitate shared decision-making. There is evidence of a differential in the effectiveness and cost-effectiveness of the interventions included to justify their order, but there is also a recognition that people have to use a treatment that is suitable for them, and hence people can start with any treatment and do not have to fail a treatment to try another treatment. The guideline recommendations have been revised to recognise that in practice, it may be appropriate to start people with less severe depression on guided self-help initially, before considering step 3 interventions such as CBT.	Thank you for your comment. The committee were aware that there may be people who express a preference for 'talking therapy' compared to 'medication' and the table of interventions and the visual summary are designed to aid discussion, take into account people's preferences and facilitate shared decision-making. There is evidence of a differential in the effectiveness and cost-effectiveness of the interventions included to justify their order, but there is also a recognition that people have to use a treatment that is suitable for them, and hence people can start with any treatment and do not have to fail a treatment to try another treatment. The guideline recommendations have been revised to recognise that in practice, it may be appropriate to start people with less severe depression on guided self-help initially, before considering step 3 interventions such as CBT.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

381	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	General	General	The stepping up procedure seems to be fundamentally changed – this would cause significant instability to current Increasing Access to Psychological Therapies (IAPT) services.	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice.
382	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	General	General	The treatments recommended in the guidance appear to be in line with symptom reduction and reliable improvement, however we would query the role of recovery as defined by Increasing Access to Psychological Therapies (IAPT). There is a risk of 'de-coupling' recommended treatments from those in which services within Primary Care can have confidence of reaching recovery focused KPIs.	Thank you for your comment. The critical outcomes in the treatment reviews for this guideline included depression symptomatology, remission (usually defined as a cut off on a depression scale) and response (usually defined as at least 50% improvement from the baseline score on a depression scale). The IAPT definition of recovery is outside the scope of this guideline and is a matter for implementation..

383	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	General	General	It would be beneficial to incorporate some of the practice based evidence from the years' worth of data collected nationally as part of the Increasing Access to Psychological Therapies (IAPT) project. It appears a significant missed opportunity for that evidence base not to be informing guidance to further refine delivery (what works for who) and improve outcomes.	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

384	SH	Tees, Esk and Wear Valleys NHS Foundation Trust	Guideline	General	General	No mention of Depression within the Perinatal population	Thank you for your comment. A link to the NICE guideline on antenatal and postnatal mental health has been included in the section of the guideline on the delivery of treatments, to remind healthcare professionals to consider the care of these women separately.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

385	SH	UK Council for Psychotherapy	Guideline	General	General	Changes made since the previous draft and engagement with stakeholders Having raised several serious concerns with the first and second version of this draft guideline as part of a stakeholder coalition, we would like to place on record our gratitude to NICE and the committee for meaningfully engaging with stakeholders around these issues, initially in meeting with representatives from our Coalition in May 2019 and subsequently in adapting the methodology that has informed the third draft. We appreciate the time and resource it took to take these measures and are grateful that NICE invested these in this hugely important guideline. In particular, we welcome the committee reviewing the inclusion of long-term follow-up data, of qualitative studies on service user experience, of quality of life and functioning data, as well as the stated commitment to recognise partial recovery from depression.We observe major improvements with the guideline as a result of this additional work. Having stressed at length in our previous responses the vital importance of patient choice, we are particularly pleased about the significant emphasis on the importance of service user choice and shared decision-making throughout this third iteration of the treatment guideline, as well as the stronger focus on personalised care. In our view, the move away from the stepped care model in this draft will, if realised, represent a major step forward in the care of people with depression. The greater flexibility and choice it could provide will empower service users and, we hope, lead to better outcomes. Having raised concerns previously about a failure of NICE and the committee to fully demonstrate how certain	Thank you for your comment. Responses have been provided to the outstanding methodological concerns referenced in this comment in response to your other comments where these concerns are outlined.

						recommendations were reached, we would also like to acknowledge the greater overall transparency and clarity provided in this draft. However, in our previous responses we have emphasised that, if the methodological concerns are not addressed in full, the resulting treatment recommendations cannot be fully relied on – to the detriment of the millions of people with depression whose care is shaped by this guideline. We have also expressed concern about the real-world impact of maintaining a clear hierarchy between different treatments that have been found to be clinically and cost effective, which we believe undermines patient choice and disincentivises the diversification of provision for commissioners in the NHS at a local and national level. While we strongly welcome that some of the methodological flaws we raised have been addressed in this draft, we must highlight that not all of them have been adequately resolved (see below comments). While these methodological concerns remain unaddressed, despite a much-improved guideline, we must continue to call into question the trustworthiness of the treatment recommendations derived from these methods. We believe that a significant proportion of individuals suffering from depression could be impeded from accessing the right treatment for them. We are particularly concerned about the care of individuals who experience more complex and persistent forms of depression, for whom the clinical utility of this guideline is questionable (see below). Given the disproportionate cost burden of this group to the NHS, as well as the structural disadvantages they face, we ask that this group are prioritised as part of any further review of this	

						guideline. It has been clear during our engagement with NICE over the period that this guideline has been in development that there are differences of opinion between equally respected technical experts. We also acknowledge that the research landscape around depression treatments is disproportionately complex, and many interventions suffer from a historical absence of evidence development. However, we must emphasise the huge influence NICE has over treatment availability in the UK, as well as steering developments internationally. It rightly has a gold standard reputation. We therefore cannot accept that this hugely important guideline will be published while its methodology continues to be challenged by such a large swathe of the mental health sector, both in the UK and internationally. The lack of trust in the guideline will not only be damaging for patients, it will also create further unnecessary division around mental health provision. So, while we are grateful for NICE's meaningful engagement with our concerns up to this point, we urge the committee to seek greater consensus with the broader mental health sector around the delivery of this guideline before the final version is published.	

386	SH	UK Council for Psychotherapy	Guideline	General	General	Why was the extremely large IAPT dataset comparing outcomes from different types of therapies, which has been collected for over a decade and is high quality practice-based evidence, not included alongside RCT evidence?	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.

387	SH	UK Council for Psychotherapy	Guideline	General	General	Why were family interventions for depression not considered such as family therapy for depression based on the McMaster model, (Miller et al., 2005; Ryan et al., 2005); behavioural family therapy for families of depressed mothers of children with disruptive behaviour disorders (Sanders and McFarland, 2000); and various types of individual family and multifamily therapy for older adults with depression (Stahl et al., 2016)?	Thank you for your comment. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions.
388	SH	UK Council for Psychotherapy	Guideline	General	General	The committee made the recommendations on the use of lithium and the use of antipsychotics by informal consensus and based on their knowledge and experience. This seems inconsistent with recommendations made about other interventions including psychological therapies.	Thank you for your comment. The recommendation on use of lithium and use of antipsychotics provide practical information on how these medicines should be used in practice and monitored, and this is not the sort of information that is best obtained from a systematic review of the evidence. These recommendations were therefore based on pre-existing national guidance such as the BNF, and the committee's knowledge and experience. The place in therapy of lithium and antipsychotics was based on systematic

							reviews of the evidence for the treatment sections of the guideline.
389	SH	Association for Family Therapy and Systemic Practice	Guideline	General	General	Absence of systemic and narrative family therapies from the guidelines AFT members have noted the absence of family and systemic therapies within the guidelines, and the exclusion of behavioural couples therapy from the visual summaries. There is significant evidence that working with families, carers and significant others improves health outcomes (see review of the literature on this area in Carr, A. (2019), Couple therapy, family therapy and systemic interventions for adult-focused problems: the current evidence base. Journal of Family Therapy, 41: 492-536. https://doi.org/10.1111/1467-6427.12225; pages 20-23). There is a consensus that the exclusion of systemic evidence for depression from the guidelines will result in people with depression not being routinely offered treatments that includes families, carers and significant others; this significantly impacts on treatment choice and potential positive treatment outcomes. In his review of the evidence for depression, Professor A Carr (2019) notes “Depressive episodes occur and persist when genetically vulnerable individuals become involved in stressful social systems in	Thank you for your comment. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions. There are recommendations in the choice of treatment section of the guideline that people with depression should be given the

						which there is limited access to socially supportive relationships, and in which they erode the quality of support available to them through depressive behaviour." Furthermore, we recognise that the exclusion of family members and informal carers from therapies would have a significant negative impact on the health of those who support people with depression, as evidenced in the literature on caregiver burden (for example, Pinquart, M., & Sörensen, S. (2003). Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 58(2), P112-P128) and that this exclusion will therefore have wider implications for the health system.	option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. It is also recommended in the access to services section that commissioners and providers of mental health services should promote access, and increased uptake and retention, by ensuring that pathways have in place procedures to support active involvement of families, partners and carers (if agreed by the person with depression).
390	SH	Association for Family Therapy and Systemic Practice	Guideline	General	General	Research evidence appraised We note the reliance on specific forms of evidence and outcomes. This has significant impact on what has been included as an option for treatment despite the availability of literature and practice-based evidence that might support a range of other treatments as being useful for people with depression. Outcomes in depression treatment are likely to go beyond reduction in depressive symptoms; they might include partial remission, increased access to social support and improved relationships.	Thank you for your comment. The guideline includes continuous changes in scores on depression scales as a critical outcome for every treatment question, which will show changes for people who have both fully and partially recovered. This was agreed by the committee to be a better way to capture this data than the use of a dichotomous outcome for partial recovery, as continuous data avoids losing detail compared to dichotomised outcomes. Personal, social, and occupational functioning, and quality of life outcomes were also included for all treatment reviews.

391	SH	Association for Family Therapy and Systemic Practice	Guideline	General	General	DiversitySystemic and narrative family interventions are responsive to the growing diversity and complexity of family structures and may be of particular value to individuals from minoritised groups. Practice-based evidence suggests it may be the treatment of choice for some people from ethnic and cultural groups, and may be especially appropriate where there are close kinship ties, collective family structures or where individuals find it difficult to access services alone. The evidence for interventions needs critical appraisal to ensure people from diverse and minoritised groups are not excluded; some groups are less likely to access and successfully complete research trials.	Thank you for your comment. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions. There is a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include: services delivered in culturally appropriate or culturally adapted language and formats; and procedures to support active involvement of families, partners, and carers.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

392	SH	Camden and Islington NHS Foundation Trust	Guideline	General	General	There are several concerns about this draft guidanceOne is that stepped care model for the treatment of depression which was a key part of the earlier NICE depression guidance has been removed and this will have a huge negative impact on the way IAPT services are delivered. The IAPT programme has been built on this stepped care model - with a significant number of people with mild-moderate depression being seen at step 2 and offered guided self-help interventions. The clinical outcomes from IAPT services (as reported by NHSD) have been very positive – but this does not seem to have been considered at all in the draft guidelines. The draft guidelines suggest that high intensity CBT should be offered as first line treatment and if this is followed then there will be a need for many more people to be seen by CBT therapists and very little role for PWPs. The impact of this would be to massively increase the waits for treatment and mean that a lot less people will be seen overall in IAPT services.This will have a very detrimental effect on the overall level of depression treatment in the country. We would urge the guideline group to reconsider this removal of the effective stepped care approach consider the NHSD data in the next draft.	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice.
393	SH	The Challenging Behaviour Foundation	Guideline	General	General	Across all recommendations it should be noted that discussion with the individual alone will not suffice for understanding the needs, preferences, and experiences of some individuals with learning disabilities. While reference to involvement of family and support staff is made sparingly, it should be recognised that this involvement is needed in all 'discussions' where appropriate for the individual. Mention of capacity is also sparing throughout the recommended guidelines, yet this	Thank you for your comment. As you state, there are recommendations relating to adapting communication and involving family in the over-arching sections at the front of the guideline so it has not been repeated every time a discussion in advised, as healthcare professionals would be

						ought to play a larger role in designing and agreeing treatments.	expected to apply these principles in all situations.
394	SH	The Challenging Behaviour Foundation	Guideline	General	General	Recommendations, particularly 1.5.3 to 1.6.1, require greater cross referencing to NG54, regarding the treatments appropriate for individuals with learning disabilities.	Thank you for your comment. We have added a cross-reference to NG54 from the section on the delivery of psychological treatments, and so have not repeated it in both 1.5 and 1.6.
395	SH	Anxiety UK	Guideline	General	General	We welcome again, the range of treatment options detailed in Table 2 as this offers clients choice.	Thank you for your comment and support for these recommendations.
396	SH	Mental Health Matters	Guideline	General	General	The stepped care model has been removed, however all IAPT services still utilise this model of care .	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice.
397	SH	Mental Health Matters	Guideline	General	General	It would be helpful to have a definition of what a 'less severe depression' presentation is	Thank you for your comment. The guideline now includes definitions at the beginning which clarify that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression

							includes the traditional categories of moderate and severe depression.
398	SH	The College of Mental Health Pharmacy	Guideline	General	General	The flow of the whole document is rather hard to follow, not intuitive to follow; it seemed to jump back and forth on the topic of medication, meaning that the reader often missed aspects of the guidance e.g., 1.3 is titled “Choice of treatment” but there is no specific guidance in that section about the choice of antidepressant, this is elaborated on in a new section called “Delivery of treatment”.It did not match the patients’ pathway through treatment.	Thank you for your comment. Some reordering of the document has been carried out to reflect the patients' journey.
399	SH	The College of Mental Health Pharmacy	Guideline	general	general	No clear guidance about the times when it IS appropriate to abruptly stop an antidepressant. The whole tenor of the text was about the risks of stopping, but did not advise clinicians how to proceed if a patient developed an acute adverse reaction or presentation eg serotonin syndrome, mania, GI bleed etc where following the advice to slowly reduce the dose of many months or weeks would be extremely dangerous.	Thank you for your comment. The committee agreed that in some circumstances it was necessary to stop antidepressants abruptly if there were serious side-effects and have clarified this in their recommendation about factors to consider when stopping antidepressants.
400	SH	The College of Mental Health Pharmacy	Guideline	general	general	In section 1.8.4 there is reference to antidepressants increasing the risk of bleeds. This needs to be expanded on, explain that this is serotonin related, and that PPIs should be prescribed to patients in high at risk groups.	Thank you for your comment. This recommendation has been clarified to state that not all antidepressants lead to these effects, but the committee agreed that in the context of this recommendation, which is about risk, it was not appropriate to

							provide supporting information on the rationale or treatment for this.
401	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	Quality of life and functioning outcomes We are particularly pleased about the inclusion of functioning and quality of life measures. We regret to learn that of those studies included in the reviews, only a few had reported on these outcomes. We would like to suggest that a sentence be added in the relevant sections in all documents, particularly within the research recommendations section, referring to the importance of (a) future studies reporting on such outcomes, and (b) existing studies to publish these findings where the data was collected, especially given that these are the measures of greatest priority to service users.	Thank you for your comment. The committee agree that quality of life and functioning outcomes are important. The committee noted the limited evidence for these outcomes, and included quality of life and functioning outcomes for the research recommendations in the guideline.

402	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	https://www.nice.org.uk/guidance/GID-CGWAVE0725/documents/supporting-documentation-23 and https://www.nice.org.uk/guidance/GID-CGWAVE0725/documents/supporting-documentation-24Both diagrams could feature Social prescribing and PHBs and Shared Decision Maki	Thank you for your comment. The committee noted that this review covered people with depression comorbid with a personality disorder, but that there are different types of personality disorder and it was not always clear from the evidence which types had been included, or if all types had been combined and considered. The committee agreed that one of the most common types is emotionally unstable personality disorder (previously known as borderline personality disorder) and they were aware that there is existing NICE guidance about the treatment of people with borderline personality disorders with comorbid depression which recommends treatment within a well-structured treatment programme for borderline personality disorder. The committee therefore wanted to make recommendations that were in line with this existing NICE guideline and so recommended that referral to a specialist personality treatment disorder programme should be considered. The committee discussed placing this recommendation at the beginning of the section but did not consider it appropriate as the focus of this recommendation was about treatment of

							the personality disorder, rather than treatment of depression. The committee did not consider the recommendations as contradictory to those in the NICE guideline on borderline personality disorder. There is a recommendation in that guidance that drug treatment may be considered in the overall treatment of comorbid conditions, and that when treating a comorbid condition in people with borderline personality disorder the NICE clinical guideline for the comorbid condition should be followed. While the recommendation about short-term psychological interventions is for treatments specifically for borderline personality disorder or for the individual symptoms of the disorder, and is not relevant to the treatment of depression in people with coexisting personality disorder. The committee noted that there was some evidence of benefit on depression symptomatology for 2 of the comparisons of monotherapies: CBT alone compared to pill placebo, and behavioural therapy alone compared to short-term psychodynamic psychotherapy. There was also evidence for

							clinical benefit from studies with combined psychological (either IPT or short-term psychodynamic psychotherapy) and pharmacological treatment when compared with pharmacological monotherapy. Other evidence comparing psychological treatments to pill placebo, pharmacological treatments to pill placebo, one psychological treatment with another, one pharmacological treatment with another, or a psychological treatment to a pharmacological treatment showed no significant differences. The committee therefore recommended that in people with depression and coexisting personality disorder, their depression should be treated with a combination of an antidepressant and a psychological therapy. The committee were aware, based on their clinical experience and knowledge, of the significant problems in engaging, and ensuring uptake of treatment, for people with depression and a coexisting personality disorder. They therefore recommended that support should be provided to encourage uptake and engagement. A multi-disciplinary setting was considered by the committee to be important due to the

							complexity of the difficulties experienced by this population, as this allows access to appropriate expertise. On the basis of their knowledge and clinical experience, and their concerns that some people may not receive an adequate 'dose' of treatment, the committee decided that it was important to specify that it may be necessary to extend the duration of treatment, relative to the length and frequency of treatment that individuals experiencing a depressive episode without a coexisting personality disorder may receive. They noted that this will not always be appropriate, and therefore decided to add the qualifying statement 'if needed' to indicate that this is best left to clinical judgement. The committee considered the recommendations in the risk assessment and management section of the guideline, adequately addressed the need to assess and manage the risk of self-harm and suicide for people with depression, including those with a coexisting personality disorder.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

403	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	The categorisation of depression We noted during both previous consultations that the draft guideline is out of step with US and European guideline methodologies, leading to erroneous and unhelpful classification of research studies which do not match clinical or service user experiences. In particular, we expressed our concerns about (a) the dichotomisation of depression into 'less severe' and 'more severe' in the evidence review of treatment of a new episode of depression, and (b) the separation of the more complex forms of depression into distinct groups. We remain very concerned that these two key methodological issues have not been changed as advised. Given that the treatment recommendations are based on these unvalidated distinctions of depression, their generalisability and applicability to clinical practice is highly questionable. We therefore urge NICE to reconsider these categorisations. We stress again that any treatment recommendations based on methodological choices that have not been validated will need to be viewed with caution.	Thank you for your comment. The committee considered the current NICE classifications of mild to moderate and moderate to severe depression, and agreed that although these classifications have been adopted quite widely there is potential uncertainty with regards to the management of moderate depression. The committee agreed that a dichotomy of less and more severe depression was clearer, and the guideline includes definitions (that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression includes the traditional categories of moderate and severe depression) in order to improve practical utility. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line

							presentations of depression are managed in primary care). The committee did not consider it problematic that the categorisations of depression used in this guideline were not in line with US and European guideline methodologies as there was no reason to believe that the different guidelines would be used in conjunction (thereby creating confusion), and the committee prioritised alignment with clinical practice in the UK. For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of psychotic depression, depression with coexisting personality disorder and chronic depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee

							reviewed the European Psychiatric Association classification but did not consider it appropriate to change the term to 'persistent depression' but considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered.

404	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	The distinction between less severe and more severe depression We uphold that there is neither methodological/statistical nor clinical validity of the categorisation of first episode depression into 'less severe' and 'more severe'. Most researchers and clinicians have a common understanding that depression severity levels fall into three broad categories of mild, moderate and severe (e.g., Wahl et al., 2014). Indeed, in the guideline itself these are referred to as the "traditional subcategories" (e.g., evidence review B, p.10, l.26). Having asked for it on numerous occasions, we are still short of a plausible explanation as to why the committee decided to diverge from traditional categorisations found in the majority of literature and, in so doing, adopt an unvalidated and unreliable methodology. We are particularly disappointed as in the last response that we received it stated: "these have been updated and are now based on published work". This, however, is inaccurate. None of the studies cited (Carmody, 2006; Rush, 2003; Uher, 2008; Wahl, 2014) provide evidence of a dichotomisation of depression severity. Moreover, Wahl et al (2014) clearly advocates the three traditional severity levels and provides clear threshold values for mild, moderate and severe depression (see their Table 3, p. 81). We further are concerned about the stringent inclusion/exclusion criteria for the two treatment reviews for new depression episodes. Many bona fide RCTs were excluded as their study populations reported > 20% of patients with chronic depression (> 2 years), > 20% of patients with a personality disorder, and > 20% receiving additional treatment (e.g.,	Thank you for your comment. The committee considered the current NICE classifications of mild to moderate and moderate to severe depression, and agreed that although these classifications have been adopted quite widely there is potential uncertainty with regards to the management of moderate depression. The committee agreed that a dichotomy of less and more severe depression was clearer, and the guideline includes definitions (that less severe depression includes the traditional categories of subthreshold symptoms and mild depression, and more severe depression includes the traditional categories of moderate and severe depression) in order to improve practical utility. The committee considered the distinction between less severe (subthreshold/mild) and more severe (moderate/severe) depression to be clinically meaningful in terms of supporting effective clinical decision making and being aligned with how clinicians conceptualize depression (in particular, GPs and other primary care staff, given that the majority of people with depression and almost all first line

						antidepressants or psychiatric care). Research has shown that 45% of patients diagnosed with depression are also suffering from a comorbid personality disorder (Friborg et al., 2014). In addition, usage of antidepressants is highly prevalent, with 17% of the adult population in the UK (7.3 million people) taking antidepressants between 2017-2018 (https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary). Not only is it rather uncommon for meta-analyses of psychotherapy trials for depression to exclude studies with more than 20% use of antidepressants (e.g., Cuijpers et al., 2021a, Cuijpers et al., 2020), exclusion of these and other criteria limits the representativeness and generalisability of the results.	presentations of depression are managed in primary care). As highlighted in your comment, for the first-line treatment review, studies were not included if more than 20% of participants were already receiving treatment for depression. While in the further-line treatment review, studies were required to have at least 80% of the participants showing no or limited response to previous treatment for the current episode of depression. The guideline review questions focus on specific populations – first-line treatment, further-line treatment/TRD, and there is not a question that specifically looks at a heterogeneous population where 21-79% are already on antidepressants and then have a psychological therapy added. Although the committee were aware that this may reflect standard care settings, the aim of the first-line treatment review question (RQ 2.1-2.2) is to estimate the effect size for psychological treatments, for antidepressants, and for combined psychological and antidepressant treatment and if the psychological studies include a

							significant proportion of participants who are actually receiving combined treatment this has the potential to give a misleading estimate of the effect of psychological treatments, and this is particularly problematic where these might be recommended as monotherapy. The committee discussed this at length and although it was appreciated that it was unfortunate that studies would be excluded on this basis, it was agreed that the line had to be drawn somewhere based on the rationale above. The evidence from the further-line treatment/TRD depression review is applicable to the population who are already on antidepressants, and the first-line review is applicable to those who are not, or who receive combination antidepressants and psychological therapies from the outset. Whereas, looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. This may mean that some studies are missing, because the population doesn't fit into either review, but there is evidence for psychological therapies for people who are already on antidepressants and those who

							aren't, and for psychological and pharmacological interventions used in combination, and this evidence has been used to inform recommendations. It should also be noted that there are still a significant number of psychological intervention studies, conducted in standard care settings, included. Although these studies including mixed populations may be representative of standard care, the recommendations are for the treatment of an individual and not for the whole of primary care or IAPT, and therefore it is preferable to have the cleanest evidence about what the effects of combination treatment are (if someone is already on antidepressants) or what the effects of psychological treatment alone is if they are not. For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of psychotic depression, depression with coexisting personality disorder and chronic

							depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee reviewed the European Psychiatric Association classification but did not consider it appropriate to change the term to 'persistent depression' but considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered.

405	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	Network Meta-Analysis (NMA)We appreciate the inclusion of pair-wise meta-analyses alongside the NMA for the review of first episode depression. However, we remain very concerned about the fact that NMA continues to be the primary data analysis and that, in the end, pair-wise analyses were only used for comparison reasons. As stated on p.39 in evidence review B, the decision was made to utilise only the NMA results based on the finding that there were only very few differences in the comparison of findings between both. A problem with such a comparison, however, is that it can only be made for those comparisons for which direct evidence is available. As we have emphasised during all consultations on this guideline, the validity or trustworthiness of statistical evidence derived from NMA is highly controversial (Faltinsen et al., 2018; Leucht et al., 2016). Given that it has no formal expert consensus, such an analytical approach can be viewed only as an experimental technique, and we believe that a national health treatment guideline should not be based on an experimental technique.In line with leading scientists, we strongly maintain that NMA should only be used when certain conditions are met. As repeatedly pointed out, these conditions seem not to have been met adequately here, showing evidence that transitivity and consistency assumptions are violated. Our concerns are supported by various statements within the draft guideline that point to these limitations. Moreover, given that the economic modelling carried out in this draft guideline is heavily influenced by the NMA (and therefore its limitations), we are similarly concerned about the trustworthiness of the outcome	Thank you for your comment. NMA was the main method used to synthesise evidence on pharmacological, psychological, psychosocial, physical and combined interventions, consistently with previous drafts of this guideline, in order to allow estimation of the relative effectiveness, acceptability and tolerability across all treatments for a new episode of less severe or more severe depression. Pairwise meta-analysis was employed to synthesise data on all critical outcomes of the clinical analysis in order to compare the results of the NMA with those of pairwise meta-analysis (MA) and explore any differences between them and possible reasons for any differences. Moreover, pairwise MA was used to synthesise follow-up data as well as data on functioning and quality of life. However, the decision was (right at the start rather than in the end of the process) that results of pairwise MAs on critical outcomes would not be considered as the primary source of evidence when formulating recommendations. This decision is stated under Summary of methods, Evidence synthesis, in Evidence review B. Nowhere on page 39 is it stated that there was a decision to utilise only the NMA results

						of the economic analysis of treatments. We therefore reiterate our advice that until there is consensus and evidence of the validity of such a statistical analysis for this type of complex dataset that combines three different modalities of treatment (pharmacological, psychological and physical), the primary method to synthesise the evidence should be through direct comparison (standard meta-analysis).	based on the finding that there were only very few differences in the comparison of findings between NMA and standard pairwise MA. It is only stated that, where relevant, results were overall consistent between the NMA and the pairwise meta-analysis. This finding was reassuring for the committee and increased its confidence in the NMA results. It is true that the comparison between NMA and pairwise MA results cannot be made for comparisons between treatments for which direct evidence is not available, and this is an important advantage of NMA over pairwise MA: that it allows estimation of effects between interventions that have not been directly compared in a head-to-head comparison via indirect comparisons. This is essential in order to estimate the relative effectiveness of all pairs of treatments assessed in the review. It also allows simultaneous comparison of the effects and ranking of all treatments. Interestingly, Faltinsen et al. (2018) report that WHO have started advocating the use of NMA to inform clinical guidelines and that the scientific production of network meta-analyses is increasing rapidly over the

							world. (They also report that NICE guidelines typically prefer direct evidence from RCTs and conventional meta-analyses to indirect evidence – this is not entirely true, as NICE prefer RCTs to indirect evidence, but "when multiple competing options are being appraised, a network meta-analysis should be considered" according to the NICE Guidelines Manual.) The authors recommend further methods for reporting and statistical testing of NMAs – which is fully agreed. Full reference to Leucht et al. (2016) could not be identified in your comments, but perhaps you refer to the paper "Network meta-analyses should be the highest level of evidence in treatment guidelines" (EUR ARCH PSY CLIN N 2016; 266, 477–480) where the authors conclude: "in our opinion, systematic reviews based on network meta-analyses should generally be the highest level of evidence in treatment guidelines, but we need to assess them carefully and in certain situations (such as if a meta-analysis is mainly composed of small trials)". In the area of mental health only, there are several NMAs published on treatments for depression, anxiety, PTSD, schizophrenia etc. NICE has used NMA in the past to

							inform other mental health guidelines, including PTSD, bipolar disorder and schizophrenia, and in several other diverse disease areas such as epilepsy, acne, and induction of labour. There are also several NMAs published in the area of psychotherapies for Depression (e.g. Barth et al, PLOS Medicine 2013, 10(5): e1001454; Cuijpers et al, JAMA Psychiatry 2019, 76(7):700-707; Cuijpers et al, World Psychiatry 2020, 19(1):92-107; Cuijpers et al, World Psychiatry 2021, 20(2):283-293; Zhou et al, World psychiatry 2015, 14(2):207–222; López-López et al, Psychological medicine 2019, 49(12):1937–1947), many of which have compared different types of therapy such as pharmacological vs psychological interventions, online vs. face-to-face interventions, etc. There are also published NMAs of psychotherapies for anxiety disorders (Mayo-Wilson et al, Lancet Psychiatry 2014, 1(5):368–376; Chen et al, Journal of psychiatric research 2019, 118:73–83), panic disorder (Pompoli et al, The Cochrane database of systematic reviews 2016, 4(4):CD011004), and PTSD (Merz et al, JAMA Psychiatry 2019, 76(9):904–913; Mavranezouli et al,

							Psychological medicine 2020, 50(4): 542–555; Coventry et al, PLoS medicine 2020, 17(8):e1003262; Mavranezouli et al, J Child Psychol Psychiatry 2020, 61(1):18-29). The above suggest that NMA is recognised as an established method of evidence synthesis and not as an experimental technique. Consistency between direct and indirect evidence and transitivity are met when the distribution of the effect modifiers is the same across treatment comparisons. It is correct that, for a valid analysis, due consideration must be given to the evaluation of effect modifiers across all comparisons. Balanced distribution of effect modifiers cannot happen when there is heterogeneity in populations and/or interventions. This is relevant to both pairwise meta-analysis and NMA and should be considered prior to conducting the meta-analysis, and when interpreting the results. In the guideline NMA a large part of heterogeneity was controlled by splitting populations with less and more severe depression, using detailed treatment definitions [including treatment intensity and mode of delivery for psychological interventions] and categorising them using

							a class random effects model. Heterogeneity was assessed by examining for model fit and checking for inconsistency between direct and indirect evidence. Other parameters, such as sex, socio-economic factors, therapist factors, may also contribute to heterogeneity, in particular in such a large and complex dataset, but this would also be a problem had exclusively pairwise MA of the 142 RCTs for less severe depression and 534 RCTs for more severe depression included in the systematic review been conducted. Considering heterogeneity when assessing the hundreds of pairwise, independent comparisons of this dataset would make interpretation of the findings and conclusions as to which interventions are the best options highly problematic. Between-study heterogeneity in the NMA was formally assessed for each network; results of this assessment were taken into account when interpreting the results of the NMA and making recommendations. Moreover, for the SMD outcome, a non-pharmacological subgroup of the overall dataset was analysed separately as a sensitivity analysis, to explore whether transitivity issues between pharmacological and non-pharmacological

							trials might have impacted on the results of the NMA. In addition, also for the SMD outcome, a sub-group analysis including only studies at low risk of bias for the attrition domain in the RoB tool has now been conducted. Detailed results of inconsistency checks and comparison between mixed (NMA) and direct evidence as well as additional sensitivity and sub-group analyses have been provided in Appendix M of Evidence review B, and supplements B5 and B6. The committee considered all these issues when making recommendations alongside the results of the pairwise MA, the economic modelling results and newly reviewed qualitative evidence. Recommendations take also into account individual patient needs and preferences, which might be argued to be an effect modifier the distribution of which could potentially differ across pharmacological, psychological and physical treatment trials. Consideration of cost-effectiveness is an essential element of NICE guidelines. The economic analysis assessed concurrently the relative cost-effectiveness of all effective treatments with an adequate

							evidence base for less and more severe depression. Economic modelling would not be possible to carry out had the guideline utilised only pairwise MA and not NMA. This is because, in order to assess the relative cost-effectiveness across all treatments, the economic model must be informed with data on the relative effects (discontinuation, response, remission in this particular model) across all treatments, and this simultaneous reference to relative effects is only possible with NMA and not with pairwise MA.

406	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	Appropriate methods for determining treatment effect We are pleased that the third draft of the guideline includes continuous changes in scores on depression scales in every review question. However, we remain concerned that full recovery is still a critical outcome and that partial recovery, as we had advised, has not been added. It furthermore appears that the decisions for treatment recommendation have been influenced by these recovery rates. Moreover, the economic analysis focuses primarily on full remission. As previously pointed out, full remission or recovery from a severe depression baseline might be difficult or impossible to achieve, yet smaller positive changes might still be clinically meaningful. Treatment which helps some service users move from severe depression to mild or moderate depression (i.e., 'partial recovery'), for example, would be worth recommending. Failing to do so risks the wellbeing of service users who may otherwise be denied these potentially transformative changes. We therefore recommend refining the interpretation of the evidence to inform treatment recommendation accordingly.	Thank you for your comment. The guideline includes continuous changes in scores on depression scales as a critical outcome for every treatment question, which will show changes for people who have both fully and partially recovered. This was agreed by the committee to be a better way to capture this data than the use of a dichotomous outcome for partial recovery. The economic analysis does not focus primarily on full remission. The economic analysis of treatments for a new episode of less severe depression has modelled only response (defined as at least 50% improvement in depressive symptoms) which may reflect full remission or not (depending on the starting point of depressive symptoms). Full remission was not considered in this population, due to lack of sufficient data in the respective NMA. The economic analysis of treatments for a new episode of more severe depression has considered full remission (i.e. a score on a depressive symptom scale that was below the cut-off point for a depression diagnosis) and also response that did not reach full remission (i.e. 50% improvement in depressive symptoms that

							was however not adequate to reach the scale cut-off point characterising full remission). The utility data attached to the model health states also reflected, as relevant, symptom improvement not reaching remission and/or symptom improvement reaching remission. Therefore, partial remission has been considered in the economic analysis for both populations.

407	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	Limiting the evidence to RCTsAs stressed during the previous stakeholder consultations, given the various limitations of RCTs specifically in the field of mental health that have been pointed out repeatedly by experts from many scientific disciplines and positions - irrespective of any modality allegiance - creating sound policy requires that we draw on a diverse range of evidence. We are disappointed that the evidence reviewed in this draft guideline continues to be limited to RCTs. We strongly uphold that this is a restrictive science and therefore leads to limiting patients' choice. We would like to signpost you to the NICE manual where it is states: "In order to formulate recommendations, the guideline Committee needs to consider a range of evidence about what works generally, why it works, and what might work (and how) in specific circumstances. The Committee needs evidence from multiple sources, extracted for different purposes and by different methods." (p.67)We would like to stress that the exclusion of available "important and well-known" UK-based pragmatic trials and real-world data collected from millions of patients treated for depression within the NHS in the very setting where the evidence from the guideline must closely followed, cannot be justified.The guideline itself makes reference to these studies, however, only appears to consider these partially to aid interpretation of clinical and cost effectiveness. We therefore ask that this draft is amended by the inclusion of such evidence from real-world data and pragmatic trials into the review. At the very least, we ask that their results are not merely used partially and selectively in order to justify the arbitrary treatment	Thank you for your comment. When making recommendations, the committee interpreted the RCT evidence in light of their knowledge of the clinical context (including drawing on their knowledge of the IAPT dataset) so that the 'reality' for people experiencing depression was taken into consideration. In response to stakeholder comments, the committee have re-structured treatment recommendations in order to take into account implementation factors. The committee were also aware of pragmatic RCTs that were excluded from the NMA typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. By way of illustration some of these studies were listed in Evidence report B, however, in response to stakeholder comments the committee agree that it would be more consistent to name all UK-based studies which were excluded on this basis but which the

						hierarchy (e.g. p. 141, l. 21f; and p.146, l.31f of the evidence review B).	committee were aware of when making recommendations. In January 2020 NICE published a statement of intent signalling the ambition for the future use of wider sources of data and analytic methods (including sources commonly referred to as real-world data and evidence). To make decisions about the relative effectiveness of interventions, RCTs will continue to be prioritised in line with the NICE guidelines manual, in order to ensure that the populations treated with various interventions are equivalent. However it is possible that in the future, high-quality real-world datasets such as the IAPT dataset, could inform questions about access and engagement.

408	SH	UK Council for Psychotherapy	Guideline, all Evidence Reviews	General	General	Omission of therapeutic approaches and supporting evidence Many studies that have shown to provide an evidence base for many interventions were not considered. We notice, for example, the omission and therefore non-recommendation of family therapy, couple therapy for depression, and the creative therapies, which many service users may benefit from (e.g. Albornoz, Y., 2011; Baucom et al., 2018; Nan & Ho, 2017), and may want to choose. We also notice the absence of longer-term psychological treatments. Research and clinical practice have shown that many individuals with chronic or complex forms of depression have tried the available and recommended first or second-line short-term treatments without success (e.g. Leichsenring & Rabung 2011; Maj et al. 2020). In complex mental disorders, longer-term psychotherapy proved to be superior to short-term psychotherapy (Leichsenring & Rabung, 2011, Leichsenring et al., 2013). However, in the guideline the recommendation for those classified as having treatment-resistant depression, chronic depression, and depression with PD defaults back to first or further-line treatment recommendation - i.e. once again to a short-term treatment, instead of recommending a longer-term treatment. This is particularly perplexing as there is evidence of the effectiveness of longer-term treatments, both for long-term CBT (e.g. Leuzinger-Bohleber et al., 2019) and long-term psychodynamic psychotherapy (e.g. Fonagy et al., 2015; Leuzinger-Bohleber et al., 2019; Knekt et al., 2008/2013/ 2016) for individuals diagnosed with treatment-resistant/chronic depression.Although the Leuzinger-Bohlehber et al (2019) study was excluded from the chronic	Thank you for your comment. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression and consequently the evidence was not reviewed and the committee were not able to recommend family interventions. Studies on couple interventions (including behavioural couples therapy) were sought for the reviews on first-line treatment but only for a subgroup of people with depression and problems in the relationship with their partner, and for the reviews on depression with coexisting personality disorder, and psychotic depression. For other review questions, these interventions were not specified in the review protocols. The guideline includes a recommendation for behavioural couples therapy for people with either less or more severe depression who have problems in the relationship with

						depression review as >20% had previous treatments, it should have been included under the further-line treatment review. We also cannot find any reason as to why the Knekt study (2008, 2013, 2016) was also not included there. Although the Fonagy et al., 2015 study was included, their important findings that both depression severity and functioning improved over the long-term have been ignored. All three studies not only provide important evidence of the effectiveness of long-term treatment, but moreover that the effects sustained over a 2–3-year follow-up. Given the scarcity of studies on longer-term psychological treatments, the omission of those is futile.As a consequence, all recommended treatment options are brief interventions (with an average of 8 sessions). As pointed out above, given that these have already been shown to be non-beneficial for many individuals who experience more persistent and complex depression, we are not only concerned that this guideline may exacerbate the existing revolving-door problem, but would also deny people the choice of longer-term treatments. There are further omissions that may also harm the goal of achieving patient choice. There is evidence for the effectiveness of various forms of Humanistic and Integrative Therapy, such as Transactional Analysis, Gestalt, Integrative Psychotherapy and Person-Centred Counselling (Van Rijn et al, 2011; Van Rijn and Wild, 2013; 2016; Elliott and Freire, 2010), systemic therapy (Stratton 2011; Pinquart, Olesen and Teubert, 2016) next to evidence for Short Term Psychodynamic Therapy (Steinert et al, 2017). There is also growing evidence for the use of creative and embodied methods in psychotherapy in	their partner, if the relationship problem(s) could be contributing to their depression, or involving their partner may help in the treatment of depression. There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. There is also a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways have a number of components in place in order to promote access and increased uptake of services and these include procedures to support active involvement of families, partners, and carers. Albornoz 2011 is included in the network meta-analysis for the treatment of a new episode of more severe depression. However, this was the only included study for music therapy, and the committee considered the evidence too limited to

						modalities such as Dance Movement Psychotherapy and Body Psychotherapy; see for example the Cochrane Reviews by Meekums, Karkou and Nelson (2015) and Aalbers, Fusar-Poli, Freeman, et al (2017), meta-analyses by Koch, Kunz, Lykou and Cruz (2014), Ritter and Low (1996), the new multi-centred RCT from Finland (Hyvonen, Pylvainen and Isotalo (2018) and the RCT in the UK by Röhricht et al, (2013) and Röhricht (2015). Furthermore, evidence suggests that both with generalised psychological approaches to mental health as well with more focused approaches, counselling and psychotherapy are not inferior to CBT (Steinert et al, 2017; Pybis, Saxon, Hill, Barkham, 2017; Ward, King, Lloyd, et al, 2000; King, Marston, Bower, 2014; Saxon, Ashley, Bishop-Edwards et al 2017; Bower, Knowles, Coventry, Rowland, 2011; Freire, Williams, Martina-Messow et al 2015;). Given NICE's endorsement of choice, and the evidence accepted in this draft about its positive impacts on clinical outcomes, we are concerned that the omission of evidence concerning a broader range of modalities will have a negative impact on clinical practice.	make a recommendation. Nan 2017 is included in the further-line treatment review. However, this was the only included study for art therapy, and the committee considered the evidence too limited to make a recommendation. The further-line treatment recommendation that cross-refers to psychological treatment options for more severe depression is for people whose depression has had no or a limited response to treatment with antidepressant medication alone. There was no evidence that specifically examined switching to a psychological intervention for those who have not responded to initial antidepressant treatment, however, the committee drew on the evidence for first-line treatments in more severe depression. The committee agreed that the psychological interventions that had been identified as effective and cost-effective for first-line treatment of more severe depression could be used for people who had not responded to antidepressants and wished to try a psychological therapy instead.

							As you point out Leuzinger-Bohleber et al 2019 was considered for the chronic depression review and was excluded. This study also did not meet eligibility criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line treatment, participants were not randomised at the point of non-response, and it could not be regarded as an augmentation study following limited or no response to antidepressants as only 36% of participants were taking antidepressants at baseline. This study has now been added to the excluded studies list in supplement D. Knekt et al 2008/2013/2016 was considered under first-line treatment as detailed in your comment, and did not meet criteria. It also did not meet criteria for the further-line treatment review as the inclusion criteria of the study was not limited to those receiving further-line treatment (in fact those receiving psychotherapy within the previous 2 years were excluded), participants were not randomised at the point of non-response, and it could not be regarded as an augmentation study following limited or no response to

							antidepressants as only 22% of participants were receiving psychotropic medication at baseline. This study has now been added to the excluded studies list in supplement D. There was only single-study evidence (Fonagy et al. 2015) for augmenting antidepressant treatment with long-term psychodynamic psychotherapy, and the committee considered the evidence too limited to make a recommendation for long-term psychodynamic psychotherapy specifically. However, a treatment option in the recommendation for people whose depression has had no or a limited response to treatment with antidepressant medication alone, includes changing to a combination of psychological therapy and medication, which could include long-term psychodynamic psychotherapy although it is not listed as an example due to the limited evidence. Baucom et al. (2018), Van Rijn et al. (2011), Van Rijn and Wild (2013, 2016), and Pybis et al. (2017) were not considered for the treatment review questions as they do not meet study design eligibility criteria as they are not randomised controlled trials. Elliott

							and Freire (2010) also does not meet study design eligibility criteria as it is a review of meta-analyses and a book section. Meekums et al. (2015), Koch et al. (2014), Ritter and Low (1996), and Bower et al. (2011) had not been identified by the searches but, in response to your comment, these systematic review have been checked for additional relevant studies and no new eligible studies were identified. These systematic reviews (and any associated studies included within them for which full text was checked to assess eligibility) have been added to the excluded studies list of Supplement B1. Aalbers 2017 and Steinert 2017 were identified by the searches and have been checked for additional eligible studies and are listed in the excluded studies list (as not appropriate to include in their entirety due to different review questions) of Supplement B1. Hyvonen, Pylvainen and Isotalo (2018) does not meet eligibility criteria as it presents preliminary results and is not published in a peer-reviewed journal.

							Röhricht 2013 was identified by the searches but did not meet inclusion criteria for the chronic depression review (Evidence report E) as participants were not receiving first-line treatment or treatment to prevent relapse (prior to entering the study patients had completed a mean of 4 treatment courses with different antidepressants, and were receiving ongoing antidepressant medication at study entry). This exclusion is in line with the eligibility criteria outlined in the review protocol. Röhricht (2015) was not considered by the committee as it does not meet eligibility criteria as a non-systematic review. Ward 2000 is included in the NMA for more severe depression. King 2014 is not included as it is a secondary analysis of Ward 2000 but it is listed in the excluded studies list of Supplement B1. Saxon 2017 is not included as it is a protocol but it is listed in the excluded studies list of Supplement B1. Freire 2015 was identified by the searches.

							However, the study did not meet inclusion criteria for Evidence review B as less than 80% of participants had non-chronic depression (46% dysthymia). This study is listed in the excluded studies list of Supplement B1.

409	SH	UK Council for Psychotherapy	Guideline, Evidence review D	General	General	The distinction between more complex forms of depression We uphold that there is no evidence that warrants the distinctions between chronic depression, treatment-resistant depression, depression with personality disorder and psychotic depression. By doing so, this draft guideline provides erroneous and unhelpful classification of research studies with the consequence that treatment recommendations may also be erroneous. We notice that the review question for further-line treatment has been changed and now includes studies of psychotic depression, depression with personality disorders, chronic depression, and so-called treatment-resistant depression. However, in light of having kept the other reviews, we feel it has not really addressed the issue and may in fact lead to further confounding outcomes. In addition to being out of step with European and US guidelines, we are in particular concerned that it will be out of step with the clinical understanding of the groupings in the UK, especially with respect to chronic depression, and will thus lead to confusion instead of providing helpful guidance. Most individuals suffering from chronic depression (as defined here as lasting for at least two years) would have sought previous help; in particular when experiencing functional impairment and suicidality, as well as high rates of hospitalisation. It therefore seems contradictory and unhelpful to create such a sub-group of depressed patients. The configuration of the guideline could also lead to confusion among clinicians seeking treatment recommendations for chronic depression irrespective of whether an individual has sought previous help. As previously highlighted, the terms	Thank you for your comment. For the further-line treatment review, studies were sought that included adults with depression showing an inadequate response to at least one previous intervention for the current episode and this included the further-line treatment of psychotic depression, depression with coexisting personality disorder and chronic depression. First-line treatment or relapse prevention of chronic depression (including dysthymia), and first-line treatment or relapse prevention of depression with coexisting personality disorder were separate reviews, as the committee did not feel that it was appropriate to combine these populations for first-line treatment or relapse prevention. The committee reviewed the European Psychiatric Association classification but did not consider it appropriate to change the term to 'persistent depression' but considered that the grouping together of psychotic depression, depression with coexisting personality disorder and chronic depression for the further-line treatment review should allow the effectiveness of interventions for a more clinically complex population to be considered.

						treatment-resistant and chronic depression are often used interchangeably and study populations often meet criteria for both (Abbass, 2006; Town & Abbass, 2016; Fonagy et al., 2015). This is also true for depression with a comorbid personality disorder (Abbass & Town, 2011; Friborg et al., 2014; Skodol et al., 2011).Taken together, we continue to be concerned that the categorisation and applied exclusion criteria for studies will have provided artefacts and led to treatment recommendations that cannot be easily applied to clinical practice. We therefore continue to stress the importance to address these concerns by (a) adopting the traditional classifications for the review of a new episode of depression, which may indeed include a fourth group of individuals whose depression is longer-lasting, (b) adjusting the exclusion criteria as advised above, and (c) combining the evidence review for all more complex forms of depression.	

410	SH	UK Council for Psychotherapy	Guideline, Supporting Documentation – Less severe depression, Supporting Documentation – More severe depression, Evidence Review B	General	General	Treatment ranking The results of the network meta-analysis (NMAs) and cost analysis for individuals with a first episode of depression showed that the treatments included in this synthesis were all found to be clinically effective. Furthermore, the economic models overall show high levels of uncertainty related to the relative effectiveness and cost effectiveness of all the interventions, including a very high degree of uncertainty about estimates of cost. This is expressed in the relatively modest difference in overall quality of life gains, cost per quality-adjusted life year (QALY) gains, and net monetary benefits between most interventions, and wide 95% credible intervals (CrIs) around their mean rankings. Therefore, despite some treatments falling outside the lower NICE cost per QALY threshold of £20,000 – and we would welcome an explanation for why this threshold has been chosen given the more complex nature of psychological therapies compared with pharmacological interventions and the relative lack of confidence in the cost effectiveness calculations – all included interventions were found to be cost effective. Notwithstanding our methodological concerns around these analyses (see below), these findings call into question the committee's decision to list the interventions hierarchically in the guideline – albeit with a much-welcome focus on patient choice. We believe it is critical to consider the real-world impact of this guideline when assessing the merits of listing the treatments in this way. Demand for mental health services has been steadily increasing over the past decade and, following an initial lull at the beginning of the coronavirus	Thank you for your comment. Although NMA and economic results were characterised by uncertainty, there was evidence that some treatment classes had higher effects than others. For example, in less severe depression, the effect of group CT/CBT class vs TAU (based on an evidence base of N=480) was -1.01 (95%CrI -1.76 to -0.06), whereas the respective effect of counselling (based on a narrower evidence base of N=55) was -0.20 (95%CrI -2.82 to 2.50), i.e. one fifth of the effect of group CT/CBT class, although both treatments were recommended – see bias-adjusted results in Table 9, evidence report B. Similarly, in more severe depression, the effect of individual CT/CBT + AD class vs placebo (based on an evidence base of N=192) was -1.18 (95%CrI -2.07 to -0.44), whereas the respective effect of IPT (based on an evidence base of N=145) was -0.45 (95%CrI -1.36 to 0.47), i.e. almost a third of the effect of individual CT/CBT + AD class – see bias-adjusted results in Table 24, evidence report B. Regarding clinical effectiveness derived from the NMAs, the committee considered not only the mean effects of treatment classes vs the reference treatment, but the uncertainty around them

						outbreak, the wider impacts of the pandemic have now made a clear impact on demand for mental health support, with demand for both antidepressants (NHSBSA, 2021) and talking therapies (NHS England, 2021) reaching an all-time high in 2021 in England. Indeed, the Centre for Mental Health has estimated that up to 10 million people in England will need new or additional mental health support as a result of the pandemic (Centre for Mental Health, 2020). Given this record-setting demand, and the considerable waiting times for treatment in parts of the UK, it has never been more important to ensure that evidence-based support is available to whoever needs it. This guideline has a direct, real-world impact on centralised NHS workforce planning, as well as localised decision making by commissioners. It will have a direct impact on which trainings Health Education England will fund to support increasing capacity in England's IAPT service, where so much of this rising demand is felt. Given NICE's assessment that all the listed treatments are clinically and cost-effective, removing the hierarchical ranking of treatments is a simple way to enable capacity-building in the NHS mental health workforce. Increased workforce capacity is essential to meeting the rising demand, as well as offering commissioners greater flexibility in assessing both the needs of a local population and the immediate local workforce capacity. This would not preclude the guideline from commenting on the relative strength of evidence for different treatments. However, in a time of great mental health need, the guideline should avoid creating needless barriers to support for service users. As a professional body representing	(as expressed in 95%CrI), the volume of the evidence base for each treatment, and the evidence of effect or the lack of it (as shown by 95%CrI crossing or not the no effect line) of the classes but also of individual interventions within each class, versus the reference treatment. They also considered the results of pairwise meta-analysis of follow-up data and additional outcomes (quality of life and functioning). Regarding cost-effectiveness, highly ranked interventions in the guideline economic analysis were more cost-effective than interventions lower in ranking, although there was uncertainty in the results and differences might be small in some cases. Overall, uncertainty in relative cost-effectiveness may be higher for interventions in close places in ranking, but is lower between interventions ranked further apart, e.g. at the top and at the bottom of the ranking. As you noted, some interventions were found to be less cost-effective than GP care (reference treatment) in less or more severe depression (or both). For example, counselling was found to be less cost-effective than GP care in less severe

						psychotherapists, we have excellent insight into the potential impact of a less hierarchical depression guideline on workforce capacity. We have 11,000 members, over 8,500 of whom are fully qualified. Of those qualified members, only 21% work in an NHS-funded role and the vast majority of those work part-time, meaning the full-time equivalent (FTE) figure is much lower. However, 45% of our members who don't currently work in the NHS are interested in doing so. And well over 80% of our 2,500 student and trainee members are interested in working in the NHS in the future, highlighting the huge potential for future workforce growth (UKCP Member Survey, 2020).We also have a strategic partnership with the British Association for Counselling and Psychotherapy (BACP) and the British Psychoanalytic Council (BPC). Collectively, we represent more than 70,000 therapists, yet fewer than 5,000 of these work in the NHS and, again, even fewer on a FTE basis. Highly trained psychotherapists and counsellors are considerably under-utilised by the NHS as it stands, and many of them ready to step in to fill workforce gaps and support the NHS in meeting the growing demand for therapy. There was already an ambitious target to recruit 2,940 therapists to the IAPT programme by 2023/24 before the pandemic hit (NHS Mental Health Implementation Plan, 2019). Removing the treatment ranking from the guideline would allow much quicker rollout of evidence-based therapies to those who need them. Moreover, it appears in the development of this guideline, the qualification costs associated with HITs are based on the costs associated with the CBT training (Economic Analysis, Intervention Costs tab;	depression, IPT was found to be less cost-effective than GP care in more severe depression, and short-term psychodynamic psychotherapy was found to be less cost-effective than GP care in both less and more severe depression. The NICE cost-effectiveness threshold was considered and used in decision-making in a consistent way with the NICE guidelines manual and other NICE guidance. According to the NICE guidelines manual (Box 7.2) "in general, interventions with an ICER of less than £20,000 per QALY gained are considered to be cost effective. […] Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors. The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis. The presence of strong reasons indicating that the assessment of the change in the quality of life has been inadequately captured, and may therefore misrepresent, the health

						Evidence Review B, pp328-329). This does not reflect the reality that 5-day person-centred experiential – counselling for depression (PCE-CFD) and dynamic interpersonal therapy (DIT) trainings are available for qualified counsellors and psychotherapists at considerably less cost than appears to have been costed for HIT training – £4,125 per person for training, supervision, case study and rating of tapes for DIT (https://www.annafreud.org/training/dynamic-interpersonal-therapy/5-day-dit-training-programme/) and £3,300 for CfD (https://www.nottingham.ac.uk/education/study/counselling-depression/index.aspx). This provides further evidence of the potential positive impact on workforce expansion of a less hierarchically ordered list of treatments in this guideline.As pointed out above, we strongly welcome the stronger focus on individualised care and the emphasis on the importance of service user choice and shared decision-making throughout this third iteration of the treatment guideline. This could be a hugely positive step forward in patient care. We welcome the recognition in the guideline that any additional resource invested in longer consultations with service users to have a meaningful discussion around treatment options will be repaid through greater adherence and better outcomes. However, we remain concerned that the current configuration of the guideline could hamper both patient choice and the availability of support in certain areas. With respect to this, we suggest that the text, the tables within the document and the helpful visual summaries be amended accordingly, with interventions listed in a neutral order (such as alphabetically).	gain. When the intervention is an innovation that adds demonstrable and distinct substantial benefits that may not have been adequately captured in the measurement of health gain. As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." In the case of the guideline economic modelling results, there were no strong indications of the presence of any of the conditions above (and in particular of differential presence of any of these conditions across interventions) that would dictate use of the NICE upper threshold of £30,000/QALY. Psychological interventions are not considered to be more or less innovative than other psychological interventions included in the economic analysis, and therefore there was no need to apply the NICE upper cost-effectiveness threshold. Based on these findings, the committee considered appropriate to rank

							recommended treatments taking into account clinical and cost-effectiveness as well as other issues such as side effects (antidepressants), applicability of the evidence (e.g. for individual problem solving), structure of IAPT services, but also taking account of patient clinical needs and preferences. Interventions are arranged in the tables in the suggested order in which options should be considered, based on the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors. However, this is not a rigid hierarchy, all treatments included in Tables 1 and 2 can be used as first-line treatments, and it may be appropriate to recommend an intervention from lower down in the table where this best matches the person's preferences and clinical needs. The committee were aware of the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee expressed the view that listing interventions in alphabetical order would not reflect the evidence base nor

							serve as a guide to choose for those who do not have pre-existing preferences. Considering cost-effectiveness issues when making recommendations ensures most efficient use of NHS resources and maximum health gains for the whole population. Prioritisation of treatments according to cost-effectiveness benefits not only the patient receiving the selected treatment but other patients whose needs must be covered by existing NHS resources. Nevertheless, the guideline also recommends shared decision on treatment choice, based on patients' clinical needs and preferences. The guideline update has a stronger focus on individualised care and an emphasis on the importance of service user choice and shared decision making. The recommendations enable choosing among a wide range of evidence-based interventions for a new episode of less and more depression based on patient preferences. Therefore, they do not create barriers to support for service users. As you point out, it is expected that additional resources invested in longer consultations with service users to discuss treatment options will be repaid through greater adherence and better outcomes.

							The qualification costs in the guideline economic analysis were not exclusively based on CBT training. It was acknowledged that "the qualification cost of a band 7 high intensity therapist is variant, ranging from the qualification cost of a therapist originally trained as PWP to the qualification cost of a clinical psychologist. Other high intensity therapists (counsellors, nurses) have qualification costs that lie between the PWP and the clinical psychologist qualification cost. For simplicity, the mean qualification cost of a band 7 high intensity therapist was calculated as the average between the PWP and the clinical psychologist qualification cost." It is noted that the DIT and CfD courses are accepting already trained therapists (either psychoanalytically/ dynamically trained practitioners or 'person-centred counsellors and psychotherapists as well as those already employed by IAPT') so the quoted costs of £4,125 and £3,300 per person, respectively, would have to be added to previous training costs in order to estimate the total qualification costs of psychotherapists and counsellors, respectively. In any case, consideration of

							qualification costs has had a rather small contribution to the unit cost of a band 7 therapist (around 8-10% of the final unit cost per hour of client contact). Thank you for the information you have supplied on the size of the psychological therapist workforce, and the number of these who currently work in the NHS. However, as described above, the guideline advises choice of treatments which are evidence-based and cost effective and it is approaching treatment for depression in this way that is likely to lead to better use of NHS resources and enable an increased NHS workforce.

411	SH	Royal College of Psychiatrists	Guidelines	035-036	Table 2.	Section on “self-help with support”. We note the comments made on why the committee made the recommendations in table 2 for severe depression, and in particular p. 68, lines 20-25 stating “… and so advised they [self help with support and group exercise] should not be usually be used as the sole interventions in people with more severe depression. This is not clear in Table 2. The only related comment (p 35-36; column “Other things to think about”) says “In more severe depression, the potential advantages of providing more intensive treatment should be carefully considered”. This is not entirely consistent with self help and support usually being used in combination with another intervention. In addition, it is unclear what is meant by “more intensive treatment”.	Thank you for your comment. The committee considered it important to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. It was recognised by the committee that people who have had prior episodes of depression may have preferences for their treatment based on prior experience or insight into their own depression patterns. Self-help with support and group exercise appear at the end of Table 2 and this is consistent with these interventions being considered for use after taking into account the other treatments that appear higher in the table. In response to stakeholder comments, the term 'more intensive' has been replaced with 'other treatment choices with more therapist contact '.

412	SH	Royal College of Psychiatrists	Guidelines	36	Table 2	Section on “Group exercise”. We note the comments made on why the committee made the recommendations in table 2 for severe depression, and in particular p. 68, lines 20-25 stating “… and so advised they [self help with support and group exercise] should not be usually be used as the sole interventions in people with more severe depression. This is not clear in Table 2. The only related comment (p 36; column “Other things to think about”) says “In more severe depression, the potential advantages of providing more intensive treatment should be carefully considered”. This is not entirely consistent with group exercise usually being used in combination with another intervention. In addition, it is unclear what is meant by “more intensive treatment”.	Thank you for your comment. The committee considered it important to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. It was recognised by the committee that people who have had prior episodes of depression may have preferences for their treatment based on prior experience or insight into their own depression patterns. Self-help with support (now called guided self-help) and group exercise appear at the end of Table 2 and this is consistent with these interventions being considered for use after taking into account the other treatments that appear higher in the table. In response to stakeholder comments, the term 'more intensive' has been replaced with 'other treatment choices with more therapist contact '.

413	SH	Association for Family Therapy and Systemic Practice	Guidelines	37	3	Rec 1.7.1 – Behavioural couples therapy is the only recommended family-inclusive therapy option and may be of value to some people from minority ethnic and cultural groups who may find it harder to engage with services. A reliance on only individual-focussed treatments does account for the diversity of family systems and cultures within the UK. Not all individuals share individualistic values and treatments that include family members may provide a better fit in terms of helping some people understand their difficulties and establish the support which enables recovery.	Thank you for your comment. Studies on family interventions were sought for the reviews on depression with coexisting personality disorder, and psychotic depression. However, no eligible studies were identified. For other review questions, these interventions were not specified in the review protocols as the committee did not consider family interventions to be in regular clinical use for the treatment of depression. On this basis, the committee did not consider it appropriate to recommend family interventions for the treatment of depression. There are recommendations in the choice of treatment section of the guideline that people with depression should be given the option to include family members or carers in the discussion of treatment options, and to attend (some or all of) treatment with a family member or friend. There is also a recommendation in the access section of the guideline for commissioners and providers of mental health services to ensure that pathways

							have a number of components in place in order to promote access and increased uptake of services and these include: services delivered in culturally appropriate or culturally adapted language and formats; and procedures to support active involvement of families, partners, and carers.
414	SH	Royal College of Psychiatrists	Guidelines	39	8	Section 1.8.5. This section refers to the use of antidepressants for up to 2 years to prevent relapse. We acknowledge that the evidence base does not significantly extend beyond this time point. However, individual patient circumstances and clinical experience may support continuing treatment beyond 2 years, and we are concerned that clinicians will read this statement and feel that they have to discontinue treatment after 2 years. We agree that careful review and consideration of ongoing treatment is required (as stated in section 1.8.11 stating that people continuing on antidepressants should be reviewed at least every 6 months). There also should be caution regarding antidepressant use just continuing	Thank you for your comment. The committee agree that after 2 years treatment may need to be reviewed and continued, but that the evidence for treatment for longer than 2 years is limited. The decision to continue would therefore be an individualised clinical decision, and so the committee removed the cut-off point of 2 years from the recommendation.

						indefinitely. However, we believe that whether they are continued beyond 2 years should be a clinical judgement between clinician and patient. We recommend that this is made clear in this section.	
415	SH	Royal College of Psychiatrists	Guidelines	041-042	020-022, 001-002	Section 1.9.2. We fully endorse the importance of making an assessment as to why a patient's depression is proving difficult to treat, including the possibility of comorbid conditions. While it might be implied from this section of the guideline, we believe that it would be helpful to make an explicit recommendation regarding the treatment of any comorbidity AND the depression. The concern is that if a person's depression is seen as being due to, or not responding because of, a comorbidity, clinicians may focus on the depression of the comorbidity and not both.	Thank you for your comment. The committee agreed the recommendation advise consideration of comorbidities, but as these may be very variable, it was not feasible to suggest solutions to all the possible individual issues that may be raised, and which will require an individualised approach to address.

416	SH	Royal College of Psychiatrists	Guidelines	47	11	Section 1.11.1. We have some concerns regarding this section since there is a lack of guidance regarding the diagnosis of personality disorder. It is unclear if the guidance refers to any type of personality disorder or not. There is also a major concern that people with depression which does not respond to treatment end up being re-diagnosed as having a personality disorder. We believe that it is important to include a statement around assessing whether or not the evidence of a personality disorder pre-dates the episode of depression or not. This has significant clinical and treatment implications.	Thank you for your comment. The depression guideline is not able to make recommendations about the diagnosis of personality disorders. The committee noted that this review covered people with depression comorbid with a personality disorder, but that there are different types of personality disorder and it was not always clear from the evidence which types had been included, or if all types had been combined and considered. The committee agreed that one of the most common types is emotionally unstable personality disorder (previously known as borderline personality disorder), they were aware that there is existing NICE guidance on borderline personality disorder, and wanted to make sure that recommendations were in line with the existing NICE guidance.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

417	SH	Royal College of Psychiatrists	Guidelines	47	11	It is unclear on what basis the treatment recommendation is being made. There is evidence for the use of antidepressants and the stated psychological interventions for the treatment of depression. However, it is unclear what evidence has been used to arrive at this recommendation for people with depression plus a personality disorder. There is additional evidence that is relevant and should be considered e.g. a randomised controlled trial in the UK of radically open dialectic behaviour therapy (Lynch et al. 2020 DOI: 10.1192/bjp.2019.53).	Thank you for your comment. Lynch 2020 was identified by the searches. However, it did not meet inclusion criteria for any of the treatment reviews. It did not meet criteria for the first-line or relapse prevention of depression with coexisting personality disorder review as less than 80% of participants had coexisting personality disorder. It did not meet criteria for the further-line treatment review as although refractory depression was defined as either chronic depression (depression lasting at least 2 years) or treatment-resistant depression, 72% were chronically depressed and not receiving further-line treatment. Finally, the study did not meet criteria for the chronic depression (first-line treatment or relapse prevention) review as more than 20% of participants had a coexisting personality disorder. Lynch 2020 is listed in the excluded studies of Supplement D. These were stipulations of the review protocols in order to create a homogenous data set, and there is not a question that specifically looks at a heterogeneous population where 21-79% of participants have depression with a coexisting personality disorder and are receiving first-line treatment for depression. The

							committee appreciated that it was unfortunate that studies would be excluded on this basis. However, the rationale was that looking at the evidence from a very heterogeneous population would not provide good evidence for any of these groups. The committee did, however, use their knowledge of pragmatic studies, such as this study, when interpreting the evidence from the systematic review and making recommendations. The committee noted that there was some evidence of benefit on depression symptomatology, for people with depression and coexisting personality disorder, for 2 of the comparisons of monotherapies: CBT alone compared to pill placebo, and behavioural therapy alone compared to short-term psychodynamic psychotherapy. There was also evidence for clinical benefit from studies with combined psychological (either IPT or short-term psychodynamic psychotherapy) and pharmacological treatment when compared with pharmacological monotherapy. The committee noted that although, based on the evidence, treatments combining an antidepressant with a high-intensity

							psychological intervention appeared to be the most effective, the evidence base for this question was limited in volume, with only small RCTs of low or very low quality. Consequently, they were only able to recommend combination treatment be 'considered' and they were not able to recommend a specific antidepressant or psychological therapy, but agreed that this would depend on the person's preference.

418	SH	Royal College of Psychiatrists	Guidelines	48	6	Section 1.12 on psychotic depression. This section is greatly improved compared with previous drafts, showing pragmatism and being more aligned to clinical practice. There is one notable exception though, and that is the lack of mention of ECT. Clinically psychotic depression is often seen as an indication for ECT. Indeed, while not universally recommended in guidelines from around the world, it is recommended by many (Leadholm et al. 2013 DOI: 10.1016/j.jad.2012.07.036). This is based on a range of evidence including response rates to ECT in psychotic depression being as high or high than in non-psychotic depression (Petrides et al. 2001 DOI: 10.1097/00124509-200112000-00003), and relapse rates lower (Birkenhager et al. 2005 DOI: 10.1097/01.yct.0000183269.62735.89).	Thank you for your comment and your support. The committee discussed the evidence for ECT in the treatment of psychotic depression. There was no eligible evidence for ECT in the acute treatment of psychotic depression, although the committee were aware of data that suggests a higher remission rate in psychotic depression compared with non-psychotic depression. There was evidence from a small single study of the benefit of ECT in relapse prevention that was considered too limited to form the basis of a treatment recommendation.
419	SH	Royal College of Psychiatrists	Guidelines	49	009-016	Section 1.13.1. This refers to indications for ECT for severe depression. We recommend this be expanded to include:a) psychotic depression. Clinically psychotic depression is often seen as an indication for ECT. Indeed, while not universally recommended in guidelines from around the world (Leadholm et al. 2013 DOI: 10.1016/j.jad.2012.07.036). This is based on a range of evidence including response rates to ECT in psychotic depression being as high or high than in non-psychotic depression (Petrides et al. 2001 DOI: 10.1097/00124509-200112000-00003), and relapse rates lower (Birkenhager et al. 2005 DOI: 10.1097/01.yct.0000183269.62735.89).see point 10 aboveb) pathological or physiological phenomena eg. glaucoma, chronic kidney disease, hyponatraemia, pregnancy or breastfeeding, which render other treatments less suitable or safe than ECT.	Thank you for your comment. The committee discussed the evidence for ECT in the treatment of psychotic depression. There was no eligible evidence for ECT in the acute treatment of psychotic depression, although the committee were aware of data that suggests a higher remission rate in psychotic depression compared with non-psychotic depression. The committee did not consider it appropriate to make the change to the recommendation suggested in your comment.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

420	SH	Royal College of Psychiatrists	Guidelines	49	009-016	1.13.1 The strength of evidence that patients with psychotic depression may be preferential responders is sufficient that this should be included as the third bullet point in recommendation 1.13.1. (See for example the meta-analyses: van Diermen L, van den Ameele S, Kamperman AM, Sabbe BCG, Vermeulen T, Schrijvers D, Birkenhäger TK. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. Br J Psychiatry. 2018 Feb;212(2):71-80. doi: 10.1192/bjp.2017.28. Erratum in: Br J Psychiatry. 2018 May;212(5):322. PMID: 29436330.Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. J Clin Psychiatry. 2015 Oct;76(10):1374-84. doi: 10.4088/JCP.14r09528. PMID: 26528644.	Thank you for your comment. The committee discussed the evidence for ECT in the treatment of psychotic depression. There was no eligible evidence for ECT in the acute treatment of psychotic depression, although the committee were aware of data that suggests a higher remission rate in psychotic depression compared with non-psychotic depression. The committee did not consider it appropriate to make the change to the recommendation suggested in your comment.
421	SH	Royal College of Psychiatrists	Guidelines	50	015-017	1.13.4 We would prefer to see the word 'valid' inserted before the word 'advanced decision'	Thank you for your comment. The word 'valid' has not been added, as the committee agreed that 'informed consent' described the process and that the word 'valid' was unnecessary.
422	SH	Royal College of Psychiatrists	Guidelines	51	006-008	1.13.8 We accept the analytical decision made about the PRIDE study on tapered ECT. However, it seems wrong to make an unqualified recommendation (1.13.8) to stop ECT immediately on remission when there is not a strong evidence base for this particular unqualified conclusion. Perhaps this could read 'unless ECT has previously been associated with remission followed by rapid relapse, in which case tapering of ECT treatment can be considered'. We note that repetitive Transcranial Magnetic Stimulation is the subject of separate guidance (IPG542) but do not understand why it was out of	Thank you for your comment. The committee did not have any evidence upon which to base a recommendation about tapering ECT so were unable to amend this recommendation. TMS was not included in the scope of this guideline update as it has already been considered by NICE as an interventional procedure guidance. Implanted vagus nerve stimulation has also been considered by NICE as an

						scope from this overarching Guidance. Vagal Nerve Stimulation and Transcranial Direct Current Stimulation are forms of neuromodulation which we hope will be in scope for future iterations.	interventional procedure guidance and so a link to this guidance has now been included in the depression guideline. The committee have reiterated their call for more research into the place in therapy of ECT, and will also recommend to NICE that it explore doing future work on neuromodulatory techniques (and/or rapidly acting treatments) including ECT.
423	SH	Royal College of Psychiatrists	Guidelines	51	009-014	Section 1.13.9. We endorse the recommendations in section 1.13 regarding ECT in the guidelines. Section 1.13.9 is regarding relapse prevention following successful treatment with ECT. Two recommendations are made, which we concur with. However, an area of significant debate is the role of continuation and maintenance ECT (cECT and mECT respectively) and when, especially the latter, might be considered. We believe that some guidance from NICE would be helpful regarding this. A recent randomised controlled trial of mECT + pharmacotherapy vs pharmacotherapy alone found a lower relapse rate (35% vs 61%) that was non-significant because of the study being under-powered (Martinez-Amoros et al. 2021 DOI: 10.3390/brainsci11101340), while multiple observational studies of discontinuation of mECT due to the COVID pandemic report high risks of relapse (44% within 6 months; Lambrichts et al. DOI: 10.1111/acps.13334; 60%, Van de Velde et al. 2021 DOI: 10.1097/YCT.0000000000000785; 75% rehospitalisation over 6 months Methfessel et al. 2021	Thank you for your comment. The studies you have identified were published after the cut-off period for the searches for this guideline, but they will be passed to the NICE surveillance team which monitors guidelines to ensure they are up to date.

						doi: 10.1111/acps.13314). We believe this supports the use of mECT in selected situations.	
424	SH	Royal College of Psychiatrists	Guidelines	51	015-017	Section 1.14 regarding transcranial magnetic stimulation (TMS). We believe there is a major deficiency in this section, and the guideline in general, make no recommendations regrading the place of TMS in the treatment of depression. Section 1.14 simply has a link to the NICE Interventional Procedure Guidance. This states "The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable. Repetitive transcranial magnetic stimulation for depression may be used with normal arrangements for clinical governance and audit." (NICE IPG542, section 1.1). Our reading of this is that the IPG is saying that TMS is appropriate for use in normal clinical situations. However, the IPG gives no recommendations regarding the precise place of TMS in the treatment of depression. We are unclear why recommendations regarding the use of TMS have not been made in the Clinical Guideline for depression in adults. Specifically, why is TMS not included in Table 2 as a treatment option, or in section 1.9 on further-line treatment? If the	Thank you for your comment. Transcranial magnetic stimulation (TMS) was not in the review protocols, and is outside the scope of this update. The committee have reiterated their call for more research into the place in therapy of ECT, and will also recommend to NICE that it explore doing future work on neuromodulatory techniques (and/or rapidly acting treatments) including ECT.

						committee feel that there is insufficient evidence to include TMS in the recommendations, it would be helpful if that was included in the recommendations for research.	
425	SH	Royal College of Psychiatrists	Guidelines	55	016-022	Section 1.15.9. We feel that it is helpful to explicitly state reasons for referral of people with depression to secondary care, and this sub-section appears reasonable. However, as written it includes referral after a failure of just an "initial treatment". This causes some concern. For example, Table 2 in the guideline includes options for the treatment of severe depression of counselling, which the committee acknowledges was a weak evidence base (p68, lines 9-10), and self-help and group exercise, which the committee recommends should ideally be in combination with another treatment (p68, lines 20-25). It would seem potentially premature for a person to be referred to specialist care if they have only ever tried one of these three treatment options. We therefore wonder if the wording of section 1.15.9, might be amended.	Thank you for your comment. The wording of this section has been amended to state that referral should be when people have not benefited from previous treatments.

426	SH	The Federation of Holistic Therapists	Guidelines	61	1	Recommendations for research: "3. Further-line treatment" proposes the following research – "What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical treatments (alone or in combination), for adults with depression showing an inadequate response to an initial psychological treatment for the current episode?" Physical interventions referenced in the research are acupuncture, electroconvulsive therapy, exercise, yoga, and light therapy (for depression, not SAD)." We propose that touch therapy be included within the definition of physical treatments in order to expand on the existing body of evidence in respect of these treatments for helping to manage and reduce the symptoms associated with poor mental health. As yet, NICE, whilst acknowledging that existing research has shown positive results, has not supported touch and massage, aromatherapy and reflexology as a therapies for mental health, citing potential flaws with the research methodologies carried out outside of the UK. This is an ideal opportunity to expand on this. If the proposed research was expanded to explore the benefits or potential harms of a range of touch therapies as a means of combatting, preventing and avoiding a relapse of depression we are confident these lines of treatment could be offered to patients with positive results.Given the potential benefits directly from personal care services to the UK economy and health and wellbeing, we would recommend further research be carried out in the UK to replicate the benefits seen elsewhere.	Thank you for your comment. Touch therapies have been added into the list of suggested interventions for this research recommendation. The research recommendation question is designed to guide future research and the actual nature of the interventions included would depend on the final protocol developed to answer this question.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

427	SH	Mental Health Matters	Guidelines – relapse	40	20	You recommend a client having at least 4 x further sessions, however you have not clarified whether this in within or above the earlier session amounts	Thank you for your comment. The recommendation has been clarified to state that these are additional sessions (and based on other stakeholder feedback the limit of 4 sessions has been removed.)
428	SH	NHS England and Improvement	NICE Specific question no 4:	Question no 4	COVID considerations	NICE asked if there are any particular issues relating to COVID-19 that you should take into account: Surveys of older people have suggested they have suffered from more loneliness and increased physical pain both risk factors for increasing depression. Older carers' mental health has also been particularly negatively impacted especially for those people who care for someone with dementia	Thank you for your comment and for telling us about the impact of the Covid pandemic on the mental health of older people. The committee were aware of the link between the Covid pandemic and mental health problems but agreed not to make pandemic-specific recommendations as these may soon become outdated.
429	SH	Mental Health Matters	Stepped care	59	28	We think it would be useful to document stepped care earlier on in the guideline specially next to the treatments listed identifying which steps these are provided in	Thank you for your comment. The concept of using the least intrusive and least resource intensive interventions first has now been included much earlier, in the beginning of the treatment section of the guideline.
430	SH	University of South Wales	Supplement 1 Methods	5	023 - 025	This states that recognition and assessment were not included in this update. But NICE recommendations in CG90 (2009) were diagnosis specific. Treatment without a precise knowledge of what is being treated is likely to be fruitless. The Proposed Guidance de facto rubber stamps the current practice in IAPT of delivering an intended depression treatment on the basis of an elevated PHQ9 score, notwithstanding that this latter could have arisen in the context of a wide variety of disorders including adjustment disorder, PTSD, panic disorder etc. There is nothing in the	Thank you for your comment. The guideline includes a number of recommendations on assessment which are designed to ensure that a full assessment of need is undertaken and decisions on treatment are not made solely on the basis of a score on a depression scale. The guideline also includes specific recommendations about the treatment of depression in people with an anxiety disorder, or acquired cognitive

						Guidance to orientate the clinician to the appropriate disorders and treatment protocols. The Guidance takes little account of the common comorbidities of depression.	impairment, or those with depression and a coexisting personality disorder.

431	SH	Society for Psychotherapy Research	Supplement 1: Methods	29	General	The Supplement 1: Methods document outlines the methodology that underpins the development of this guideline. Under the heading 'validation process' on p.29 it states: "This guideline was subject to a 6-week public consultation and feedback process. All comments received from registered stakeholders were responded to in writing and posted on the NICE website at publication."Whilst we acknowledge that stakeholder involvement is indeed an important part of the validation process of the methodologies used in NICE guideline in general, we would like to emphasise that it cannot be the only process. We want to point out once again that all RCTs and systematic reviews require a protocol that describes their methods and analysis plans including the rationale before a study begins. The purpose of such common practice is that adherence to ethical and scientific standards can be assessed and monitored, and as such validated adequately (e.g., Tetzlaff et al, 2021). Furthermore, as the NICE Guideline manual, stipulates: "the review protocol should make it possible for the review to be repeated by others at a later date" (p. 72). We noticed that after our concerns were raised, that the systematic review for "less and more depression" was registered on PROSPERO in October 2019 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=151328). Whilst we are pleased that it was at that point registered at all, we point out that it (a) still was not peer-reviewed and followed after a considerable amount of the work including the data synthesis had already been carried out, and (b) consists of a basic registration that for	Thank you for your comment. As acknowledged in your comment, at the start of this latest update of the guideline, review protcols were agreed with the committee, and were registered on PROSPERO in October 2019. Changes had been made to previous versions based on stakeholder consultation comments. For example, stakeholder consultation on the 2016 version of the guideline raised concerns about the non-validated thresholds on which studies were categorised into less or more severe depression populations, and inconsistencies in thresholds across different scales. As detailed in the methods and process section of Evidence review B, an anchor point of 16 on the PHQ-9 was selected as the cut-off between less severe and more severe depression, on the basis of alignment with the clinical judgement of the committee and eligibility criteria in the included studies. Published standardization of depression measurement crosswalk tables (Carmody 2006; Rush 2003; Uher 2008; Wahl 2014) were used in order to 'read-across' different symptom severity scales that were used in different studies. These thresholds were outlined in the protocol that was registered on PROSPERO

						example omits details of how the less severe and more severe depression categories were defined and justified, and (c) does NOT include all the other review questions at all. A sentence referring those further reviews will be carried out is not sufficient, especially as these are based on different depression populations, studies, and the analysis plan. Moreover, we were thus far unable to locate the pre-registration and peer-review of the health economic analysis. Not having a transparent, clearly defined and peer-reviewed protocol can lead to inflated effect sizes (Gelman and Carlin, 2014) and type I errors (Luck and Gaspelin, 2017), risk researcher allegiance, which has been demonstrated to significantly affect the results of meta-analyses (Munder et al., 2013) and contribute to low replication rates of psychological studies (Open Science Collaboration, 2015). Failing to define inclusion/exclusion criteria prior to analysing the data or failing to disclose changes to inclusion/exclusion criteria is a key source of questionable research practices (Baldwin and Goldberg, 2021).Throughout the three iterations of this draft guideline, various aspects of the methodology have been changed, some of them without the provision of a transparent rationale, making it impossible to rule out various problems and biases, including those mentioned above. For example, the threshold for defining whether a study should contribute to the review of less severe or the review of more severe depression was amended in this third draft to the PHQ-9 anchor point, which was changed from 18 to 16 without any explanation provided. (See our serious concerns with this dichotomisation below).	prior to the update of the data analyses for this latest iteration of the guideline. In addition to the protocol for the first-line treatment review (Evidence review B), protocols for the reviews on relapse prevention (Evidence review C), patient choice (Evidence review I), service delivery models (Evidence review A), and further-line treatment (Evidence review D) were also registered on PROSPERO in October 2019. It is not common practice to pre-register de-novo economic analyses (except where they are conducted alongside RCTs) and the technical team was not aware of a pre-registration site for primary economic analyses that are based on economic modelling. It is noted that developing economic models is an iterative process, with models evolving and methods and data sources being modified throughout the model development process, so pre-registration of modelling method details is not useful or practical. The guideline de-novo economic analyses were prioritised, and their overarching methods described in an 'economic plan', as recommended in the

							NICE Guidelines Manual. The models followed the NICE 'reference case' for decision-analytic economic models, as described in the NICE Guidelines Manual, which specifies the NICE's principles and preferred methods for economic evaluation. All guideline models were quality assured by independent technical staff at NICE. All technical work undertaken for the guideline (including de-novo economic analyses and the respective executable models) is available for peer-review and comments by stakeholders during consultation. A number of comments on the economic analysis were received during consultation and addressed accordingly.

432	SH	Mental Health Matters	Treatment options for less severe depression	24	Group CBT Group BA	You recommend a usual group size of 8. It would be helpful if the guidance could include a minimum and a maximum group size based on the evidence available. Some IAPT services are offering treatment in much larger groups. Having too small a group size may lead to the group being converted into 1:1 treatment due to attrition. Having a minimum and maximum group amount will help to standardise the treatment offer across IAPT services.	Thank you for your comment. The recommended resource use was based on relevant information reported in the RCTs that informed the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. This information has now been added in evidence review B, under Appendix N. Few studies made specific reference to the number of participants per group. For group CBT and group BA in less severe depression this ranged between 4-8 participants per group. This reported use, combined with the committee's considerations on optimal delivery of psychological interventions have been reflected in the respective recommendations, which suggest that group CBT and BA should 'usually' have 8 participants per group, which is not restrictive but allows flexibility around the number of participants per group. It is noted that this resource use refers to high intensity group psychological interventions.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

433	SH	Mental Health Matters	Treatment Options for Less Severe Depressio n	25	Individ ual CBT BA	This states that 8 x 60 mins sessions of individual CBT will be offered for clients with less severe depression. However, in IAPT services these clients will firstly be offered a supported self help treatment/group treatment initially and then stepped up to step 3. We are concerned that this recommendation to offer 6 x 60 min sessions at step 3 to clients with less severe depression will significantly increase the waiting times at step 3 for those with less severe depression and severe depression.	Thank you for your comment. In response to stakeholder comments, in particular around implementation issues in the context of IAPT, some changes have been made to the tables of interventions for the treatment of a new episode of depression guided by the principles of offering the least intrusive intervention first, reflecting clinical and cost effectiveness, and reinforcing patient choice.
434	SH	Mental Health Matters	Treatment Options for Less Severe depression	26	Self help with suppor t	Online cCBT sessions would be 15 minute reviews. However in IAPT services telephone/face to face guided self help is 30 mins per week. The recommendation suggests 8 sessions however IAPT services offer on average 6 sessions of guided self help. The guideline is missing self help with support groups offered at step 2.	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions. For the same reason, the suggested number of sessions has now been changed to usually '6-8' sessions. The guideline has now placed emphasis on guided self-help offered at step 2.

Depression in adults: treatment and management
Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

435	SH	Mental Health Matters	Treatment options for less severe depression	27	Group mindfulness or meditation	Mindfulness has always been recommended for depression relapse prevention; however it is being offered here as a client choice for anyone with less severe depression. We are concerned regarding this recommendation based on the lack of funded training available for IAPT practitioners to attend mindfulness based CBT. ****We are concerned regarding the term 'group mindfulness or meditation' – this should be identified as Mindfulness Based CBT. To prevent practitioners/services offering meditation outside of a mindfulness based CBT treatment.	Thank you for your comment. Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the network meta-analysis (NMA) or in the pairwise meta-analyses would not be feasible and would require particularly complex consideration and interpretation of the evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the analyses utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. The committee agreed that mindfulness based cognitive therapy (MBCT) should be given as an exemplar of this class and in Table 1 of the recommendations, in considering how to deliver group mindfulness or meditation it is recommended that 'a programme such as mindfulness-based cognitive therapy specifically designed for people with depression' is used. Table 1 includes the

							recommendation that this intervention should be delivered by trained practitioners, however, the committee did not consider it appropriate to further specify the training and experience necessary to deliver this intervention as this is a matter for implementation.

436	SH	Mental Health Matters	Treatment options for less severe depression	28	Counselling	This should specify that the counsellor should be trained in counselling for depression.	Thank you for your comment. All the evidence for counselling that was included in the review for the treatment of a new episode of depression was non-directive counselling, and the committee therefore did not consider it appropriate to recommend a specific intervention (for example, Counselling for Depression/Person-Centred Experiential Therapy [PCET]) as the evidence was not reviewed for these interventions. However, based on informal consensus, the committee agreed that counselling should use an empirically validated protocol developed specifically for depression and this was included in the recommendation.
437	SH	Mental Health Matters	Treatments for more severe depression	031 - 032	Individual CBT & BA	Protocols for BA and Cognitive therapy can be up to 20 sessions, however the guidance states 12-16	Thank you for your comment. The recommended number of sessions was based on relevant information reported in the RCTs that were considered in the guideline NMA and economic analysis of treatments for a new episode of depression, supplemented by the committee's clinical experience on optimal delivery of interventions within the NHS. This information has now been added in evidence review B, under Appendix N. The recommended ('usually') 12-16 sessions for individual BA in more severe depression are

							consistent with the reported resource use in the respective RCTs. The recommended sessions for individual CBT have been amended to 'usually' 16, to be consistent with the reported resource use in the respective RCTs. All recommended numbers of sessions serve only as a guidance and can be modified depending on individual needs. This has now been clarified in the recommendations.
438	SH	Mental Health Matters	Treatments for more severe depression	33	Counselling	This should specify that the counsellor is training in counselling for depression.	Thank you for your comment. All the evidence for counselling that was included in the review for the treatment of a new episode of depression was non-directive counselling, and the committee therefore did not consider it appropriate to recommend a specific intervention (for example, Counselling for Depression/Person-Centred Experiential Therapy [PCET]) as the evidence was not reviewed for these interventions. However, based on informal consensus, the committee agreed that counselling should use an empirically validated protocol developed specifically for depression and this was included in the recommendation.

439	SH	Mental Health Matters	Treatments for more severe depression	33	Individual problem solving	Individual problem solving is not a stand alone intervention/protocol. This is an intervention used within behavioural activation	Thank you for your comment. Individual problem solving has been evaluated as a stand-alone intervention and some of those trials were assessed in Evidence review B. In fact, individual problem-solving appeared to be the most cost-effective therapy based on the bias-adjusted ranking of interventions for adults with a new episode of more severe depression. The committee agreed to recommend individual problem-solving based on the clinical and cost-effectiveness and the importance of offering a choice of treatments. However, the committee agreed that it was not appropriate to move individual problem-solving any higher up in terms of the order of recommended use as the committee noted that in some conceptualisations, it is only a variant of CBT, with very similar efficacy with individual CBT but higher uncertainty around the mean effect (as demonstrated by the network meta-analysis on depression symptomatology outcome).

440	SH	Mental Health Matters	Treatments for more severe depression	35	General	Online cCBT sessions would be 15 minute reviews. However telephone/face to face guided self help is 30 mins per week. The recommendation suggests 8 sessions however IAPT services usually offer 6-7 sessions maximum of guided self help.	Thank you for your comment. The committee agreed that PWPs may need more time and flexibility to fulfil their role and responsibilities. Therefore, the indication about the duration of sessions has now been removed from the recommendations, to allow flexibility and ensure effective delivery of low intensity interventions. For the same reason, the suggested number of sessions has now been changed to usually '6-8' sessions.

441	SH	NHS England and Improvement	Visual Summaries	023 - 024	General	https://www.nice.org.uk/guidance/GID-CGWAVE0725/documents/supporting-documentation-23 and https://www.nice.org.uk/guidance/GID-CGWAVE0725/documents/supporting-documentation-24 Both diagrams could feature Social prescribing and PHBs and Shared Decision Making - all interventions to consider in place of or as part of 'self-help with support')	Thank you for your comment. The committee noted that a personal health budget is not an intervention but a way of spending health funding to meet the needs of an individual. On this basis, personal health budgets were outside the scope of this guideline. Evidence for social prescribing was also not sought or reviewed. However, all the treatment recommendations in the guideline emphasise the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The committee also recognised that people with depression, like everyone, might benefit from a healthy lifestyle but recognised that people with depression might find this harder to achieve. On this basis, a new recommendation was added to advise people with depression that maintaining a healthy lifestyle may help improve their sense of wellbeing. A link to the NHS advice on mental wellbeing was also added, which lists 5 steps to mental wellbeing: connect with other people; be physically active; learn new skills; give to others; pay attention to the present moment (mindfulness).

							Shared decision making was not considered as a stand-alone intervention but the committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion.

442	SH	Active Partnerships National Team	Visual summary	General	General	We feel a ranking approach of intervention options on the treatment wheel undermines true patient choice. We are concerned how a patient will be informed of exercise as a treatment option, particularly should they have no preference and limited understanding of what could be available to them.We feel the starting point for treatment options should not be the most cost-effective interventions. We suggest a method that starts with understanding patient needs through appropriate questioning and responding with the most relevant treatment option/s would be useful. Evidence suggests that exercise could be a particularly attractive treatment option for those intrinsically motivated by sport and physical activity or have had a previous positive experience of this. There is a strong positive association between internal, motivations and activity levels. For the total population, internal motivations are amongst the biggest drivers of behaviour, with enjoyment being the biggest driver for how active individuals are, followed by importance. For example, 82% of those people who strongly agree that they find exercise enjoyable are active, compared to 65% of those who just agree and 28% of those who strongly disagree (Active Lives Adult Survey. Understanding Behaviour, Sport England, 2019)	Thank you for your comment. The visual summary is designed to supplement the tables of interventions included in the guideline and is arranged in order of effectiveness and cost-effectiveness. Cost-effectiveness is important to the NHS to optimise the use of scarce resources. The visual summary is to aid discussions and shared decision-making between clinicians and people with depression and it is made clear that patient preference should also be taken into consideration when making an individualised choice of treatment. However, the visual summary makes it clear that people starting a first-line treatment for depression can start at any point in the circle and do not have to fail earlier treatments to pass to a later treatment. The tables of interventions and the visual aid include treatments that were shown by the evidence to be effective and cost-effective, and so interventions for which there was not good evidence were not included. For example, the evidence for effectiveness was for structured group exercise and that is why that is included (although an additional recommendation for less structured physical activity has now been added to the

							guideline, based on the committee's expertise and stakeholder feedback).
443	SH	University of South Wales	Visual Summary	General	General	Patient choice is recommended for a range of 11 psychological interventions for 'less severe' depression– this is impractical in a number of ways. Therapists and clients could not hold complex information about 11 different treatments in mind and services could not deliver this range of treatments Similarly, for 'more severe' depression, meaningful patient choice could not be made with 10 recommended treatment options.	Thank you for your comment. The visual summary is designed to supplement the tables of interventions included in the guideline and is arranged in order of effectiveness and cost-effectiveness, as well as taking into account implementation factors. The tables provide more detailed information to aid discussions and shared decision-making between clinicians and people with depression and it is made clear that patient preference should also be

							taken into consideration when making an individualised choice of treatment. As all the interventions included in the table are effective and cost-effective, it is hoped that NHS commissioners will ensure these interventions are available to all people with depression.
444	SH	University of South Wales	Visual Summary	General	General	This suggests that for the less severe depression beginning discussion with depressed clients by asking them to consider group interventions. No account has been taken of what happens in routine practice when group treatments are offered, see Scott and Stradling (1990) and detailed further on Group CBT (2011) published by Routledge. There is an inherent obstacle to overcome in discussing group interventions at the start of contact and the marketing of group interventions is by no means easy. However, the hurdles can be negotiated to a degree by offering a blend of individual and group CBT, weighted to the latter. Without due care, the marketing of group interventions at the outset could simply be alienating. The Proposed Guidance makes no distinction between efficacy trials and effectiveness studies, it is the latter that have salience for implementation. The Guidance is a product of a top-down analysis of studies, rather than a bottom-up process in which clients are asked whether	Thank you for your comment. Group interventions are offered because they are more cost-effective than individual interventions for people with less severe depression, but the guideline and the visual summary make it clear that people's preference should be taken into account, and that if people do not wish to attend groups they can opt for individual therapy. The committee used a large quantity of evidence from randomised controlled studies to determine the relative efficacy and cost-effectiveness of interventions, and then reviewed and interpreted these data in light of a large qualitative review on choice of treatments for depression, which took into account the perspectives of people with depression.

						treatment made a difference they care about, and the questions are posed in the setting of a non-research centre.	
445	SH	Mental Health Matters	Why the committee made the recommendations	74	3	Specialist personality disorder services will often not accept clients who are not presenting as a current risk to themselves or others. This may leave clients with a personality disorder excluded from primary care depression treatment	Thank you for your comment. The recommendation to consider referral follows on from the recommendations about treatment, so people should be offered treatment for their depression, and then referral can be considered.

Depression in adults: treatment and management

Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022

Depression in adults: treatment and management

Consultation on draft guideline - Stakeholder comments table

23 November 2021 - 12 January 2022