National Institute for Health and Care Excellence

4-year surveillance (2017) – Psychosis and schizophrenia in adults (2014) NICE guideline CG178

Appendix B: stakeholder consultation comments table

Consultation dates: 15 August 2017 to 4 September 2017

Do you agree with the proposal not to update the guideline?

Stakeholder	Overall response	Comments	NICE response
The Pernicious Anaemia Society	No	The existing guidelines make no mention of assessing the Vitamin B12 status of patients during the Prodromal Period and First Episode Psychosis. Many members of the Pernicious Anaemia Society experience 'memory and concentration problems, unusual behaviour and ideas, disturbed communication and affect, and social withdrawal, apathy and reduced interest in daily activities'. Similarly 'behavioural disturbances' are a common symptom experienced before the patient is diagnosed and treated for PA. We would recommend that all patients who are suspected as suffering from Psychosis have their B12 status checked though the current 'standard' serum B12 test is now largely discredited and there is no consensus on what constitutes a deficiency or sub-clinical deficiency. Consider assessing the patient's MMA and Homocysteine along with the Holotranscobalamin test in order to rule out any B12 Deficiency being the cause of the patient's symptoms. We know that patients who have had their replacement therapy injections stopped by their physician (an all too common practice for various reasons) can and do go on to experience psychotic episodes that are resolved once their injections are started again	Thank you for your comment. The remit provided for this guideline covers the prevention and management of schizophrenia and psychosis, therefore the diagnosis of psychosis is outside the scope for this guideline. As such, no action will be taken in relation to CG178. However, NICE has produced a Medtech innovation briefing (MIB40) which describes NICE's consideration of the evidence regarding the Active-B12 assay.
Rotherham Doncaster and South Humber NHS Foundation Trust	No	No comment	Thank you for your response.
University of Nottingham	Yes	Page 16 refers to the use of qrisk2 for CVD risk assessment. Please note that qrisk3 was published in the BMJ in 2017[1]. http://www.bmj.com/content/bmj/357/bmj.j2099.full.pdf.	Thank you for your comment. The recommendations in CG178 cross-refer to other relevant NICE guidance. This includes CG181, which currently recommends the use

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<td>QRISK3 includes severe mental illness and antipsychotic use as two risk factors since both are independently associated with an increased CVD risk.
- Atypical antipsychotic drugs were associated with a 29% increased cardiovascular risk in women and 15% increased risk in men.
- Severe mental illness was associated with a 14% increased risk of cardiovascular disease for women and a 13% increased risk for men
The validation statistics for QRISK3 among patients with severe mental illness are shown in the supplementary tables and are reproduced here for ease of reference. Performance was substantially better for women with QRISK3 compared with the PRIMROSE score[2]. Values for men were comparable.
references
1. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357 doi: 10.1136/bmj.j2099
2. Osborn DP, Hardoon S, Omar RZ, et al. Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. JAMA psychiatry 2015;72(2):143-51. doi: 10.1001/jamapsychiatry.2014.2133 [published Online First: 2014/12/24]

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<tr><td></td><td></td><td>QRISK3 validation in women with SMI</td><td>PRIMROSE validation in women with SMI</td><td>QRISK3 validation in men with SEMI</td><td>PRIMROSE in men with SMI</td></tr>
<tr><td></td><td>D statistic</td><td>2.16 (2.1 to 2.22)</td><td>1.58 (1.48-1.68)</td><td>1.94 (1.87 to 2.02)</td><td>.92 (1.80-2.03)</td></tr>
<tr><td></td><td>Harrell's C</td><td>.844 (.837 to .851)</td><td>0.77 (0.73-0.81)</td><td>.817 (.809 to .825)</td><td>0.80 (0.76-0.83)</td></tr>
<tr><td></td><td>R2</td><td>52.6 (51.2 to 54.1)</td><td>Not reported</td><td>47.4 (45.6 to 49.3)</td><td>Not reported</td></tr>
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<td>of QRISK2 for evaluating cardiovascular disease risk. CG181 should be used alongside CG178 during the treatment and management of people with schizophrenia or psychosis when considering cardiovascular health.
The evidence highlighted (Hippisley-Coz, 2017 and Osborn, 2015) has been identified and included in the current ongoing surveillance review of CG181. As well as this, other risk assessment tools specific to people with severe mental health have been evaluated during the review of CG181 and if appropriate will be incorporated into an update of the guideline. No impact is anticipated in light of this evidence on the recommendations in CG178.</td>
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<td>Royal College of Psychiatrists</td>
<td>Yes</td>
<td>Although we agree that the guidance does not need to be updated at this time, future updates should explicitly state that it is primarily for adults of working age and does not cover psychosis in older adults.

There doesn't appear to be any NICE specific guidance on psychosis in older adults. There has been a blurring of inclusive terminology in recent years to subsume older adults into the "adults" category for certain guidance, without clarification on which topics actually exclude older adults in their methodology and recommendations.</td>
<td>Thank you for your comment. The scope for CG178 includes the treatment and management of schizophrenia or psychosis in people aged 18 years or older and with onset before 60 years. This is also described in the introduction section of the guidance. CG178 therefore is relevant for people over the age of 60 with schizophrenia or psychosis and only excludes people who receive a diagnosis after 60. During a 4-year surveillance review, areas outside of the scope of the guideline are considered for inclusion. However, during the search for systematic reviews and</td>
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			randomised controlled trials, no evidence specifically evaluating treatment for people with late onset schizophrenia or psychosis was identified. This area will be evaluated at the next surveillance time point and included in the scope if evidence is identified which prompts a full review.
Janssen	No	We thank NICE for the opportunity to comment on the surveillance proposal consultation document for NICE CG178: psychosis and schizophrenia in adults: prevention and management. We are disappointed that NICE has chosen not to review the CG 178 guideline based on the current surveillance review, as we believe there has been significant new data published since the last full update of the guideline. We are specifically aware of the availability of new evidence for long acting injectables (LAIs), which we believe should be included into an update of the guideline. In addition, the guideline should be reviewed in conjunction with the recommendations made in the publication of Mental Health Taskforce to NHS in England's Mental Health Five Year Forward View (MHFYFV) [1]. We believe that the recommendations made within the MHFYFV for improving care in mental health, including access to effective interventions presents an opportunity to review the evidence base and address some of the remaining significant issues with the current treatment of psychosis and schizophrenia [2]. We believe that there is sufficient new evidence published to review the pharmacological section of the guideline. We understand that NICE in their surveillance proposal consultation document has identified a 'large volume of newly identified evidence, especially in psychological and pharmacological interventions. We also understand that a lack of consistency in the available evidence identified is the main reason for not incorporating this new evidence into guideline [pg.2-3]. However, we strongly believe there is enough evidence to review the current treatment pathway for pharmacological therapies. In particular, the cost-effective sequence of pharmacological and psychological therapies to provide stronger recommendations on the sequencing of interventions for people with psychosis and schizophrenia, which has not been reviewed since the 2009 update of CG178. We believe that LAIs have a larger role to play in improving	Thank you for your comment. During a 4-year surveillance review of NICE guidelines, we search for systematic reviews and randomised controlled trials to identify new evidence that could have an impact on current recommendations. Other types of evidence highlighted by topic experts and stakeholders are also considered, as long as it is within the evidence types specified in the relevant review question. For the review question regarding long acting injectables, this only includes randomised controlled trials and systematic reviews. As you highlighted, a number of studies were identified through surveillance on long acting injectables and it is recognised that new formulations have been licensed since the last update of CG178 which have not been specifically considered. All the references highlighted were evaluated, with 3 of these being added to Appendix A: summary of new evidence (Weiden, 2017; Berwaerts, 2015 and Savitz, 2016). (A summary of the reasons for exclusion for the remaining references can be found below.) CG178 currently provides a recommendation (1.5.5.3) to consider the use of depot/long-acting injectable antipsychotics, including when compliance is an issue for that patient. Recommendation 1.5.6.1 states that service user preferences and organisational

		patient care and NHS outcomes in schizophrenia by reducing treatment discontinuation, relapse and associated hospitalisations. Schizophrenia has the second highest number of hospitalisations of any diagnosis within the UK and patients suffer from significant variation in the care they receive across the country [2,3]. Evidence suggest that LAIs can have a significant impact on reducing relapses and associated hospitalisations [4]. We believe that the new evidence for all interventions should be reviewed in an update of NICE CG178, especially new evidence available for LAIs. There has been significant evidence published on the use of LAIs since this section of the guideline was last updated with a systematic review conducted in 2009 [Full guideline, Section 10.6.3 pg 348-349]. Including the availability of new long acting antipsychotics like Xeplion (paliperidone palmitate 1-monthly LAI, Abilify Maintena (aripiprazole LAI) and Trevicta (paliperidone palmitate 3-monthly LAI). NICE has not reviewed these treatments as part of their NICE technology appraisal process or included their evidence within NICE CG 178. Indeed, the SMC and the AWMSG have found these treatments to be cost effective options for the maintenance treatment of schizophrenia compared to risperidone LAI, an older existing SG LAI, which was included in NICE CG178 [5]. However, the current NICE guideline has not considered these treatments or looked at their cost-effective use within the current treatment pathway since 2009. We note that the surveillance review has identified evidence for LAIs which has suggested a reduction in the relapse rate compared to oral medications from systematic reviews and RCTs and that some of this evidence may be at odds with other systematic reviews identified looking at specific LAIs [pg. 39]. However, it is important to note that some of the evidence regarding these treatments has not been identified in the surveillance review, including Randomised Clinical Trial evidence for paliperidone palmitate 3-monthly [6,7]. Data published from these trials suggests that LAI antipsychotic formulations may provide substantial delays over oral equivalents in times to relapse when patients discontinue therapy [8]. Furthermore, significant observational evidence for the use of paliperidone palmitate 1-monthly in UK studies suggests significant reductions in the number of hospital admissions and bed days [9-13]. Large country wide observational studies have also corroborated the impact of LAIs and clozapine and the impact that they have had on	procedures should be considered, as well as benefits and side effects when making a choice to prescribe an antipsychotic. It is therefore considered that the evidence presented is in support of the current recommendations as the evidence suggests that long acting injectable antipsychotics are effective. However, we do not believe that at this point there is sufficient evidence to suggest that one long acting injectable antipsychotic is more effective than another, and therefore the method of choice currently recommended is appropriate. This evidence will be considered again, alongside any newly emerging evidence at the next surveillance review, however it is not sufficient to prompt an update at this time. All references provided were evaluated for potential inclusion in the surveillance review. However, NICE bases recommendations on the best available evidence of the effectiveness of particular interventions, and the outcomes of these interventions. Therefore, the following references were not formally included in the summary of new evidence for the following reasons: • The Five Year Forward View for Mental Health, 2016 – this was excluded as it is not primary intervention based evidence • The Abandon Illness, 2012 – this was excluded as it is not primary intervention based evidence • Hospital Admitted Patient Care Activity, 2015-16 – this was excluded

		preventing relapse in schizophrenia and reducing the risk of hospitalisation by 20% to 30% compared to oral formulations [14]. We also note that the topic expert suggested that the *use of antipsychotics* section of the guideline would benefit from being updated. The topic expert also suggested that the cost of drugs and services are likely to have changed which may have a material impact on recommendations [pg. 37]. We agree with this assessment and believe that the cost effectiveness of treatment should be reviewed providing more up to date recommendations on the optimal sequence of treatments and interventions. This will in turn help clinicians to have a wider choice of cost effective interventions to treat people living with schizophrenia. Overall, we feel that the evidence in the current version of NICE CG 178 and the recommendations based on it are out of date, in respect, to the use of antipsychotics and psychological interventions. This is especially relevant regarding the evidence for LAIs and given the availability and clinical use of new second generation LAIs since this section of the guidelines was last updated. A review of these interventions to assess their clinical and cost effectiveness will help align the guidelines with the policy goals of the Mental Health Five Year Forward View which has called for cost-effective treatments to be made available to people with mental health issues including schizophrenia and psychosis [1]. 1. Independent Mental Health Taskforce to the NHS in England, The Five Year Forward view for Mental Health. Published February 2016. Available from https://www.england.nhs.uk/wp-content/uploads/2016/02/Mental-Health-Taskforce-FYFV-final.pdf Accessed 1st September 2017 2. Schizophrenia commission. The Abandon illness. Published November 2012. Available from https://www.rethink.org/media/514093/TSC_main_report_14_nov.pdf Accessed 31st August 2017. 3. NHS Digital, Hospital Admitted Patient Care Activity, 2015-16. Publication date: November 09, 2016. Hospital Admitted Patient Care Activity, 2015-16: External causes [.xlsx]. Available from http://content.digital.nhs.uk/article/2021/Website-Search?productid=23488&q=HOSPITAL+EPISODES+STATISTICS&sort=Relevance&size=10&page=3&area=both#top Accessed 31st August 2017. 4. Munro J et al. Hospital treatment and management in relapse of schizophrenia in the UK: associated costs. The Psychiatrist Online 2011;35:95-100 5. Scottish Medicine consortium. Paliperidone palmitate 50mg, 75mg, 100mg and 150mg prolonged release suspension for injection (Xeplion) Detailed Advice Document. Published 7th November 2011. Available from	as it is not primary intervention based evidence • Munro, 2011 – this was excluded as it is a study type (observational) that was excluded from the original guideline review protocol for this question • Scottish Medicine Consortium, 2011 – this was excluded as it is not primary intervention based evidence • Bressington, 2015 – this was excluded as it is a study type (observational) that was excluded from the original guideline review protocol for this question • Taylor, 2014 – this was excluded as it is a study type (observational) that was excluded from the original guideline review protocol for this question • Pappa, 2016 - this was excluded as it is a study type (observational) that was excluded from the original guideline review protocol for this question • Hodgson, 2016 – this study could not be found • Nikolic, 2017 - this was excluded as it is a study type (observational) that was excluded from the original guideline review protocol for this question

		https://www.scottishmedicines.org.uk/SMC_Advice/Advice/713_11_paliperidone_palmitate_Xeplion/paliperidone_palmitate_Xeplion_Resubmission Accessed 1st September 2017. 6. Savitz AJ, Xu H, Gopal S, Nuamah I, Ravenstijn P, Janik A, Schotte A, Hough D, Fleischhacker WW. Efficacy and Safety of Paliperidone Palmitate 3-Month Formulation for Patients with Schizophrenia: A Randomized, Multicenter, Double-Blind, Noninferiority Study. 7. Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, Coppola D, Schotte A, Remmerie B, Maruta N, Hough DW. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. AMA Psychiatry. 2015 Aug;72(8):830-9. 8. Weiden PJ, Kim E, Bermak J, Turkoz I, Gopal S, Berwaerts J Does Half-Life Matter After Antipsychotic Discontinuation? A Relapse Comparison in Schizophrenia With 3 Different Formulations of Paliperidone. J Clin Psychiatry. 2017 Jun 20[Epub ahead of print]. 9. Bressington D, Stock J, Hulbert S, MacInnes D. A retrospective observational study of the effectiveness of paliperidone palmitate on acute inpatient hospitalization rates. International clinical psychopharmacology. 2015 Jul;30(4):230-6. 10. Taylor D, Olofinjana O. Long-acting paliperidone palmitate - interim results of an observational study of its effect on hospitalization. International clinical psychopharmacology. 2014 Jul;29(4):229-34. 11. Pappa S, Bishop D, Larkin F, Marriott R, Mason K. The impact of long acting paliperidone palmitate on clinical outcomes and hospital stay in routine clinical practice: a UK service evaluation. Int J Neuropsychopharmacol. 2016;19(Suppl_1):50. 12. Hodgson RE, Chandan A, Davenport B. Two-year mirror image evaluation of paliperidone palmitate in an English health trust. American Psychiatric Association (APA). 2016;Abstract no: 50. 13. Nikolic N, Page N, Akram A, Khan M. The impact of paliperidone palmitate long-acting injection on hospital admissions in a mental health setting. International clinical psychopharmacology. 2017 Mar;32(2):95-102. 14. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, Enkusson D, Leval A, Sermon J, Tanskanen A, Taipale H. Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia. JAMA Psychiatry. 2017 Jul 1;74(7):686-693	
Medicines and Technology programme	Yes	No comment	Thank you for your response.
Otsuka Pharmaceutica ls limited	Yes	No comment	Thank you for your response.

Royal College of Nursing	Yes	No comment	Thank you for your response.

We have identified evidence which indicates that cognitive behavioural therapy (CBT) may not be effective for the treatment of negative symptoms of psychosis and schizophrenia. Does this concur with observations in clinical practice?

Stakeholder	Overall response	Comments	NICE response
The Pernicious Anaemia Society	N/A	Unable to comment	Thank you for your response.
Association for Family Therapy	No comment	No comment	Thank you.
Rotherham Doncaster and South Humber NHS Foundation Trust	No response	No comment	Thank you.
University of Nottingham	No response	No comment	Thank you.
Royal College of Psychiatrists	No response	No comment	Thank you.
Janssen	N/A	No comment	Thank you.
Medicines and Technology programme	No response	No comment	Thank you.

Otsuka Pharmaceutical Is limited	Yes	No comment	Thank you for your response. Feedback from stakeholder consultation has been considered alongside the evidence identified but is not sufficient to prompt an update of this area.
Royal College of Nursing	Yes	There are a lot of concerns that CBT is not suitable for everybody, there is the need for clear evidence of when it should be used or not	Thank you for your response. During a 4-year surveillance review of NICE guidelines, we search for systematic reviews and randomised controlled trials to identify new evidence that could have an impact on current recommendations. Through this, we identified conflicting evidence on the effectiveness of CBT for certain populations. It is not clear from the identified evidence for which subgroups of people CBT may be more or less effective for. Feedback from stakeholder consultation has been considered alongside the evidence identified but is not sufficient to prompt an update of this area. Therefore NICE will not update this area of the guideline at this time. Any emerging evidence will be evaluated at the next surveillance time point, alongside the evidence and feedback highlighted during this surveillance review.

How often are arts therapies offered to, and taken up, by people with psychosis and schizophrenia in the UK? What clinical observations can be made about the effectiveness of these treatments?

Stakeholder	Overall response	Comments	NICE response
The Pernicious Anaemia Society	N/A	No comment	Thank you.

Association for Family Therapy	N/A	No comment	Thank you.
Rotherham Doncaster and South Humber NHS Foundation Trust	N/A	No comment	Thank you.
University of Nottingham	N/A	No comment	Thank you.
Royal College of Psychiatrists	N/A	No comment	Thank you.
Janssen	N/A	No comment	Thank you.
Medicines and Technology programme	N/A	No comment	Thank you.
Otsuka Pharmaceutica ls limited	N/A	No comment	Thank you.
Royal College of Nursing	N/A	We have received no comments to submit	Thank you.

In practice, which pharmacological treatment options are given to people with schizophrenia or psychosis who are in remission?

Stakeholder	Overall response	Comments	NICE response

The Pernicious Anaemia Society	N/A	No comment	Thank you.
Association for Family Therapy	N/A	No comment	Thank you.
Rotherham Doncaster and South Humber NHS Foundation Trust	N/A	**Individual 1:** Currently I suspect that the patient is offered the same drug/dose that was found to be effective when they were unwell – any changes in drug/dose/format are due to • Emerging side-effects, • Emerging compliance problems or • patient's mental health deteriorating I don't feel that the drug/dose/format are changed due them going into remission **Individual 2:** Remission needs exploring: complete remission can only be used when patients are off medication, so we never actually know whether there has been remission until meds have been stopped. So I would say – no pharmacological treatments will be being used in those in complete remission	Thank you for your comments. This provides useful information regarding treatment for people with schizophrenia or psychosis during remission and implementation of the recommendations in CG178.
University of Nottingham	N/A	No comment	Thank you.
Royal College of Psychiatrists	N/A	No comment	Thank you.
Janssen	N/A	We believe that long acting treatments offer an important role in treating people with schizophrenia or psychosis who are in remission, especially as there is now a 3-monthly LAI treatment option, which can help with compliance challenge associated with taking daily oral medications over a significant period. Other psychological interventions, also have a role to play for people in remission, however, access to these interventions remains an issue with only 1 in 10 people, who could benefit rom cognitive behavioural therapy (CBT), having access to treatment [2]. 2. Schizophrenia commission. The Abandon illness. Published November 2012. Available from https://www.rethink.org/media/514093/TSC_main_report_14_nov.pdf Accessed 31st August 2017.	Thank you for your comment. During a 4-year surveillance review of NICE guidelines, we search for systematic reviews and randomised controlled trials to identify new evidence that could have an impact on current recommendations. Evidence was identified indicating that long acting injectable antipsychotics are effective for the promotion of recovery of people with schizophrenia and psychosis. However, evidence comparing either long acting injectables to oral antipsychotics or to other long acting

			injectables is contradictory across studies, indicating varying efficacy of each type of preparation. CG178 currently provides a recommendation (1.5.5.3) to consider the use of depot/long-acting injectable antipsychotics, including when compliance is an issue for that person. However, there is no consistent evidence indicating that a particular drug over another is more advantageous. This evidence will be reviewed during the next surveillance review, however at this time point, there will be no update of this area. It is appreciated that access to CBT is low, as highlighted in your comment. Recommendations in CG178 state that CBT should be offered to people with schizophrenia or psychosis during a first episode (1.3.4.1), subsequent acute episodes (1.4.4.1) and during recovery (1.5.4.1), as well as to people who are at risk of developing schizophrenia or psychosis (1.2.3.1). However, as no evidence concerning how to improve access to CBT for people with schizophrenia or psychosis reporting appropriate outcomes has been identified during this surveillance review, there will not be an update to the guideline to address this point.
Medicines and Technology programme	N/A	No comment	Thank you.
Otsuka Pharmaceutica ls limited	N/A	No comment	Thank you.

Royal College of Nursing	N/A	We have received no comments to submit	Thank you.

Currently, recommendation 1.3.5.1 recommends that the choice of antipsychotic should be made by the service user and healthcare professional together, through discussion of the benefits and a number of listed potential side effects. In practice, does this recommendation provide appropriate guidance, or if appropriate according to the evidence available, would more specific guidance on the choice of drug in specific circumstances be welcomed?

Stakeholder	Overall response	Comments	NICE response
The Pernicious Anaemia Society	No response	Unable to comment	Thank you.
Association for Family Therapy	No response	This wording pre-supposes that the choice discussed will be between antipsychotic medications. Recommendation 1.3.4.2 explicitly advises that psychological treatments are more effective in conjunction with antipsychotic medication. We would hope that choice could also include effective support (for example as evidenced in the Open Dialogue research) for those people who want to find ways of responding to their experiences without the use of antipsychotic medication.	Thank you for your comment. The current recommendation (1.3.4.2) which states that people who want to try psychological interventions alone should be advised that these are more effective alongside antipsychotics, is based on the best available evidence during guideline development. During a 4-year surveillance review, areas outside of the scope are considered, providing they are within the remit of the guideline. At this surveillance time point, we search for systematic reviews and randomised controlled trials to identify new evidence that could have an impact on current recommendations. We did not identify any evidence on an open dialogue approach, however the evidence highlighted (Seikkula et al., 2011) has been considered. The evidence highlighted is not sufficient to prompt an update in this area, as it relies on a single observational study which was not conducted

			in a UK setting. However, the ongoing trial highlighted (Razzaque and Stockmann) on open dialogue research will be evaluated at the next surveillance review following publication of results.
Rotherham Doncaster and South Humber NHS Foundation Trust	Yes	**Individual 1:** I think the premise that the choice of drug is made by the patient and HCP is absolutely right - • although it feels a little open ended ie do they expect that we discuss ALL antipsychotics as part of that or only those which would be a reasonable choice (eg we would not wish to talk about haloperidol with a patient with a cardiac history) • some additional specific guidance might be useful were there may be demonstrable clear water between drugs eg using newer APs, with a lesser physical health impact, earlier in treatment so that those benefits are realised – rather than later in the treatment schedule because of the relative expense **Individual 2:** We do not yet know which medication to give to which patient. We do sometimes split into – sedation then a sedative one, if not then aripiprazole. If someone has diabetes we do not give olanzapine. That is about it. In reality, we do often talk about two or three medications (in the capacitious patient) and discuss the pros v cons of each one. We are yet to have any evidence from studies as to which med we match to which patient. RDaSH is part of a multimillion pound research grant to look at how we predict which med will give which side effect in which patient.	Thank you for your comments. This has provided useful information on the implementation of the recommendations in CG178. In response to the comments regarding the imprecision of the recommendations on the choice of antipsychotic, we have considered the development of a patient decision aid. However, it has been concluded that other resources are available for this purpose, and that this would provide little additional value. Other resources available include the choice and medication website which is widely used and offers information about mental health conditions and the treatments available to help make informed decisions about choosing the right medicine. A large number of NHS mental health Trusts subscribe to this to make it available for their service users.
University of Nottingham	No response	More information is needed ton the relative risks and benefits of different types of antipsychotics and this needs to be personalised to an individual. For example, prior to starting a particular type of antipsychotic, the individuals baseline risk of adverse outcomes could be assessed. For cardiovascular risk, this could be done using the QRISK3 equation. https://www.qrisk.org/three/ The additional risk conferred by atypical antipsychotics can be taken into account when deciding on treatment for an individual. Similarly the baseline risk of diabetes can be considered using www.qdiabetes.org (note a new version of this risk calculator has been developed which includes SMI and also atypical antipsychotics and is currently undergoing review by the BMJ). However, neither of these tools currently enable the user to drill down to particular types of drugs – just the classes. Research is needed to quantify the comparative risks and benefits of individual drugs which can be included as a research question.	Thank you for your comment. This has provided useful information on the implementation of the recommendations in CG178. Recommendation 1.3.6.1 states that before starting antipsychotic medication, baseline investigations of a number of physical health measures should be made. Therefore, when choosing antipsychotic medication, the evaluation of baseline risk can be made. We have considered the development of a patient decision aid, which could incorporate tools to measure baseline

			risk. However, it has been concluded that other resources are available for this purpose, and that this would provide little additional value. Other resources available include the choice and medication website which is widely used and offers information about mental health conditions and the treatments available to help make informed decisions about choosing the right medicine. A large number of NHS mental health Trusts subscribe to this to make it available for their service users. Any future research quantifying the comparative risks and benefits of individual drugs will be identified in future surveillance reviews, however there is not an opportunity to add additional research recommendations at this point.
Royal College of Psychiatrists	No response	No comment	Thank you.
Janssen	Yes	We believe that people with schizophrenia are still not being offered a sufficient choice of effective interventions. This is born out in the data from the national audit of schizophrenia that shows large proportion (up to 50%) of people did not receive written information about their medication and that 25%-35% of people had not had their views considered [15]. This is confirmed by a recent patient survey where nearly half of respondents (46%) said they did not understand the different medication options available to them and a similar proportion (47%) felt that they were not part of the decisionmaking process when their medications were prescribed [16]. We believe that the people with psychosis and schizophrenia would benefit from more support and consultation which would help them make informed choices based on a shared understanding of the risk-benefit profile of all available antipsychotic treatments. As with other NICE guidelines, the development of a patient decision aid to help patients make these informed decisions is desperately needed in the prevention and management of psychosis and schizophrenia	Thank you for your comment. Recommendations in CG178 state that choice of antipsychotic medication should be made by the service user and healthcare professional together. The references highlighted (Royal College of Psychiatrists, 2014; Rethink Mental Illness, 2016) have indicated that this recommendation is not being met in all cases. During the search for systematic reviews and randomised controlled trials, no evidence was identified which reported on interventions to increase knowledge regarding antipsychotic choice. As the issue highlighted is with guideline implementation and no new evidence to prompt the addition of recommendations in

		in adults [17]. We fully agree and support the inclusion of more specific guidance on the choice of drugs in CG178 through a patient decision aid. 15. Royal college of Psychiatrists, Report of the second round of the National Audit of Schizophrenia (NAS2). Published October 2014 Available from http://www.rcpsych.ac.uk/pdf/FINAL%20report%20for%20the%20second%20round%20of%20the%20National%20Audit%20of%20Schizophrenia%20-%208.10.14v2.pdf Accessed 31st August 2017. 16. Rethink Mental Illness. Failure to provide regular health checks and basic information about medication is still leaving people with mental illness at risk of a dramatically shortened life. Published 17th May 2016. Available from https://www.rethink.org/media-centre/2016/05/medication Accessed 1st September 2019. 17. NICE CG 181 Cardiovascular disease: risk assessment and reduction, including lipid modification. Published September 2016. Available from https://www.nice.org.uk/guidance/cg181/resources/cg181-lipid-modification-update-patient-decision-aid2 Accessed 1st September 2017.	this area was identified, the guideline will not be updated. We have considered the development of a patient decision aid. However, it has been concluded that other resources are available for the purpose of choosing antipsychotic medication, and that this would provide little additional value in this case. Other resources available include the choice and medication website which is widely used and offers information about mental health conditions and the treatments available to help make informed decisions about choosing the right medicine. A large number of NHS mental health Trusts subscribe to this to make it available for their service users.
Medicines and Technology programme	Yes	Also 1.5.6.1. Product licences will influence product choice. If prolonged release intramuscular injection will be required in future (eg anticipated compliance issues) then the patient should be stabilised on the corresponding oral formulation first eg. Aripiprazole.	Thank you for your comment. Following consideration of this issue, it is recognised that the current recommendations are not appropriate for all long acting injectable antipsychotics. Therefore, an editorial amendment will be made to incorporate this change in practice following the recent advances in long acting injectable antipsychotics (see Appendix A: summary of new evidence for details).
Otsuka Pharmaceutica ls limited	Yes	From Otsuka's perspective we believe this is of paramount importance and we fully support shared-decision making in the treatment of mental illnesses. However, we would hope that the guidelines produced would be in line with the recent adult schizophrenia pathway updates produced by NICE, which remark the need for using agents that are prolactin sparing and do not contribute to worsening metabolic abnormalities on patients.	Thank you for your comment. During the search for systematic reviews and randomised controlled trials, we did not identify any evidence regarding the use of prolactin sparing agents, however, current recommendations suggest that metabolic side effects should be considered during the choice of antipsychotic (1.3.5.1). This recommendation also states that choice should be made by the service user and

			healthcare professional together, which is supported by your comments.
Royal College of Nursing		More guidance around this would be welcome, which can then inform a choice made together by the service user and HCP.	Thank you for your comment. We have considered the development of a patient decision aid. However, it has been concluded that other resources are available for the purpose of choosing antipsychotic medication, and that this would provide little additional value in this case. Other resources available include the choice and medication website which is widely used and offers information about mental health conditions and the treatments available to help make informed decisions about choosing the right medicine. A large number of NHS mental health Trusts subscribe to this to make it available for their service users.

Do you agree with the proposal to remove the research recommendation:

What are the short- and long-term benefits to physical health of guided medication discontinuation and/or reduction in first episode psychosis and can this be achieved without major risks?

Stakeholder	Overall response	Comments	NICE response
The Pernicious Anaemia Society	No response	No comment	Thank you.
Association for Family Therapy	No	People experiencing symptoms labelled ‘Psychosis’ or ‘Schizophrenia’ may experience significant adverse effects from medication. Following through on this research recommendation would give important evidence which could impact significantly on treatment decisions and allow better information for people experiencing these symptoms to make the choices that work better for them.	Thank you for your comment. Following the responses received during consultation, NICE has decided not to remove this research recommendation as ongoing research has been highlighted in this area.
Rotherham Doncaster and	No	**Comments from S Davies RDaSH Chief Pharmacist** This should stay in there as it fits with the consequences of my answers to Q4	Thank you for your comment. Following the responses received during consultation, NICE

South Humber NHS Foundation Trust		**Comments from Consultant psychiatrist. (A Phillipson)** The RADAR study (Joanna montcrieff – university of London) aims to address this question	has decided not to remove this research recommendation as ongoing research has been highlighted in this area.
University of Nottingham	No response	Yes but I think it should also include starting medication not just stopping	Thank you for your comment. Following the responses received during consultation, NICE has decided not to remove this research recommendation as ongoing research has been highlighted in this area. This research recommendation was written as guided medication discontinuation/reduction was deemed an important area which required more evidence before recommendations could be made. The evidence base on the physical health effects of starting antipsychotic medication is large, and has been considered during guideline development. Therefore, the research recommendation will kept and remain published as it was at guideline development.
Royal College of Psychiatrists	No response	No comment	Thank you.
Janssen	No	We are not aware of any new published evidence applying to this research recommendation. But note that NIHR have funded the Research into Antipsychotic Discontinuation and Reduction (RADAR) study to evaluate a structured antipsychotic medication reduction and discontinuation programme for people with long-term schizophrenia and similar problems. We believe that it is an important question to retain in terms of the research recommendations section of the guideline. Both guided medication discontinuation and reduction in first episode psychosis will have important short and long term benefits on physical health of people with schizophrenia. Therefore, any new evidence addressing this research question from the RADAR study or from other sources should be included in future versions of the guideline.	Thank you for your comment. Following the responses received during consultation, NICE have decided not to remove this research recommendation as ongoing research has been highlighted in this area.

Medicines and Technology programme	No response	No comment	Thank you.
Otsuka Pharmaceutical Is limited	Yes	While we agree to the removal of this research recommendation, Otsuka does believe that the focus on physical health must not be diminished, as highlighted by 'OP100. Improving the physical health of adults with severe mental illness: essential actions'. A report of the Academy of Medical Royal Colleges and the Royal Colleges of General Practitioners, Nursing, Pathologists, Psychiatrists, Physicians, the Royal Pharmaceutical Society and Public Health England, published in October 2016.	Thank you for your comment. Following the responses received during consultation, NICE have decided not to remove this research recommendation as ongoing research has been highlighted in this area.
Royal College of Nursing	Yes		Thank you for your response. Following the responses received during consultation, NICE have decided not to remove this research recommendation as ongoing research has been highlighted in this area.

Do you have any comments on areas excluded from the scope of the guideline?

Stakeholder	Overall response	Comments	NICE response
The Pernicious Anaemia Society	No response	The B12 status of patients should be assessed as part of the diagnosis process. Around 10% of the UK's population is deficient in B12 and it is a worldwide problem which is not helped by the lack of consensus on what constitutes a deficiency or sub-clinical deficiency and the lack of a robust tool to assess the patient's B12 status.	Thank you for your comment. The remit provided for this guideline covers the prevention and management of schizophrenia and psychosis, therefore the diagnosis of psychosis is outside the scope for this guideline. As such, no action will be taken in relation to CG178.
Association for Family Therapy	Yes	The constructs of 'Schizophrenia' and 'Psychosis' represent particular ways of understanding people's experiences as 'mental disorders'. This does not represent the only useful perspective. The prevalence of 'psychotic symptoms' without distress in the general population, the importance of socio-cultural understandings, including where such experiences have a positive cultural understanding, the relevance of early traumatic experiences and social deprivation are all relevant ways of understanding these experiences. Continuing to use terms denoting 'mental disorder' continues to prioritise the location of the 'problem' in the individual and points to 'treatment / intervention' solutions, whilst giving less space for relational, social, cultural and political understandings which could point towards different potential effective solutions.	Thank you for your comment. During a 4-year surveillance review, we search for systematic reviews and randomised controlled trials to identify new evidence that could have an impact on current recommendations. This includes areas which are outside the current scope. Through this process we did not identify any evidence which could be

			considered as social, cultural, relational or political interventions. Therefore, it is not likely there will be any impact on the guideline at this time point.
Rotherham Doncaster and South Humber NHS Foundation Trust	No	No comment	Thank you for your response.
University of Nottingham	No response	No	Thank you for your response.
Royal College of Psychiatrists	No response	No comment	Thank you.
Janssen	No	No other comments	Thank you for your response.
Medicines and Technology programme	No	No comment	Thank you for your response.
Otsuka Pharmaceutica ls limited	No	No comment	Thank you for your response.
Royal College of Nursing	No	No comment	Thank you for your response.

Do you have any comments on equalities issues?

Stakeholder	Overall response	Comments	NICE response

The Pernicious Anaemia Society	No response	None	Thank you.
Association for Family Therapy	Yes	Diagnosis can be biased with respect to gender, race and culture, meaning that there are likely to be continuing equality issues, as noted in your report.	Thank you for your comment. The remit provided by the Department of Health for the development of this guideline includes the prevention and management of schizophrenia and psychosis. Therefore diagnosis is not within the scope of this guideline and so no action will be taken.
Rotherham Doncaster and South Humber NHS Foundation Trust	No	No comment	Thank you.
University of Nottingham	No response	Yes – for CVD risk assessment then it is very important to use a tool which takes account both of deprivation and also ethnicity to avoid exacerbating inequalities.	Thank you for your comment. Cardiovascular risk assessment tools are being considered as part of the ongoing surveillance of CG181, including QRisk3 which takes account of deprivation and ethnicity. If evidence is sufficient to prompt an update of CG181 to include this risk assessment tool, this would complement the recommendations in CG178 which state that physical health checks should include monitoring cardiovascular disease.
Royal College of Psychiatrists	No response	No comment	Thank you.
Janssen	Yes	There remains a gap in the parity of esteem with regards to mental health compared to physical health conditions, as noted in the recently published Mental Health Five year forward view [1]. We also acknowledge that progress has been made with regards to addressing this disparity since it	Thank you for your comment. NICE bases its recommendations on the best available evidence, and the strength of the current recommendations reflects the evidence

		was enshrined in the Health and Social Act, which was published in 2012. Nevertheless, patients with mental health conditions account for 28% of the overall burden of disease, including psychosis and schizophrenia, yet only 13% of NHS spending goes towards mental health [18]. People with mental health conditions continue to have poorer access to services and effective interventions. NICE can play an important role in addressing the parity of esteem issue between mental and physical health by strengthening its recommendations for effective treatments, focusing on medicines optimisation, promote further shared and informed decision making and develop patient decision aids, as has been done in other disease areas [17]. All these elements should be addressed within an update of the NICE CG178 to enable people with psychosis and schizophrenia access to effective and evidence based interventions to improve their chances of leading normal lives and reducing the burden on the healthcare system as outlined in the Mental Health Five Year Forward View [1]. 1. Independent Mental Health Taskforce to the NHS in England, The Five Year Forward view for Mental Health. Published February 2016. Available from https://www.england.nhs.uk/wp-content/uploads/2016/02/Mental-Health-Taskforce-FYFV-final.pdf Accessed 1st September 2017 17. NICE CG 181 Cardiovascular disease: risk assessment and reduction, including lipid modification. Published September 2016. Available from https://www.nice.org.uk/guidance/cg181/resources/cg181-lipid-modification-update-patient-decision-aid2 Accessed 1st September 2017. 18. Center for Mental Health. 'Parity of Esteem'. https://www.centreformentalhealth.org.uk/parity-of-esteem Accessed 31st August 2017.	available at the time of development. NICE recognises that when appropriate, alignment with reports such as the Mental Health Five Year Forward View is important and the highlighted references have given an understanding of the context that the current evidence base sits within. However, it is outside of NICE's remit to consider the NHS spending distribution, but instead to recommend the cost effective and clinically effective treatments where evidence supports their use. No evidence was identified during the surveillance review to prompt the addition of recommendations on medicines optimisation or methods to promote shared and informed decision making. Therefore, CG178 will not be updated to incorporate these changes at this time. Furthermore, NICE has developed guidance on medicines optimisation (NICE guideline NG5) and patient experience in adult NHS services (NICE guideline CG138 and NICE quality standard QS15), which is aimed at addressing medicines optimisation and promoting shared and informed decision making. We have considered the development of a patient decision aid. However, it has been concluded that other resources are available for the purpose of choosing antipsychotic medication, and that this would provide little additional value in this case. Other resources available include the choice and medication website which is widely used and offers information about mental health conditions and the treatments available to help make informed decisions about choosing the right

			medicine. A large number of NHS mental health Trusts subscribe to this to make it available for their service users.
Medicines and Technology programme	No	No comment	Thank you for your response.
Otsuka Pharmaceuticals limited	Not answered	No comment	Thank you.
Royal College of Nursing	No	No comment	Thank you for your response.