NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2020 surveillance of Generalised anxiety disorder and panic disorder in adults: management (2011)

Consultation dates: 9am Wednesday 18 December 2019 until 5pm, Friday 10 January 2020

1. Do you agree with the proposal to not update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Anxiety UK	No	We feel very strongly that it is disappointing that some 9 years on from the last review of the guideline having taken place, that nothing new is available so as to be put forward as an option in the treatment of anxiety. We recognise that it isn't NICE's remit to generate treatment options, however we think it is important to make the point that given the rise in anxiety presentations in society, that there is now an urgent need for new treatment options to be developed and evidenced beyond those already available and which can then be endorsed by yourselves.	Thank you for your comments. Although we did find new evidence for transdiagnostic approaches to therapy and growing evidence for the effectiveness of internet delivered therapies on balance there was not enough new evidence to make specific recommendations. This was also the case when the guideline was last reviewed in 2015. It is hoped that the CG113 research recommendations will serve to stimulate developments in treatment.
Dr Karen Heslop-Marshall	Yes	Overall, I agree the evidence does new published evidence does not impact on existing guideline recommendations.	Thank you for your comments.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

British Association for Psychopharmacology (BAP)	No	1.Although generalized anxiety disorder and panic disorder often overlap in clinical practice, they are distinct medical conditions, and each is worthy of its own guideline. 2.DSM-5 diagnostic criteria for both conditions were published in 2013, and ICD-11 diagnostic criteria for both conditions are available and will be implemented internationally within two years. 3.Potential adverse effects of psychological interventions are not mentioned alongside potential adverse effects of pharmacological interventions (despite the good evidence for adverse effects from psychotherapies in a some patients in the spotlights conducted within the framework of National Clinical Audits).	1. Thank you for your comments. We recognise that generalised anxiety disorder and panic disorder are separate conditions although they often overlap. This is reflected in the lay out of the guidance which separates the recommendations for the conditions. The surveillance review also took this approach by separating the evidence and information for the different conditions as far as possible. The original remit from the Department of Health asked NICE to prepare a clinical guideline for the NHS for anxiety and related common mental disorders, including both generalised anxiety disorder (GAD) and panic disorder (with or without agoraphobia), which is why the recommendations are contained in one guideline. 2. Thank you for comments. Differences in diagnostic criteria between DSM IV and DSM V were compared and were assessed as not impacting on CG113 as changes to diagnostic criteria were judged to be not substantive. This is discussed specifically in relation to panic disorder on p. 45 of appendix A. With respect to ICD-11, NICE will monitor the implementation of this system and assess its impact on the guideline when ICD-11 is fully implemented in 2 to 3 years' time. 3. Thank you for your comments. Recommendation 1.2.26 advises offering a high intensity psychological interventions or drug treatment and providing written information about the benefits and disadvantages of both. This should include any information about known adverse effects or either treatment. The guideline advises high intensity therapies should be based on the treatment manuals for CBT and applied relaxation and delivered by trained and competent practitioners. It is reasonable to expect those delivering the therapy will consider and communicate potential adverse

		4.The statement 'Base the choice of treatment on the person's preference as there is no evidence that either mode of treatment (individual high-intensity psychological intervention od drug treatment) is better' is misleading. See the meta-analysis reported by Bandelow et al. (Int Clin Psychopharmacol 2015; 30: 183-192), which indicates that the effectiveness of psychological interventions for GAD, panic disorder (and social anxiety disorder) is not significantly different from that of a pill placebo. See also the wise caution about the inadvisability of making direct comparisons between the effectiveness of pharmacological and psychological treatments, given substantial differences in trial methodologies (Carl E et al. Cogn Behav Ther 2019; 14: 1-21), and the recent analysis of the effects of psychological interventions in GAD which showed that no intervention had greater effects than a psychological placebo (Chen et al. J Psychiatr Res 2019; 118: 73-83).	effects. During surveillance we did not find any evidence for generalisable adverse effects for psychotherapies. 4. Thank you for your comments. We acknowledge that directly comparing the effectiveness of psychological and pharmacological therapies directly is difficult and, in some instances, not appropriate. This recommendation is communicating that both are effective while advising that overall the evidence for which is 'better', based on a number of considerations, is uncertain. The guidance is written with the understanding that the treatments are not necessarily mutually exclusive, and that people may elect to have either or both following discussion with a clinician and based on monitoring response to treatment. This is covered by recs 1.2.33-1.2.36 inadequate response to step 3 interventions. We acknowledge that larger effects sizes are often observed for placebo-controlled drug outcomes compared with psychological therapies, but where attempts have been made to directly compare treatments the results are equivocal. During surveillance a Cochrane review (Imai) was identified (see p. 50 of appendix A) that compared psychological therapies with pharmacological therapies in people with panic disorder and concluded it was not possible to attribute superiority of one therapy over another because of poor study quality. Thank you for drawing our attention to the Bandelow study. This study reports results for a mixed population of people with GAD, panic disorder and social phobia. The surveillance review was attempting to consider the impact of interventions, as far as possible, in specific populations with GAD or panic disorder. The Bandelow study suggests that on average pharmacological therapies produce a greater average pre-post effects size than psychological therapies but that both treatments produce an effect. They report

			that the difference in size varies depending on drug class and psychotherapy. The Chen study is included in the surveillance review (see Appendix A p.28) and draws similar conclusions that overall pharmacological therapies produce a greater effects size than psychological therapies but that both produce an effect. However, there are two issues with trying to make indirect comparisons in this way: 1). the difference in methodologies used when investigating the different treatments that you have highlighted with Carl et al. 2) side effects and withdrawal syndromes that are associated with pharmacological therapies but not psychological treatments. This can affect treatment tolerance and lead to treatment drop out and the issue of which treatment is 'better' needs to take this into account. The Bandelow study concludes that choice of treatment should consider patient preference because drugs may have side-effects and contraindications not associated with psychological therapies.
		5.It may no longer be the case that sertraline (which still does not have a product licence for the treatment of GAD) is the 'most cost-effective drug'. This statement is based on a 2011 economic model and it cannot be assumed that similar costs and benefits are present almost a decade later. We are unaware of any published placebo-controlled evidence demonstrating that sertraline is effective in relapse prevention in patients with GAD.	5. Thank you for your comments. All new evidence (see appendix A) suggests sertraline remains effective and well tolerated. Despite escitalopram's reduced price, sertraline. remains the cheapest SSRI except for paroxetine which is associated with adverse effects. A large network meta-analysis by Slee (2019) indicates that sertraline is as efficacious and well tolerated as escitalopram and supports the existing recommendations. For these reasons the recommendation to consider sertraline as a first choice SSRI is judged as still being valid.

		6.In Step 4, the 'focus of the intervention' for GAD does not explicitly mention comorbid conditions (such as alcohol use disorders).	6. Thank you for your comments. Recommendation 1.2.37 recommends a specialist needs and risk assessment should proceed step 4 treatment. This includes an assessment of comorbidities. Recommendation 1.2.8 in the assessment and education section advises that harmful and dependent substance misuse should be treated first and includes footnote 6 which cross-refers to NICE guidance on alcohol use disorders.
		7.Paragraph 1.2.22 states 'Informed consent should be obtained and documented' but it is unclear whether this relates solely to sertraline (because of the lack of a supporting product licence).	7. Thank you for your comment. This statement is to draw attention to the specific requirements when prescribing sertraline outside the terms of its licence in line with GMC good prescribing practice.
		8.Pregabalin is mentioned a few times (e.g. in 1.2.24) but the current guidance does not refer to its Schedule 3 controlled drug status (which was implemented in April 2019).	8. Thank you for your comment. Recommendation 1.2.24 includes footnote 8 which links to the full-text of the MHRA drug safety update dated April 2019. This link with some brief explanatory text will be added to the recommendation.
		9.The wording of 1.2.41 states 'evidence for the effectiveness of combination treatments is lacking' is insufficiently nuanced: for example, there is evidence for the effectiveness of pregabalin augmentation after SSRI or SNRI non-response, and for olanzapine augmentation after SSRI non-response.	9. Thank you for your comments. Recommendation 1.4.21 tries to communicate that the evidence was too inadequate to make a recommendation for a specific combination of treatments. During guideline development evidence from 4 trials of antipsychotic augmentation therapy (including olanzapine) were identified. The results indicated limited benefit but an association with discontinuation due to adverse events.

			During this surveillance we identified studies investigating several combination treatments including CBT plus D-cycloserine, escitalopram plus pregabalin, antidepressants plus L-theanine and antidepressants plus benzodiazepine. Little effect was found for these combinations compared to various controls. There was evidence from some small single studies (less than 50 people) that reported positive outcomes for sertraline plus saffron and CBT plus aerobic exercise, but it was not enough to base recommendations on. Evidence for pregabalin augmentation therapy was seen during 2015 surveillance (Rickels et al. 2012) which concluded that further evidence was needed before a specific treatment could be recommended. No further evidence for pregabalin augmentation or for olanzapine augmentation was identified during this surveillance.
		10.The statement in 1.4.21 'Benzodiazepines are associated with a less good outcome in long term and should not be prescribed for the treatment of individuals with panic disorder' needs some revision. For example, a recent meta-analysis indicates that the 'number needed to benefit' for benzodiazepines is 4 whereas that for antidepressants is 7 (Bighelli et al. Cochrane Database Syst Rev 2018; Apr 5. 4. CD010677), and another meta-analysis indicate that there are more adverse events with SSRIs	10. Thank you for your comments. We found 3 Cochrane reviews 2 by Bighelli et al and one by Breilmann about pharmacological treatment of panic disorder; 1 investigating antidepressants (2018) (10.1002/14651858.CD010676.pub2) 1 investigating benzodiazepines and antidepressants (2016) (doi.org/10.1002/14651858.CD011567.pub2). and 1 comparing benzodiazepines to placebo from which the NNTB of 4 you refer to is taken. They are included in the review and summarised in appendix A. Bighelli 2018 indicated that response to antidepressants is greater

		than with benzodiazepines in short-term treatment (Qualito et al. J Psychopharmacol 2019; 33: 1340-1351).	than placebo and that all-cause drop out is lower with antidepressants than placebo. Although the Bighelli (2016) review did find some positive outcomes for benzopdiazepines the authors concluded that the included studies were not of sufficient quality to address the objectives of the review which were to compare the response rate and dropouts due to adverse events of benzopdiazepines with antidepressants. The authors also caution that data on the long-term tolerability of both drug classes should also be considered before prescribing. The Breilmann study concludes that low quality evidence shows a possible superiority over placebo but that the validity of the studies is questionable due to unmasking of treatments and high drop out rates. It further concludes that included studies were only short-term studies and did not examine the long-term efficacy nor the risks of dependency and withdrawal symptoms. The Quagliato study reports that SSRIs cause more adverse effects that benzodiazepines in short-term treatment (4-12 weeks). The study also reports that RCTs comparing SSRIs and benzodiazepines for the short term treatment are needed. Panic disorder is a chronic condition and benzodiazepines are associated with a risk of dependence if taken long-term.
		11.Section 1.4.31 states 'To minimise the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should be reduced gradually over	11. Thank you for your comments. We are aware of the concerns about withdrawal of antidepressants. This issue is covered in more detail by the NICE guideline on depression in adults (CG90) . There is currently a project to ensure consistency of

		an extended period of time' but this is too vague to be helpful to clinicians.	withdrawal/discontinuation symptoms with CG90 across all affected guidelines including CG113.
		12.Section 1.4.44 provides no helpful guidance on low long to continue a pharmacological treatment in panic disorder once a patient has responded to acute treatment.	12. Thank you for your comment. Recommendation 1.4.28 advises that treatment should be considered for at least 6 months if a person is showing improvement.
		13.Stakeholder consultation suggests that people with chronic anxiety care a great deal about long term outcomes and sustained wellbeing. Therefore, paying further regard to improved guidance on how long to remain on treatment and relapse prevention, the Guideline would benefit from careful consideration of new evidence from a recent meta-analysis of relapse-prevention studies investigating Anxiety Disorders including GAD (6 studies), panic disorder (6 studies), that draws attention to the important clinical findings that that discontinuation of pharmacological treatment in those who have benefitted from it results in higher relapse rates and that relapse risk is not significantly influenced by the type of anxiety disorder, duration of previous treatment, duration of follow-up, mode of discontinuation or concurrent psychotherapy. The findings	13. Thank you for your comments. The Batelaan network metanalysis was considered during surveillance and is summarised in Appendix A. It was considered to support recommendations which accommodate an approach to treatment duration based on clinical judgement. Recommendation 1.2.27 advises a discussion of pharmacological treatment options which includes providing information on the importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse.

		of this meta-analysis may be interpreted to suggest that there is no predetermined optimal length of treatment beyond which medication should be stopped. Instead, treatment should be directed by long term considerations including relapse prevalence, side effects and patients' preferences (Batelaan NM et al. BMJ 2017; 358:j3927).	
BABCP	Yes	It would be useful to make it clear in the overview of NICE guidelines (rather than just in the main text which many people will not read), that using DSM, rather than ICD, criteria is most appropriate for GAD; DSM is more focused on uncontrollable worry which is the target for most CBT protocols for GAD.	Thank you for your comment. The full version of the guideline does state that the development group used DSM rather than ICD because the evidence base for treatments nearly always used DSM. It does not specifically recommend one diagnostic system over another in relation to GAD. This is addressed on p. 11 of appendix A.

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

Stakeholder	Overall response	Comments	NICE response
Anxiety UK	Yes	We are surprised that given the technological advances that have taken place since 2011, that this does not appear to be reflected in the guidance. Additionally, our experience is that unless treatment options are spelt out in black and white in the guidelines, then it is so that such treatments are side-lined, despite the marginal benefit that they may provide. The result is that those with anxiety have a limited range of treatment options available to them which goes against what people want, - choice.	Thank you for your comments. We did find growing evidence for the use of technologies for example in delivering and augmenting behavioural therapies but not enough to make specific recommendations for them. The guideline contains research recommendations that we hope will continue to stimulate research into treatments for generalised anxiety and panic disorders where gaps in the evidence currently exist.

Dr Karen Heslop-Marshall	Yes	I do feel that the current guidelines do not include sufficient recommendations for dealing with anxiety/panic for people with long term conditions such as COPD. There has been research published in this area & there may well be more for other conditions. This NIHR research is the biggest study to date in COPD. https://openres.ersjournals.com/content/4/4/00094-2018.	Thank you for your comments and the information about the NIHR study. We had sight of this study and other studies addressing comorbidities during this surveillance. This issue is addressed by guidelines that deal with COPD. For example COPD in over 16's (NG115) which includes a section on identifying and managing anxiety and depression which cross-refers to CG113 (see recommendations 1.2.100 to 1.2.102). A full rationale is given in appendix A pp.44-45.
British Association for Psychopharmacology (BAP)	Yes	No Comment	
BABCP	No	No Comment	

3. Do you have any comments on equalities issues?

Stakeholder	Overall response	Comments	NICE response
Anxiety UK	Yes	We recognise that current treatment options tend to appeal to certain sections of society more than others and in particular, talking therapy treatments are generally speaking accessed more by women. As such, we feel strongly that a range of treatments should be made available to include non-talking therapy options to widen access to support.	Thank you for your comments. The guideline recommendations accommodate a wide range of treatments depending on the severity of the disorder including self-help therapies, high intensity therapies and pharmacological interventions. Recommendation 1.1.1 advises the practitioner to explore treatment options collaboratively with the person, indicating that decision making is a shared process and the guideline puts patient preference at the centre of all recommendations. NICE currently works with NHS England assessing the suitability of digital therapies for inclusion in the NHS improving access to

			psychological therapies programme, aimed at widening access and choice.
Dr Karen Heslop-Marshall	No	No Comment	
British Association for Psychopharmacology (BAP)	Yes	People with GAD and panic disorder, especially those with more severe or difficult to treat forms of disorder, experience disproportionate barriers in receiving appropriate care related to service configuration (unavailability of a psychiatrist to prescribe medication) and staff competencies (GPs having insufficient expertise to manage difficult to treat anxiety disorders). The recent introduction of the IAPTS services have changed service provision universally, affecting the level of care at which people with these disorders are now receiving treatment. As the level of 'risk' is viewed as low, most people with GAD and panic disorder are now being referred to IAPTS (instead of secondary care mental health services), where appropriate medication management (optimised SSRI/SNRI (sometimes using higher dosages) or augmentation for resistant cases (e.g. with pregabalin) is often not available. People with disorders such as these frequently fail to benefit or 'drop out' of care as a result. IAPTS, while providing good access for some forms of CBT, may have the unintended effect of denying people with more severe or difficult to treat forms of GAD and panic disorder the most effective form of treatment in terms of evidence-based pharmacotherapy. As a consultant psychiatrist working both in a tertiary psychiatric service	Thank you for comments. Issues around referral to IAPT by frontline services are outside the remit of this review. We will pass your comments on to our contacts in the NHS England IAPT programme.

		and as a consultant in IAPTS, I often see people 'falling through gaps" in mental health services as a result of being referred to IAPTS, because of the absence of pharmacotherapy expertise embedded within this Service.	
BABCP	Yes	More research is needed comparing the same interventions for older adults and younger adults as stated. We note the comments on lower rates of uptake for evidence based therapies amongst many BAME populations. NHSE and the BABCP recently published the IAPT Positive Practice Guide for work with BAME communities (http://www.babcp.com/files/About/BAME/IAPT-BAME-PPG-2019.pdf). This guide was commissioned by NHSE in recognition of the lower rates of uptake amongst many BAME communities and poorer clinical outcomes for those communities. This guide includes extensive evidence based approaches to improving uptake of mental health services and adapting psychological therapies to ensure that they meet the needs of those communities. We would appreciate NICE guidance taking this work into account and including robust recommendations about the need to monitor uptake of services and adapt the way that services operate and therapies are delivered to take this into account. More research in this area would also be helpful.	Thank you for your comments and for sharing the IAPT Black, Asian and Minority Ethnic service user positive practice guide. Implementation of services for specific groups is outside of NICE's remit. However, NICE works with NHS England on the NHS improving access to psychological therapies programme (IAPT) to assess digital therapies and we will share the guide and comments with colleagues in NICE who work on the IAPT programme. During this surveillance we did not identify any RCTs of interventions that increased uptake of services by BAME groups. The guideline currently contains recommendations about making information available in preferred language and the provision of independent interpreters if required. It also contains recommendations to consider cultural characteristics that may be important to care. The guideline also cross-refers to common mental health disorders: identification and pathways to care (CG123). This advises that primary and secondary care clinicians, managers and commissioners should collaborate to develop local care pathways that promote access to services for people with common mental health disorders from a range of socially excluded groups including black and minority ethnic groups. Cross referral from the guideline to common mental health disorders (CG123) will be increased and made more visible as a result of comments received by several stakeholders during this surveillance review.
