Appendix A: Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts was considered alongside the evidence to reach a view on the need to update each section of the guideline.

Evidence from previous surveillance and from an evidence update for this topic was also considered. Evidence updates are not guidance but were produced by NICE to highlight new evidence relating to published NICE guidelines.

This surveillance review has used, as far as possible, studies carried out in populations with generalised anxiety disorder (GAD) or panic disorder or that report the proportion with these disorders in the abstract. Where the evidence base in GAD or panic disorder populations is limited, studies of populations with mixed anxiety or mental health disorders that include GAD and panic disorder have been included. The composition of the population in the included studies is stated in each study summary.

This surveillance review includes discussion of computerised cognitive behavioural therapy (CCBT). CCBT is a generic term that is used to refer to several methods of delivering CBT via an interactive computer interface. It can be delivered on a personal computer, over the internet or via the telephone using interactive voice response systems. The term internet CBT (iCBT) is used in this document where included studies have explicitly used it to describe the interventions under investigation.

Experience of care for people with generalised anxiety disorder and their carers

Surveillance proposal

The section of the guideline on experience of care for people with generalised anxiety disorder and their carers should not be updated.

Previous surveillance

This guideline was the subject of an evidence update in 2012 and a surveillance review in 2015 and new evidence was identified. A full list of studies included in previous surveillance can be found in the 2015 surveillance review decision and 2012 evidence update documents. New secondary RCT data analysis identified in the 2015 surveillance review indicated that coexisting pain can negatively affect response to anxiety treatment in GAD patients. New systematic review evidence indicated a significant level of patient involvement in self-care interventions. Collectively the new evidence was considered to reinforce recommendation 1.1.1, specifically to explore treatment options collaboratively with the person in a shared decision making process, and to explore the person's worries, which may relate to coexisting pain, in order to jointly understand the impact of GAD.

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Treatment seeking behaviour

One RCT (Shafran et al. 2019) (n=306) investigated the impact of an app that enabled patients to monitor their symptoms, on the treatment seeking behaviour of a mixed population of people with anxiety and depression. Participants were randomised to information only, information plus app symptom monitoring every 6 days and information plus unrestricted app symptom monitoring. Participants were more likely to report seeking treatment the more they were able to monitor their symptoms, but only a small minority who downloaded the app completed the study.

Shared decision making

One RCT conducted in a mental health outpatient setting recruited patients with a range of mental health conditions including anxiety disorders (n=200) (Metz et al. 2018)) The study investigated the impact of an eHealth patient-clinician shared decision making tool (SDM-Digital Intake) on rates of patient engagement and satisfaction with treatment decisions (“decisional conflict”) during the patient intake process. It reported no difference in rates of decisional conflict for any conditions at 2 weeks’ or 2 months’ follow-up

compared with the usual intake routine. Patients reported some small positive effects on SDM and symptom severity at 2 months. The proportion of patients with GAD or panic disorder is not specified in the abstract.

Intelligence gathering

No intelligence was identified for this section.

Impact statement

Evidence was identified for two pieces of technology: an app that allows people to monitor their own mental health symptoms and an electronic decision making tool that is designed to encourage shared decision making. The studies suggest that using technology to enable people to monitor their own symptoms may improve treatment seeking. There was little evidence to suggest that an electronic tool to encourage shared decision making improved people's satisfaction with treatment decisions.

The current guideline recommendations state:

- explore the person's worries in order to jointly understand the impact of GAD
- explore treatment options collaboratively with the person, indicating that decision making is a shared process.

These recommendations are based on a qualitative literature review which highlighted the importance of talking with patients about their preferred treatments. The studies identified in this surveillance review are limited because of mixed populations and equivocal results but they add to the evidence on patient involvement in their own treatment identified during the 2015 surveillance review. They also highlight the potential for technology to encourage increased patient involvement in decisions about their own treatment, but alone they are not enough to impact recommendations.

New evidence is unlikely to impact on the recommendations.

Assessment and service delivery

Surveillance proposal

The section of the guideline on assessment and service delivery should not be updated.

Previous surveillance

No evidence was found for this section.

2020 surveillance summary

Collaborative care

One meta analysis (Muntingh et al. 2016) (7 RCTs, n=2105) pooled results for people with a range of anxiety disorders in a primary care setting. The study included RCTs that compared the effectiveness of care delivered by a primary care physician collaborating with, and supported by, at least one other professional with expertise in mental health (e.g. consultant psychiatrist), with care as usual. For all patients, collaborative care was superior to care as usual (CAU). In a subgroup analysis (5 studies) for patients with panic disorder, collaborative care resulted in greater reductions in anxiety compared with usual care.

One RCT (Mavandadi et al. 2018) (n=778) in community-dwelling older adults currently taking antidepressants or antianxiolytics for clinically significant mental health symptoms, compared the impact of telephone-delivered collaborative mental health care management plus symptom monitoring with symptom monitoring alone. Care management comprised measurement-based, software-aided mental health assessment and symptom monitoring and connection to community resources via telephone. At 3 months' follow-up, the care management group had reduced anxiety and depressive symptoms compared with symptom monitoring alone. The proportion of participants with GAD or details of drug prescribing in study arms at baseline and follow-up is not reported in the abstract.

Stepped care

Two RCTs (Rollman et al. 2017 and van der Aa et al. 2015) compared stepped care with CAU. One RCT (Mavandadi et al. 2018) investigated collaborative care in a primary care setting.

Rollman et al. (n=250 highly anxious patients) compared a telephone-delivered collaborative stepped care intervention with CAU. The intervention delivered by non-mental health professionals comprised: basic psychoeducation; assessment of preferences for pharmacotherapy; treatment response monitoring and liaison with primary care. At 12 months' follow-up patients reported significantly improved mental health related quality of life compared with CAU.

van der Aa et al. (2015) compared stepped care plus CAU with CAU alone in 265 patients aged 50 years and above with visual impairment and subthreshold depression and/or anxiety. The intervention, delivered by occupational therapists, social workers and psychologists comprised: watchful waiting, CBT-based guided self-help, problem solving treatment, and referral to a GP. At 24 months' follow-up the cumulative incidence of depressive and anxiety disorders was significantly less compared with usual care. Dropout rate was high (34.3%) but comparable with CAU.

Intelligence gathering

One topic expert provided feedback that older people and people from black and minority ethnic (BAME) groups found IAPT services unacceptable or difficult to access. No evidence was found that suggested IAPT services were unacceptable or difficult to access for BAME groups or older people. A second topic expert commented that CG113 should refer to the NICE guideline CG123 common mental health disorders recommendations about assessment and identification of people with GAD.

Impact statement

Accumulated evidence consistently reports stepped care is more effective than CAU for treating mental health disorders including anxiety and panic.

This is consistent with recommendation 1.2 which recommends stepped care for the treatment of GAD.

Two studies suggest that collaborative care is more effective than CAU in a primary care setting, particularly for people with panic disorder. An RCT reported that telephone-delivered collaborative care, that focussed on the monitoring of drug treatment response, reduced symptoms of depression and anxiety in an older US mixed mental health disorder population.

A meta analysis reported that collaborative care is effective in reducing the symptoms of anxiety in populations with mixed anxiety disorders. The included studies were assessed by the authors as being of medium to high-quality and included people with mixed anxiety disorders from the US, Germany and the Netherlands.

The guideline includes research recommendation 2.5 which addresses collaborative care. The research recommendation was included during guideline development because there was some evidence that a collaborative care approach involving GPs, other primary care practitioners and mental health professionals, can improve the uptake of evidence-based interventions and clinical and functional outcomes for people with GAD. These approaches had not been evaluated in primary care in the UK and the recommendation suggests an RCT in a UK primary care setting to address this gap in the evidence.

Studies identified during surveillance report conclusions from mixed disorder populations in non-UK settings and do not fully address this research recommendation.

Diagnosis is outside the scope of CG113 although it contains some recommendations on identification and assessment in step 1 care. NICE guideline CG123 common mental health disorders: identification and pathways to care contains detailed, evidence-based recommendations about identification and assessment of several conditions including GAD. It is

proposed to make a cross referral to CG123 from CG113 recommendations about GAD identification.

A topic expert commented that the trials evidence for CG113 used DSM diagnostic criteria and that clinicians should be made aware that treatment recommendations in CG113 strictly apply to GAD diagnosed using this system. This issue is acknowledged in the full guideline (see CG113 full guidance p. 17) which states “the GDG used DSM IV, rather than ICD-10 to define the diagnosis of GAD, because the evidence base for treatments nearly always uses DSM IV.” The guideline also notes that whilst DSM and ICD emphasise different diagnostic features (DSM emphasises worry, ICD emphasises somatic symptoms) it also says that there is overlap between these two diagnostic systems. For these reasons it is not proposed to amend recommendations to say that they strictly apply to DSM diagnosed GAD.

New evidence is unlikely to change guideline recommendations.

Low intensity psychological interventions

Surveillance proposal

The section of the guideline on low intensity psychological therapies should not be updated.

Previous surveillance

One Australian RCT was included in the 2012 evidence update. The 2015 surveillance review included 2 systematic reviews on media-based therapies and 13 RCTs on meditative therapies and media-based therapies. A full list of studies included in previous surveillance can be found in the 2015 surveillance review decision and 2012 evidence update documents. It was noted that the impact of the evidence on media-based treatments was limited by the unreported (in abstract) proportion of GAD or panic disorder patients in most included studies.

Meditative therapies

Evidence indicated that mindfulness-based therapy, with or without additional strategies, can improve outcomes in GAD diagnosed patients but was inconclusive. It was noted that CG113 does not currently recommend meditative therapies specifically but makes general provision for them to be offered as part of step 2 low intensity psychological interventions for GAD, within the stepped care model (recommendations 1.2.11-1.2.15)

Media-based (including computer based) treatments

Overall, evidence indicated that CCBT is effective compared with no intervention and was judged as being consistent with CG113 recommendations. One systematic review indicated that computerised CBT (CCBT) was equivalent to face-to-face CBT but a larger Cochrane Review concluded that face-to-face CBT is “probably clinically superior”. There was insufficient evidence to justify a change to the current recommendations to offer CCBT as a step 2 care option followed by CBT as a step 3 care option.

The evidence for guided versus unguided CCBT was equivocal, with neither approach demonstrating clear superiority. This is consistent with recommendation 1.2.11 step 2 of the stepped care model, which does not advise one approach over the other. It was noted during the 2015 surveillance review that research recommendation 2.2 remains ongoing because no RCTs comparing CCBT with bibliotherapy and wait list control were identified. However, it was further noted that the identified evidence had added to the evidence base for CCBT as a low intensity intervention, and that further evidence will be assessed at the next surveillance review point.

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Internet and computer-delivered therapies for people with GAD and mixed disorders

Three RCTs (Jones et al. 2016, Richards et al. 2016 and Dear et al. 2015) compared different types of internet delivered treatments (not described in abstract) with waiting list controls (WLC) in people with GAD. Jones (n=46)

found significant improvement in GAD symptoms in older people after guided internet delivered CBT (iCBT) compared with WLC. Conversely, Richards et al. (2016) (n=137) found no difference between iCBT and WLC; the abstract does not describe whether any therapist contact was involved in treatment. Dear et al. 2015 (n=338) compared transdiagnostic iCBT with disorder specific iCBT in people with GAD and panic disorder and found no difference in symptom reduction between approaches if delivered self-guided or therapist-guided.

Two systematic reviews also investigated transdiagnostic iCBT. A Cochrane Review (Olthuis et al. 2016) (38 studies (n=3214), including 5 studies with GAD populations and 8 with panic disorder populations) investigated the impact of guided transdiagnostic iCBT on anxiety symptoms in a population with mixed anxiety disorders compared with various controls. The review reported significant "clinically important" improvement in anxiety, improvement in disorder specific anxiety symptoms and non-disorder specific anxiety symptoms compared with WLC or an online discussion forum. There was no difference in the same outcome measures when therapist supported transdiagnostic iCBT was compared with face-to-face CBT. There was no difference for non-disorder specific anxiety symptoms when comparing guided with unguided iCBT. The proportion of people with GAD for each outcome measure is not specified in the abstract. The authors assessed the quality of included studies as low or very low.

A systematic review (Pasarelu et al. 2017) (19 RCTs, n=2952) investigated the effect of transdiagnostic and tailored iCBT on anxiety symptoms in a mixed population with anxiety and depression. Compared with various controls (not described in abstract), there were medium to large improvements in anxiety and QoL. but there was no difference in effects between transdiagnostic or disorder specific approaches.

A systematic review (Newby et al. 2016) (17 RCTs), of transdiagnostic CCBT in people with anxiety and depression, reported a reduction of anxiety symptoms compared with controls. This reduction was greater compared with

WLC (Hedges g=0.93) than with active controls (Hedges g=0.59) and CAU (Hedges g=0.37). The proportion of people with GAD is not specified in the abstract. An RCT (Rollman et al. 2018) (n=604 people with depression and anxiety) compared CCBT plus an online support group with CCBT alone and CAU. There were significant improvements in mood and anxiety for CCBT alone compared with CAU that persisted beyond 6 months but no difference in MHQoL, anxiety symptoms or mood between CCBT alone and CCBT plus an online support group at 6 months' follow-up.

One RCT (Berger et al. 2017) (n=139, including 36 people with a primary diagnosis of GAD and a further 22 people with a comorbid diagnosis of GAD) compared an unguided online programme comprising 6 modules based on the principles of CBT compared with WLC. For all participants, the online programme was more effective than WLC for reducing anxiety symptoms in all participants. The study also reports that 44.8% of participants with a diagnosis of GAD pre-treatment no longer fulfilled diagnostic criteria post-treatment.

Digitally delivered therapies for people with GAD and mixed anxiety disorders

Three systematic reviews compared smartphone delivered app therapies with controls. In patients with GAD (39 RCTs), Linardon et al. (2019) found a small improvement compared with controls (unspecified in the abstract), but no difference in improvement of panic disorder symptoms (3 RCTs). The study concludes that CBT-based apps and interventions that offered professional guidance or engagement reminders produced larger effects on multiple outcomes. Firth et al. (2017) (in a population with mixed anxiety disorders proportions unspecified in abstract) (9 RCTs, n=1837) found small improvements in anxiety symptoms compared with controls. Improvements were greater compared with WLCs than active controls. Domhardt (2019) (34 RCTs, n=3724) investigated internet and mobile-delivered interventions for anxiety in populations with mixed anxiety disorders. Internet and mobile-delivered therapeutic interventions (not specified in abstract) were superior to active controls (not specified in abstract) and guided therapies were superior to unguided in reducing symptom severity.

Attention bias modification therapy for people with GAD and mixed anxiety populations

Two RCTs (Dahlin et al. 2016 and Chau et al. 2019) investigated attention bias modification therapy (ABMT) in people with GAD. Chau (n=33) found no difference between ABMT and sham ABMT in reducing anxiety symptoms or attentional bias, whilst Dahlin (n=103) found significant reduction in anxiety symptoms in internet delivered guided ABMT compared with WLC. A systematic review (Linetzky et al. 2015) (11 RCTs, n=589) compared ABMT with active controls (not described in abstract). Anxiety symptoms and the proportion of participants meeting anxiety disorder diagnostic criteria were reduced. The proportion of patients with GAD or panic disorder included in the analysis is not reported in the abstract.

Intelligence gathering

One topic expert highlighted recent work on transdiagnostic psychological therapies in anxiety disorders and a second topic expert highlighted that there may be better evidence published investigating remote delivery of therapies. Evidence for these areas has been considered during this surveillance for both high and low intensity interventions and is described above and in the section on high intensity psychological interventions.

A large recently completed trial (n=2200) (REBOOT Notts) of an online non-facilitated peer support site for people with anxiety and depression called 'Big white wall' was identified. The results are due to publish 31 December 2019 and will be considered at the next surveillance timepoint.

Impact statement

Internet and computer-delivered therapies

Evidence suggests that CCBT including iCBT is more effective than WLC. CG113 recommends both guided and unguided low intensity psychological interventions as an option in step 2 treatment for GAD that has not improved after active monitoring. The evidence gathered during 2019 surveillance

considered alongside evidence from 2015 surveillance supports these recommendations.

There is some suggestion that guided iCBT or iCBT incorporating some therapist contact or support is more effective than unguided treatment. Evidence from 2015 surveillance found little evidence for a difference between guided and unguided approaches. Further evidence is required to establish the relative effectiveness of unguided compared with guided iCBT.

No evidence was found for a significant difference between transdiagnostic and disorder specific approaches for iCBT.

A large Cochrane Review reported that guided transdiagnostic iCBT is comparable with face-to-face CBT. However, this conclusion is based on studies judged by the authors to be of low to very low quality with mixed anxiety disorder populations and therefore this result must be interpreted with caution. CG113 recommends therapist delivered CBT as part of step 3 care for GAD with marked functional impairment. Currently there is little evidence to suggest iCBT or CCBT is as effective as therapist delivered CBT. Based on this evidence and evidence found for therapist delivered CBT (see high intensity psychological interventions) recommendation 1.2.18 CBT for people with GAD should be delivered by trained and competent practitioners, remains valid.

No evidence was found for iCBT or CCBT that is likely to change recommendations.

Digitally delivered therapies

Evidence suggests interventions delivered via apps produce improvements in anxiety symptoms compared with WLCs. There is some evidence that digital technologies that incorporate elements of human guidance e.g. engagement with health professionals, produce a bigger effect. This is consistent with evidence for guided iCBT and with CG113 recommendation 1.2.11 which accommodates both guided and unguided approaches in a variety of delivery modes, depending on patient preference. This evidence adds to the potential

range of remote delivery modes for unguided and guided therapies but is currently not enough to make a specific recommendation.

Attention bias modification therapy

Evidence for effectiveness of ABMT is equivocal. Studies reported no difference compared with sham ABMT in people with GAD but superiority over WLC for internet delivered ABMT and standard ABMT in populations with mixed anxiety disorders. ABMT is based on the theory that people with anxiety disorders have attention biases towards threatening information and stimuli and uses strategies to enable people to modify these biases.

CG113 does not currently recommend ABMT or accommodate it within its recommendations. The evidence identified is equivocal and further evidence for this treatment is needed before an assessment of its impact on recommendations can be made.

New evidence for ABMT is unlikely to impact recommendations.

High intensity psychological interventions

Surveillance proposal

The section of the guideline on high intensity psychological interventions should not be updated.

Previous surveillance

The 2012 evidence update included one RCT and 2 systematic reviews of RCTs of various therapy types. Four systematic reviews, 5 RCTs and 3 meta analyses were identified during 2015 surveillance and investigated a number of therapy types. A full list of studies included in previous surveillance can be found in the 2015 surveillance review decision and 2012 evidence update documents. Overall, the evidence supported the effectiveness of CBT and was consistent with the CG113 recommendations. Data from studies of populations with mixed anxieties suggested that acceptance and commitment therapy, an adaptation of CBT, is as effective as CBT for GAD. There was

some evidence that telephone CBT may be effective for people over 60 years compared with information only CBT and that face-to-face CBT may be less effective than active controls in treating older people. It was noted that further evidence was needed for both telephone CBT and for the effectiveness of CBT in older people compared with working age adults in order to assess the impact on recommendations. Evidence from 2 systematic reviews demonstrated that psychodynamic therapies were not effective in GAD and panic disorder which is consistent with CG113 recommendations.

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CBT for people with GAD and mixed anxiety disorders

Five systematic reviews (Montero-Marin et al. 2018; Carpenter et al. 2018; Cuijpers et al. 2016; Watts et al. 2015 and Zhang et al. 2019) and a Cochrane Review (Ori et al. 2015) (see table 1) compared CBT with various comparators for mixed disorder populations, and reported:

- CBT is superior to relaxation therapy based on pooled effects estimates across all anxiety outcomes for a mixed anxieties population but that the therapies are equivalent for outcomes in GAD and panic disorder populations.

- CBT is superior to placebo tablets based on pooled effects estimates for disorder symptoms and anxiety symptoms across all anxiety outcomes for a mixed anxieties population.

- CBT has significant treatment effects compared with controls on depressive and anxiety disorders treated in a primary care setting.

- CBT augmented with d-cycloserine was not superior to CBT plus placebo for pooled anxiety estimates at treatment endpoint or 12 months' follow-up.

Metacognitive therapy and augmented psychotherapies for people with GAD.

Two RCTs compared CBT with metacognitive therapy and with augmented CBT in populations with GAD.

Nordhal et al. (2018) (n=81) compared metacognitive therapy with CBT and WLC and found both were effective in reducing anxiety compared with WLC but that metacognitive therapy was significantly more effective than CBT and led to higher recovery rates (65% v. 38%). Effects were maintained at 2 years' follow-up. Westra et al. (2016) (n=85) compared motivational interviewing plus CBT (MI-CBT) with CBT alone. It found that in the MI-CBT group clients demonstrated a steeper rate of worry decline and that their odds of meeting GAD diagnostic criteria were 5 times less than with CBT alone at 12 months' follow-up.

One RCT (Delgadillo et al. 2018) (n=2233) investigated the impact of an outcome feedback technology on psychotherapy outcomes for anxiety and depression. The technology comprised an automated computer algorithm that alerted therapists to patients not meeting clinical targets and primed the therapist to review these patients. The study compared psychotherapy (not described in abstract) plus feedback technology with psychotherapy only. At 1 year of follow-up, patients in the feedback technology group had less severe anxiety and depression symptoms than those in the psychotherapy group. The proportion of participants with GAD or panic disorder is not reported in the abstract.

Older adults with GAD

A systematic review (Kishita et al. 2017) (15 RCTs, n=770) investigated the effect of CBT in both working age adults with GAD and older adults. For both groups of adults, CBT was effective compared with controls and there was no significant difference in levels of anxiety post-treatment for either group. There was a large effect size in working age adults (Hedges g=0.94) compared with a medium effect size in older adults (Hedges g=0.55), suggesting slightly reduced efficacy in older adults. The authors noted that the difference in effect

size may have been attributable to 2 studies included in the working age adults group using types of CBT (acceptance and commitment therapy and metacognitive therapy) that produced very large effect sizes and were not included in the older people group. However, they also noted that none of the older people studies used an intention-to-treat design and this could have resulted in the effectiveness for this group being over estimated. The authors conducted a content analysis and concluded that whilst the CBT protocols had a robust therapeutic approach, they did not incorporate gerontological evidence which would have improved their age appropriateness.

Two related RCTs (Brenes 2015 and Brenes 2017) compared the impact of telephone-delivered CBT with telephone-delivered non-directive supportive therapy (n=141) in older people with GAD. Telephone-delivered CBT improved general worry and GAD symptoms at 4 months and anxiety symptoms at 15 months compared with non-directive support.

Transdiagnostic therapeutic approaches for people with mixed anxiety disorders

Two RCTs investigated transdiagnostic therapeutic approaches in populations with mixed anxiety disorders. Barlow et al. (2017) (n=223) compared the unified protocol for transdiagnostic treatment of emotional disorders with single disorder protocols and with WLC. At treatment completion, the unified protocol improved clinical severity rating compared with WLC. There was no difference between the unified and single disorder protocols at 6 months' follow-up. Riccardi et al. (2017) (n=28) compared 'F-SET', a brief transdiagnostic treatment, with WLC. F-SET treatment comprised 5 sessions and focussed on the elimination of anxiety maintaining behaviours and cognitive strategies common to people with a range of anxiety disorders including GAD and panic disorder. F-SET significantly reduced anxiety and depression symptoms compared with WLC. The proportion of participants with GAD or panic disorder is not stated in the abstract.

Medication-resistant populations with mixed anxiety disorders

A secondary analysis of data from the Coordinated Anxiety Learning and Management (CALM) trial (Campbell-Sills 2016) (n=214) compared the effects of CBT on medication-resistant anxiety with CAU and with CBT plus medication management (not described in abstract) in primary care patients with mixed anxiety disorders including GAD and panic disorder. Compared with CAU, CBT-only treatment was associated with greater response at 6 months' and 12 months' follow-up and greater remission at 6, 12 and 18 months. Fifty eight percent of CBT-only patients responded to treatment and 46% remitted during the study. There was no difference in outcomes between CBT-only and CBT plus medication management groups. The proportion of participants with GAD or panic disorder is not reported in the abstract.

Mindfulness therapy for people with GAD and with mixed mental health disorders with symptoms of anxiety

One RCT (Wong et al. 2016) (n=182) compared mindfulness-based cognitive behaviour therapy with CBT-based psychoeducation and CAU in people with GAD. At 5 months' follow-up both active groups had reduced anxiety symptoms compared with CAU but when compared with each other there was no significant difference in anxiety symptom reduction.

Two systematic reviews investigated mindfulness in populations with various mental health disorders. Gotink et al (2015) (115 studies, including 4 studies with anxious populations (n=2525)) reports a reduction in anxiety symptoms compared with WLC for mindfulness-based stress reduction and mindfulness-based cognitive therapy. Blanck et al (2018) (18 studies, n=1150) also reports a reduction for stand-alone mindfulness therapies compared with unspecified (in abstract) controls.

Relaxation therapies for people with mixed anxiety disorders

A systematic review (Montero-Marin 2018) (50 studies, n=2801) was identified that investigated whether relaxation therapies were effective in treating anxiety symptoms compared with CBT in a population with mixed anxiety disorders. For anxiety symptoms across all anxiety disorders it found CBT

was superior (number needed to treat (NNT)=7). For GAD and panic disorder there was no significant difference between therapies. The proportion of people with GAD or panic disorder is not specified in the abstract.

Intelligence gathering

One topic expert stated that the relative lack of UK experts to train psychological therapists in state-of-the-art interventions developed outside the UK posed barriers to accessing these services. No evidence was found suggesting that access to therapies was being adversely impacted due to a lack of trained therapists or that health services were not providing access to the most current therapies.

A second topic expert highlighted that there was new evidence on transdiagnostic approaches to psychotherapies. A third topic expert highlighted the ongoing Physical Exercise Augmented CBT for GAD (PEXACOG) trial. No published evidence was found for CBT augmented with exercise. The PEXACOG trial is due to report after December 2021 and its results will be considered at the next surveillance time point. New evidence for exercise as a stand-alone therapy is described in the pharmacological and physical interventions section.

An ongoing trial comparing emotion-focussed therapy with CBT for people with GAD was identified. Its results are due to be published in December 2020 and will be considered at the next surveillance timepoint.

Impact statement

Cognitive behavioural therapy (CBT)

CG113 recommendation 1.2.17 states that if a person with GAD chooses a high intensity psychological intervention, they should be offered either CBT or applied relaxation CBT. Evidence identified in the 2019 and 2015 surveillance reviews indicates that these are still the most effective high intensity psychological therapies for treating GAD. Some advantage was found immediately post-treatment for a transdiagnostic approach to CBT compared

with a disorder specific approach, but outcomes were equivalent at 6 months' follow-up.

CG113 recommendation 1.2.16 states: '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 or drug treatment) is better'. Evidence from a single study suggests CBT can be effective with populations who have not responded to pharmacological therapies. but is insufficient to impact the recommendations.

Evidence suggests that whilst face-to-face CBT reduces anxiety in older adults it may be less effective in this group than in adults of working age. This finding may result from a difference in effectiveness between types of CBT rather than any age-related differences. Further limited evidence suggests that therapist delivered telephone CBT is effective for this subgroup but does not directly compare working age and older adults. Currently CG113 does not differentiate this population nor does recommendation 1.2.18 preclude the use of telephone CBT where it is judged appropriate. Overall, evidence for telephone CBT is not enough to make a specific recommendation for its use with older people.

New evidence found for CBT is unlikely to change recommendations

Metacognitive therapy and augmented psychotherapies

There is limited evidence from a single RCT that metacognitive therapy leads to higher recovery rates than CBT and that these are maintained in the long-term. Metacognitive therapy is a type of CBT that focusses on, and attempts to modify, people's beliefs about worry. CG113 recommendation 1.2.16 does not specify a specific type of CBT and this evidence adds to the evidence base for CBT but is insufficient to consider adding metacognitive therapy to the recommendation.

Evidence suggests that augmenting psychotherapies like CBT with various techniques and components can enhance its effectiveness. Incorporating computer algorithm feedback loops and motivational interviewing components

seem to improve CBT effectiveness. CG113 is not prescriptive about the components of CBT and this evidence supports current recommendations.

New evidence for metacognitive therapy and augmented psychotherapies is unlikely to impact recommendations.

Mindfulness therapies

CG113 does not currently explicitly recommend mindfulness but as noted during 2015 surveillance it does make provision for this as a low intensity therapy, based on patient preference, as part of step 2 care recommendations.

There is limited evidence that mindfulness as a stand-alone therapy is effective in reducing stress and anxiety. The evidence comes from populations with both mixed anxiety disorders and mental health disorders associated with symptomatic anxiety which makes it difficult to draw conclusions about its effectiveness for GAD.

There is evidence that mindfulness-based CBT is comparable with CBT-based psychoeducation and superior than CAU and this is consistent with recommendation 1.2.17 for step 3 care which recommends CBT as a high intensity psychological intervention. Recommendation 1.2.18 makes provision for variants of CBT if it is based on the treatment manuals used in the clinical trials of CBT for GAD and delivered by trained and competent practitioners.

Overall this evidence adds to the evidence found during 2015 surveillance for meditative therapies but considered as a whole it is not enough to impact recommendations.

Relaxation therapies

Limited evidence suggests there is no difference between relaxation therapy and CBT for people with GAD or panic disorder, but that CBT is superior when effectiveness is based on pooled effects estimates from mixed anxiety disorder populations. This is consistent with and supports recommendation

1.2.17 If a person with GAD chooses a high intensity psychological intervention, offer either CBT or applied relaxation.

New evidence for relaxation therapies is unlikely to change recommendations.

Overall, new evidence identified for high intensity psychological therapies is unlikely to change recommendations.

Pharmacological and physical interventions

Surveillance proposal

The section of the guideline on pharmacological and physical interventions for generalised anxiety disorder should not be updated.

Previous surveillance

Previous surveillance identified 22 RCTs 3 systematic reviews and 1 meta analysis investigating the use of antipsychotics, antidepressants, anticonvulsants, herbal treatments and physical interventions including acupressure and electrotherapy. The full list of references can be seen in the 2015 surveillance review. Most of the pharmacological studies recruited people with GAD. Physical intervention studies were largely carried out with mixed anxiety and mental health disorder populations. The evidence was judged to be consistent with CG113 recommendations.

Antidepressants

The evidence identified in the 2015 surveillance review was consistent with recommendation 1.2.22. Evidence of the effectiveness of vortioxetine, was inconsistent and was judged unlikely to impact on recommendations. It was noted by topic experts that the patent for the selective serotonin uptake inhibitor (SSRI) escitalopram expired on 31st May 2014 and any reductions in the cost of the drug might impact sertraline's cost-effectiveness profile. The impact of this change is considered alongside new evidence from 2019 surveillance in the impact statement for antidepressants.

Pregabalin

Evidence from 2 RCTs suggested that adjunctive pregabalin can be effective for patients who have not optimally responded to previous or prospective antidepressant monotherapies but the evidence was assessed as unlikely to impact on recommendation 1.2.24, which recommends pregabalin only if the person cannot tolerate SSRIs or SNRIs.

Quetiapine

Some new evidence in the 2015 review suggested that quetiapine monotherapy improves the symptoms of GAD compared with placebo and some limited evidence suggested it was no more effective than antidepressants in the treatment of GAD (Khan et al 2013). Evidence was also found that suggested people taking quetiapine are more likely to discontinue treatment due to adverse effects compared with placebo or active comparators. Other limited evidence suggests that adding quetiapine to an antidepressant does not improve symptoms in GAD that has not responded to the antidepressant alone. This evidence was judged to support the CG113 recommendations. It was noted that quetiapine was not included in the evidence summary for CG113 as it was the subject of a technology appraisal. A cross referral to NICE evidence summary generalised anxiety disorder: quetiapine (ESOUM 12) was made which provides evidence-based advice about quetiapine's effectiveness and tolerance.

Physical interventions and herbal preparations

No conclusive evidence was found in the evidence update or 4 year surveillance review for physical or herbal interventions. The 2015 surveillance review concluded that further research is needed on physical interventions before any potential impact on CG113 recommendations can be considered.

2020 surveillance summary

Pharmacological interventions for people with GAD and mixed disorder populations

See table 2

Antidepressants for people with GAD

Eight studies (Chen et al. 2019; de Vries et al. 2018; Fountoulakis et al. 2019; Fu et al. 2016; Li et al. 2017; Slee et al. 2019; Stein et al. 2017; Zhang et al. 2016) reported that for the treatment of GAD:

- Escitalopram, venlafaxine and duloxetine are superior to placebo with relatively good acceptability (Slee et al. 2019) (89 studies, n=25,441). One study reports treatment discontinuation rates with duloxetine are significantly greater than placebo due to a higher rate of adverse events (Li et al. 2019 (8 studies, sample size not stated in abstract).

- Mirtazapine, sertraline, fluoxetine, buspirone, and agomelatine are effective and well tolerated but these findings are limited by small sample sizes in the studies (Slee et al. 2019 (89 studies) (n=25,441)).

- Paroxetine reduces anxiety symptoms more than placebo but is poorly tolerated.

- Vortioxetine (2, 5 and 10 mg/day) is no more effective than placebo and is associated with headache and nausea.

- Venlafaxine XR (extended release) is superior to placebo for treating anxiety and inducing remission but -caused greater treatment discontinuation due to adverse events. No difference in treatment discontinuation was found when all-cause discontinuation was considered.

- Agomelatine (10 mg and 25 mg) is superior to placebo for reducing symptoms of anxiety.

- One study (Batelaan et al. 2017) reported that people with mixed anxiety disorders who discontinued antidepressants up to one year after first taking them were at higher risk of relapse compared with those who continued to take them.

Pregabalin for people with GAD

- Two studies (Generoso et al. 2017 and Slee et al. 2019) found that pregabalin is more effective than placebo. Generose reported drop out rates comparable with placebo whilst Slee described pregabalin as having “acceptable tolerability”.

- One study of people with GAD comorbid with unipolar depression (Fountoulakis et al. 2019) found no difference in effectiveness between escitalopram plus pregabalin, 75-600 mg/day compared with escitalopram plus placebo, following initial non-response to escitalopram.

- Anticonvulsants (type unspecified in abstract, Chen et al. 2019) are more effective than placebo in GAD populations.

Benzodiazepines for people with GAD

- Two studies (Chen et al. 2019 and Slee et al. 2019) reported that benzodiazepines are more effective than placebo but Slee et al. (2019) reported that they are poorly tolerated in GAD populations.

Herbal preparations for people with GAD

Five studies (Baric et al. 2018; Jafarnia et al. 2017; Keefe et al. 2016; Mao et al. 2016 and Hieu et al. 2019) investigated the effects of herbal preparations and reported:

- A modest effect for kava kava in reducing anxiety compared with placebo (Baric et al. 2018).

- Sertraline plus saffron is superior to sertraline plus placebo in reducing anxiety symptoms (Jafarnia et al. 2017)

- A 2 phase RCT (n=179) described in 2 studies (Keefe et al. and Mao et al.) reported a 51.9% response rate to therapy with chamomile extract (1,500 mg). Responders were then randomised to receive a further 26-week course of chamomile or placebo. Relapse rates were higher in

the placebo group compared with the chamomile group (not significant). Time to relapse was 11.4 weeks in the chamomile group and 6.3 weeks in the placebo group. Anxiety symptoms were significantly lower in the chamomile group compared with the placebo group at 8 weeks' follow-up.

- One study (Liu et al. 2018) reported no difference in effectiveness between probiotics and placebo in a population with mixed anxiety disorders.

- One study (Sarris et al. 2019) reported that L-theanine, 450-900 mg, as an adjunct to antidepressant treatment was not superior to an antidepressant plus placebo in people with GAD. One study (Liu et al. 2018) reported no difference in effectiveness between probiotics and placebo in a population with mixed anxiety disorders.

Quetiapine in people with GAD

In a systematic review and network meta analysis (89 studies, n=25,441) Slee et al. 2019 reported that quetiapine had the largest effect on anxiety symptoms of all drug classes in the analysis (antidepressants and anticonvulsants) compared with placebo but was poorly tolerated.

Other drug classes in GAD and mixed disorder populations

- Two studies (Durgam et al. 2016 and Gommoll et al. 2015) with GAD populations reported vilazodone, 20-40 mg, although superior to placebo, has a low response rate and small effect size (number needed to treat =10). Vilazodone was poorly tolerated and nausea and diarrhoea were common adverse effects.

- One study (Chen et al. 2019) reported that azapirones are superior to placebo in people with GAD.

- One study (Syunyakov 2016) compared afobazole with diazepam for treatment of GAD and adjustment disorder. After 30 days of treatment afobazole achieved a greater reduction in anxiety compared with

diazepam. Ten days after treatment completion, withdrawal syndrome was not observed in the afobazole group but was observed in 38% of the diazepam group.

Physical interventions for people with GAD and mixed anxiety disorders

Acupuncture for people with GAD

Two RCTs investigated the use of acupuncture in people with GAD. Mak et al. (2019) (n=80) compared electroacupuncture with sham electroacupuncture in relieving anxiety and bowel symptoms in Chinese adults with comorbid GAD and irritable bowel syndrome. It found no significant difference between treatment arms for the primary outcome measure of anxiety. Xu et al. (2016) (n=60) compared acupuncture of the scalp emotional zone (using a technique known as long retention of needles) plus buspirone with buspirone only. The study found statistically significant within group treatment difference in both groups, a significant between group difference post-treatment and significantly different recurrence between treatment group (20.0%) and control (42.1%).

Transcranial magnetic stimulation for people with GAD

One RCT (Dilkov et al. 2017) (n=40) compared repetitive transcranial magnetic stimulation (rTMS) with sham rTMS in people with GAD. It found rTMS was superior to sham rTMS and levels of anxiety were maintained at 2 and 4 weeks' follow-up.

Exercise for people with mixed anxiety disorders

Two systematic reviews investigated the effect of exercise on anxiety in people with mixed anxiety disorders.

Aylett et al. (2018) (15 studies, 9 with participants with diagnosed anxiety disorders, 6 with participants with high anxiety) (n=675) reported aerobic exercise reduces anxiety compared with WLC (small to moderate effect size) and high intensity exercise has a greater effect than low intensity exercise,. The proportion of people with GAD included in the pooled estimate is not specified in the abstract.

Stubbs et al. (2017) (6 studies) n=262) reported exercise (form not described in abstract) significantly decreased anxiety compared with controls (not specified in the abstract) with a moderate effect size. The proportion of people with GAD included in the pooled estimate is not specified in the abstract.

Yoga and massage therapy for people with mixed anxiety disorders

Two systematic reviews and one RCT investigated the effect of yoga on anxiety; the proportion of people with GAD or panic disorder is not specified in the abstract. Cramer at al. (2018) (8 studies n=319) reported that yoga produced small, short term effects in anxiety reduction compared with no treatment and large effects compared with active comparators. These effects on anxiety were not observed in people with disorders diagnosed using DSM, they were only observed in patients diagnosed by other methods, and for individuals with elevated levels of anxiety without a formal diagnosis. Hofmann et al. (2016) (11 studies, n=501) found that Hatha yoga is superior to WLC in reducing anxiety and that treatment efficacy is associated with total hours practised and level of anxiety. The diagnostic status of the participants in this study is not reported in the abstract.

A 6-week RCT (Rapaport et al. 2016) (n=40) found that although Swedish massage therapy and a light touch massage control both reduced anxiety at 3 weeks' follow-up the Swedish massage therapy was significantly more effective.

Intelligence gathering

Pharmacological interventions

Antidepressants

Two topic experts noted that the cost-effectiveness profile of sertraline may have changed as a result of the availability in the UK of the SSRI escitalopram which came off patent in May 2014. One topic expert commented that escitalopram is associated with QT-interval prolongation: see MHRA drug safety update (December 2011). A second topic expert noted that the patent for the SNRI duloxetine, licensed for GAD, had expired.

One topic expert commenting on the findings of a systematic review and network meta analysis by Slee et al. (2019) (conclusions outlined above) noted that the findings were very similar to the network meta analysis produced during CG113 development. The topic expert noted that the study adds to the evidence that SSRIs and SNRIs are generally effective and well tolerated but paroxetine and venlafaxine are more likely to result in treatment discontinuation.

Following stakeholder feedback NICE guideline CG90 depression: recognition and management antidepressant withdrawal recommendations were updated in 2019. Section 1.9.2 stopping and reducing antidepressants provides detail about symptoms associated with the sudden stopping of antidepressants; dose reduction and how to deal with withdrawal and discontinuation symptoms. CG113 contains several recommendations about antidepressant withdrawal that are affected by these changes. This issue is addressed in the antidepressant impact statement below.

Pregabalin

A topic expert commenting on the findings of Slee et al. (2019) (conclusions outlined above) suggested evidence from this study adds to existing evidence for the effectiveness of pregabalin for treating GAD. The topic expert suggests this adds to the case for pregabalin to be considered as a second line drug treatment rather than a third line treatment (following ineffective SSRI and SNRI treatment) currently recommended by CG113 recommendations 1.2.22 to 1.2.24. The topic expert notes that the British association of psychopharmacology (BAP) guidelines (2014) for anxiety disorders, PTSD and OCD currently recommends pregabalin as a second line option.

A second topic expert felt that the prescribing of pregabalin for anxiety seemed to be increasing but could not provide evidence for this.

The MHRA published a drug safety update (MHRA drug safety update Pregabalin (Lyrica), gabapentin (Neurontin) and risk of abuse and dependence: new scheduling requirements from 1 April (April 2019) for

pregabalin notifying of its reclassification as a class C drug due to evidence of abuse and dependence. NICE have added a footnote to CG113 recommendation 1.2.24 to draw attention to this safety concern.

Physical interventions

No intelligence about physical interventions was identified.

Impact statement

Pharmacological interventions in people with GAD

Antidepressants

Accumulated evidence supports the use of SSRIs and SNRIs for the treatment of GAD. Studies report that escitalopram, venlafaxine, duloxetine, mirtazapine, sertraline, fluoxetine, buspirone, and agomelatine are superior to placebo for reducing anxiety and are relatively well tolerated. There is evidence from two studies that duloxetine and venlafaxine XL are associated with greater discontinuation of treatment due to adverse events than placebo. There is evidence that paroxetine is effective in reducing anxiety but is poorly tolerated.

CG113 recommendation 1.2.22 states ‘if a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Consider offering sertraline first because it is the most cost-effective drug.’ Recommendation 1.2.23 says if sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI). No evidence was found for antidepressants that contradicts recommendations to offer an SSRI or SNRI nor was any new evidence found that suggested a specific SSRI or SNRI greatly outperformed other drugs in those classes with respect to tolerability and effectiveness.

Escitalopram came off patent in May 2014 and is available as a low-cost generic and this potentially impacts the part of recommendation 1.2.22 to consider offering the SSRI sertraline. The cost-effectiveness of pharmacological interventions relative to each other was considered by the

original CG113 guideline development group to be an area of significant resource implications. The recommendation to consider offering sertraline was made following a network meta analysis and economic analysis which compared 6 drugs: duloxetine, escitalopram, paroxetine, pregabalin, sertraline and venlafaxine XR. The drugs were compared with each other in terms of their response, tolerability and cost-effectiveness. Sertraline is recommended because it had the second highest probability of a treatment response (after duloxetine), was the least likely to result in discontinuation, and was the most cost-effective.

The new evidence suggests that sertraline remains well tolerated and effective in treating anxiety and despite escitalopram's price reduction sertraline remains the cheaper of these two SSRIs. Additionally, except for paroxetine which evidence suggests is poorly tolerated, sertraline still remains the cheapest drug considered in CG113's economic analysis.

As sertraline is effective in treating anxiety, is well tolerated and remains cost-effective the second part of recommendation 1.2.22 to consider offering sertraline remains valid.

Limited evidence suggests agomelatine is effective for treating GAD. This drug is only licensed for major depression and is not currently recommended by NICE (see NICE technology appraisal TA231). This limited evidence is unlikely to impact recommendations at this time.

NICE guideline CG90 depression: recognition and management recommendations on antidepressant withdrawal were updated in 2019 resulting in inconsistency between CG113 and CG90 recommendations in this area. NICE is aware of this discrepancy and will address this issue systematically across all guidance impacted by changes to CG90.

Two future NICE guidelines were identified that may impact CG113 antidepressant and other pharmacological recommendations. Firstly, CG90 is currently being updated to ensure currency of its remaining recommendations. Secondly, NICE is developing guidance on safe prescribing and withdrawal

management of prescribed drugs associated with dependence and withdrawal (November 2021). The impact of these developments on CG113 will be assessed at the next surveillance timepoint.

New evidence for antidepressants is unlikely to change recommendations.

Pregabalin

Recommendation 1.2.24 states that if the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. This recommendation includes a footnote to an MHRA drug safety alert warning of pregabalin's status as a class C controlled substance and the risk of dependency associated with it.

Accumulating evidence supports pregabalin's effectiveness and tolerability and this was noted by topic experts during this surveillance. No evidence indicates that pregabalin should be considered as a second line treatment ahead of SNRIs. A large network meta analysis indicates pregabalin may be of comparable effectiveness to SSRIs and SNRIs but this needs to be balanced against the risk of dependency. Considering all of these factors recommendation 1.2.24 recommending pregabalin as a third line pharmacological treatment is assessed as still being valid.

Benzodiazepines

Evidence was found that benzodiazepines are more effective than placebo in treating anxiety and evidence from one study suggests it may be poorly tolerated compared with placebo. Recommendation 1.2.25 states 'do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short term measure during crises.' This recommendation is based on evidence for the risk of dependence commonly associated with benzodiazepines. No new evidence was identified that contradicts this assessment of risk or that benzodiazepines significantly outperform other treatments, therefore there is no impact on this recommendation.

Herbal preparations

Evidence from 2 studies suggests that chamomile may be effective in reducing anxiety compared with placebo. One study reported a reduction in anxiety compared with placebo after both study arms had received an initial 8-week dose of chamomile, a second showed a reduction in anxiety symptoms at 8 weeks compared with placebo.

Currently CG113 does not contain any recommendations about herbal preparations but includes research recommendation 2.4 is chamomile/ginkgo biloba more effective than placebo in increasing response and remission rates and decreasing anxiety ratings for people with GAD? This recommendation is included as the evidence base for chamomile was identified as being very small at the time of guidance development by the guideline development committee.

The research recommendation requires a double-blind comparison with placebo and assessment of anxiety post-treatment and at 12 months' follow-up. Whilst new evidence is promising for chamomile it falls short of answering the question fully as data on the long-term effects of chamomile on anxiety symptoms are required. Both studies use 1,200 mg doses of chamomile which is larger than the standardised dose of 220-1,100 mg recommended by the research recommendation. The study results add to the evidence base for chamomile but are insufficient to fully address the research question and therefore research recommendation 2.4 still stands. Further evidence for the effectiveness of chamomile is required.

Evidence from a single study suggests saffron plus sertraline is more effective than sertraline alone in reducing anxiety. CG113 does not currently recommend saffron or any other herbal preparation for the treatment of GAD as there is limited evidence for its effectiveness. Whilst this result is promising for saffron as an add-on therapy to an SSRI it is limited by the size of the trial (n=40). Further evidence for saffron's effectiveness is needed from larger trials before an assessment of its impact on recommendations can be made.

There is also limited evidence that kava kava is more effective than placebo in reducing anxiety. This is based on pooled data from a meta analysis assessed by the authors as being highly heterogenous and for which the result is not statistically significant.

Quetiapine

A large network meta analysis (Slee et al. 2019) reported that quetiapine had the largest effect on the Hamilton anxiety subscale compared with placebo of any the 21 active treatments considered but that it was poorly tolerated compared with placebo. This study provides some evidence that quetiapine may be more effective than antidepressants in reducing symptoms of anxiety but adds to the evidence that it is poorly tolerated.

CG113 recommendation 1.2.26 says do not offer an antipsychotic for the treatment of GAD in primary care The CG113 evidence review for antipsychotics concluded that there was very limited evidence for the effectiveness of antipsychotics as an augmentation therapy and that they are associated with adverse events. It was the judgement of the development group that antipsychotics should not be offered in primary care as stand-alone or augmentation treatment as this would require specialist expertise. Conclusions from this this recent network meta analysis support this judgement.

Recommendation 1.2.26 cross refers to the NICE evidence summary on generalised anxiety disorder: quetiapine which concludes that there is some evidence that quetiapine monotherapy improves the symptoms of GAD compared with placebo but is not more effective than antidepressants or as an adjunct to antidepressants following antidepressant non-response. It also highlights that quetiapine is more likely to cause adverse events leading to treatment discontinuation compared with placebo or active comparators. The network meta analysis potentially updates this conclusion by suggesting that quetiapine may be more effective than antidepressants. It is proposed to remove the cross referral to quetiapine evidence summary as some of the information it contains is now out of date.

The accumulating evidence that the antipsychotic quetiapine is poorly tolerated and only limited evidence for its effectiveness compared with antidepressants means that CG113 recommendation 1.2.26 remains valid.

Other drug classes

Some limited evidence for effectiveness was found for 3 other drugs: vilazodone; afobazole and azopirones. These drugs are currently unlicensed in the UK for any condition so there is no impact on recommendations in this guideline.

New evidence for pharmacological interventions is unlikely to impact recommendations.

Physical interventions

Acupuncture

Evidence for acupuncture was limited by the number of studies and by the difficulty in judging their relevance to a UK population. Two studies were found for different types of acupuncture, one found no difference between electroacupuncture and sham electroacupuncture whilst another found that long needle retention was effective as an adjunct to buspirone treatment in people with GAD. Buspirone is not generally used for GAD and based on this and the study's publication in the Shanghai journal of acupuncture and moxibustion it is likely this study was conducted in China and is of questionable relevance to a UK population.

Currently the guideline does not recommend acupuncture for the treatment of GAD. New evidence for acupuncture is limited and unlikely to impact on recommendations.

Transcranial magnetic stimulation

A single small RCT (n=40) reported TRMS reduced anxiety symptoms compared with sham TRMS. CG113 does not currently recommend TCMS and new evidence is unlikely to impact recommendations. Further evidence is

required before a full assessment of TRMS's impact on recommendations can be made.

Exercise

Evidence suggests exercise reduces anxiety and high intensity exercise produces a larger effect. The guideline does not currently recommend exercise due to the availability of good quality evidence and has a research recommendation 2.3 addressing this which asks: for people with GAD who are ready to start a low intensity intervention, what is the clinical effectiveness of physical activity compared with waiting list control?

This evidence is relevant to research recommendation 2.3 but does not fully answer the research question. The recommendation specifically seeks to address an evidence gap for those with GAD and the studies are with people with mixed anxiety disorders. The recommendation also recommends an RCT design with people stepping up to a low intensity intervention. Neither of these studies (both systematic reviews) report (in their abstracts) the treatment status of participants. For these reasons the research recommendation remains valid.

Yoga and massage therapy

Evidence suggests yoga is effective for state anxiety (i.e. feelings of anxiety not caused by an anxiety disorder) but less effective in reducing symptoms in people with clinically diagnosed anxiety disorders. The guideline does not recommend yoga and limited evidence for its effectiveness in reducing state anxiety is unlikely to change current recommendations.

Evidence from a small RCT suggests massage therapy is effective in reducing anxiety and that Swedish massage therapy in particular is effective. The guideline does not currently recommend massage therapy and this small amount of new evidence on its own is unlikely to change recommendations. Further evidence for the effectiveness of massage therapies in reducing anxiety is required before a full assessment of its impact on recommendations can be made.

New evidence for physical interventions is unlikely to impact recommendations.

Principles of care for people with panic disorder

Surveillance proposal

No new information on principles of care for people with panic disorder was identified at any surveillance review.

Previous surveillance

No intelligence was identified for this section.

2020 surveillance summary

No new evidence was found for this section.

Intelligence gathering

No new key evidence was found for this section

Impact statement

No evidence or intelligence was identified

Computerised cognitive behavioural therapy for panic disorder

Surveillance proposal

The section of the guideline on cognitive behavioural therapy for panic disorder should not be updated.

Previous surveillance

2015 surveillance identified 1 meta analysis and 5 RCTs that investigated internet-based CBT. A full list of included studies can be found in the 2015 surveillance decision document. The studies recruited mixed populations and reported inconsistent results. In the absence of a high-quality systematic review the evidence was assessed as unlikely to impact on CG113

recommendations. Research recommendation 2.6 The clinical and cost effectiveness of two CBT-based low-intensity interventions (CCBT and guided bibliotherapy) compared with a waiting-list control for the treatment of panic disorder was assessed as still valid.

2020 surveillance summary

Four RCTs (Allen et al. 2016 (n=63); Ciuca et al. 2018 (n=111); Mathiason et al. 2016 (n=47) and Oromendia et al. 2016 (n=77)) compared internet CBT (iCBT) with WLC in people with panic disorders. All studies found that iCBT was superior to WLC for reducing symptoms of panic. No studies compared iCBT with active controls. Allen et al. (2016) reports an investigation carried out in 2 phases. Phase 1 (n=63) measured the efficacy of a brief (5 lesson) iCBT programme compared with WLC in people with panic disorder using change in panic symptoms and response rate as outcome measures. Phase 2 measured the effectiveness of the intervention with 330 primary care patients with panic disorder under the supervision of primary care practitioners. It reports that reduction in panic symptoms were maintained at 3 months' follow-up but lower completion rates were found in study 2 (56.1% study 2 versus 63% study 1). There was some evidence that adherence was related to therapist contact. Ciuca et al. (2018) reported no difference in self-reported symptoms of panic disorder post-treatment between guided and unguided iCBT in people with panic disorder but that fewer people met the diagnostic criteria for panic disorder following guided treatment versus unguided. These treatment gains were maintained and became superior at 6 months' follow-up.

In a mixed anxiety disorder population that included people with panic disorder, one Cochrane Review (Olthuis et al. 2016) (8 studies) reported that therapist-guided iCBT is more effective than WLC, or an online discussion forum or information only in improving anxiety symptoms.

Two NICE IAPT assessment briefings were identified that described two technologies: Velibra an online self-guided programme designed to treat panic disorder and GAD (see low intensity psychological therapies for GAD section) and FearFighter an online therapist supported programme designed to treat

panic disorder, agoraphobia and specific phobia. Velibra showed some effectiveness in reducing scores on the depression and anxiety subscale (DASS-21) compared with WLC in pooled results from a population with mixed anxiety disorders including panic disorder. Evidence for FearFighter was equivocal. One study reported that FearFighter was as effective as clinician-delivered care, another reported that FearFighter was more effective at later time points than a minimal CBT internet programme. A third reported no difference in outcomes compared with WLC.

Evidence for a third technology OCFigher, originally included in NICE technology appraisal 97 computerised cognitive behaviour therapy for depression and anxiety which was withdrawn and superseded by NICE guideline CG113, was assessed by a NICE IAPT expert committee in May 2018. The committee concluded that OCFighter did not demonstrate clear patient benefit.

Intelligence gathering

No new information specific to CCBT for panic disorder was identified.

Impact statement

On balance evidence suggests CCBT including iCBT is generally superior to WLCs for treating panic disorder symptoms.

This guideline and NICE guideline CG123 common mental health problems recommend individual facilitated and non-facilitated self-help for the treatment of mild to moderate panic disorder which does not preclude the use of CCBT. New evidence supports these recommendations.

There is a small amount of evidence to suggest that therapist supported iCBT may result in greater treatment adherence compared with unguided treatment. There is also a small amount of evidence that suggests guided treatment may be more effective than unguided treatment in treating panic disorder symptoms. This evidence is deemed insufficient at present to influence recommendations on a specific mode of delivery and further evidence for guided versus unguided therapy is required.

CG113 research recommendation 2.6 seeks to compare CCBT with other low intensity therapies in pure panic disorder populations in order to develop the evidence base for this treatment. A Cochrane Review was identified that partially answers this question. It reported therapist-guided iCBT was superior to an online discussion and information only interventions however, this was in a population with mixed anxiety disorders and from studies assessed as low quality by the authors. For this reason, research recommendation 2.6 remains valid.

Stepped care for people with panic disorder – step 1 recognition and diagnosis

Surveillance proposal

The section of the guideline on stepped care for people with panic disorder – Step 1 recognition and diagnosis should not be updated.

Previous surveillance

New systematic review evidence indicated that the best performing self reporting tests were the patient health questionnaire for panic disorder and GAD-7 for GAD. The surveillance review concluded that there was insufficient evidence on which to recommend a well-validated, self reporting screening instrument to use in the diagnostic process, and recommendation 1.4.3 remains valid. A full list of included references can be seen in the 2015 surveillance decision document.

2020 surveillance summary

No new evidence was found for this section.

Intelligence gathering

One topic expert commented that the treatment of people with respiratory problems who suffer from panic disorder and anxiety as a result requires significant specialist knowledge. The same topic expert also noted that anxiety and panic can be common comorbidities in people with respiratory problems. The expert commented that there is an argument to include a section on

principles of care for people with physical health problems with panic disorder, in CG113.

Impact statement

It is acknowledged that the treatment of anxiety and panic disorders with comorbid physical conditions, particularly respiratory diseases that can sometimes mimic panic disorders, requires specialist knowledge to treat. Because of this it was felt that anxiety and associated panic disorders in people with respiratory comorbidities are more appropriately dealt with in guidance specifically covering those conditions.

NICE guideline NG115 Chronic obstructive pulmonary disease in over 16s: diagnosis and management has recommendations on identifying and managing anxiety and depression and recommendation 1.2.102 cross refers to CG113. The current British thoracic society (BTS) and SIGN guideline on the management of asthma also includes a section on anxiety and depressive disorders (11.5.1).

Additionally, NICE guidelines CG91 depression in adults with a chronic physical health problem and NICE guideline NG56 Multimorbidity: clinical assessment and management provide general recommendations for managing people with multiple morbidities.

For these reasons it is not proposed to expand the scope of CG113 to include a specific section on panic disorder or GAD with physical comorbidities.

Intelligence highlighted changes to the diagnostic criteria for panic disorder between DSM IV and DSM V (2013). In DSM IV panic disorder is referred to as ‘panic disorder (with or without agoraphobia)’ and in DSM V as ‘panic disorder.’ Agoraphobia has a separate entry.

Changes to the DSM V entry for panic disorder are assessed as minimal as there are no substantive changes to how panic disorder is diagnosed. The purpose of the changes is to ensure clarification of diagnostic criteria.

Therefore, the changes are judged to not impact on the substance of the recommendations for panic disorder in CG113.

New evidence is unlikely to change guideline recommendations

Stepped care for people with panic disorder – Step 2 treatment in primary care

Surveillance proposal

The section of the guideline on stepped care for people with panic disorder – Step 2 treatment in primary care should not be updated.

Previous surveillance

RCT evidence indicated group and maintenance CBT is effective for panic disorder. Clinical feedback indicated that offering CBT as a first line treatment was not cost-effective and did not align with the stepped approach recommended in the more recent NICE guideline CG123 common mental health problems. Editorial amendments and a cross referral to CG123 (recommendation 1.4.7) were added to CG113 to address this disparity. Following this change CBT became a step 3 treatment for panic disorder in CG113 and therefore 2019 surveillance evidence for CBT and panic disorder is described in stepped care for people with panic disorder – step 3 review and consideration of alternative treatments.

Two RCTs indicated collaborative stepped care is effective in GAD and panic disorder and a systematic review found evidence for several interventions not included in recommendations. This evidence was assessed as insufficient to impact recommendations.

A full list of references considered during 2015 surveillance can be found in the 2015 surveillance decision document.

2020 surveillance summary

One RCT (Gensichen et al. 2019) (n=319) in people with panic disorder being treated in a primary care setting, investigated the impact of a 23-week

exercise programme plus CAU (not described in the abstract) compared with CAU alone There were significant improvement in panic attacks in the exercise group compared with CAU and reduction in the Beck anxiety index score at 6 months' and 12 months' follow-up in the exercise group.

One RCT (Ivanova et al. 2016) (n=152) compared therapist-guided and unguided internet delivered acceptance and commitment therapy, supplemented with a smartphone application with WLC for reducing panic symptoms in people diagnosed with social anxiety disorder and/or panic disorder. It reports both treatment groups had reduced general and social anxiety symptoms post-treatment compared with WLC, but not reduced panic symptoms. No difference in any outcome was observed between guided and unguided therapies.

Intelligence gathering

One topic expert commented that older people and people from BAME groups found IAPT services unacceptable or difficult to access.

Impact statement

Evidence consistently reported stepped care is more effective than CAU for treating mental health disorders including anxiety and panic. This is consistent with the existing recommendation in the guideline (1.2) which recommends stepped care for the treatment of GAD.

Evidence identified during 2015 surveillance suggested that collaborative stepped care is effective in treating GAD and panic disorder. This is consistent with new evidence found during 2019 surveillance described in assessment and service delivery which suggests stepped care is effective for people with panic disorder. This adds to the evidence for the stepped care approach described in CG113 as part of recommendations under section 1.4. It is also consistent with the stepped care model recommended for panic disorder and GAD described in recommendation 1.2 in NICE guideline CG123 common mental health disorders.

Limited evidence suggests exercise may be effective in reducing panic attacks. This is consistent with evidence described in physical interventions for people with GAD which also suggests exercise can reduce anxiety and high intensity exercise produces a larger effect in people with mixed anxiety disordersRecommendation 1.4.12 says that the benefits of exercise as part of good general health should be discussed with all people with panic disorder as appropriate. New evidence is not enough to make specific recommendations for exercise but overall the evidence is judged to support this recommendation.

New evidence is unlikely to change guideline recommendations.

Stepped care for people with panic disorder – step 3 review and consideration of alternative treatments

Surveillance proposal

The section of the guideline on stepped care for people with panic disorder – step 3 review and consideration of alternative treatments should not be updated.

Previous surveillance

Evidence for the following interventions was judged to be insufficient to impact on recommendations due to small sample sizes or inconclusive results: yoga alone; yoga and psychotherapy; repetitive transcranial magnetic stimulation or breathing therapies. A full list of evidence can be seen in the 2015 surveillance decision document.

2020 surveillance summary

Pharmacological interventions

Three Cochrane reviews (Bighelli et al. 2018; Bighelli et al. 2016 and Breilman et al. 2019) investigated antidepressants, benzodiazepine and quetiapine in people with panic disorder.

Antidepressants

Bighelli et al 2018 (41 RCTs, n=8252) investigated the effectiveness, acceptability and safety of antidepressants for panic disorder compared with placebo. Pooled results from RCTs assessed as low quality by the authors indicated that more patients responded to antidepressants of any class compared with placebo. Evidence assessed as being of moderate quality by the authors indicated that all-cause dropouts were lower in people taking antidepressants of any class compared with placebo. When all-cause dropout was analysed by antidepressant class, tricyclic antidepressants (TCAs) were superior to placebo but there was no difference between SSRIs and SNRIs when compared with placebo. Dropout caused by adverse events were higher with TCAs and SSRIs compared with placebo. Results for SNRIs and noradrenergic reuptake inhibitors included the possibility of producing no more adverse effects than placebo.

Benzodiazepines

A Cochrane Review by Bighelli et al 2016 (35 RCTs, n=5365) investigated the effectiveness in panic disorder of antidepressants and benzodiazepines as monotherapies versus any other antidepressants or benzodiazepines. Evidence assessed by the authors as being of low quality indicated no difference in response rate between antidepressants and benzodiazepines. Evidence assessed by the authors as being of very low quality suggested benzodiazepines resulted in fewer dropouts from any cause, however confidence intervals were wide. Some evidence was found that SSRIs produce fewer adverse effects than TCAs. Overall, the authors concluded that the included studies were of insufficient quality to address the review objectives.

A Cochrane Review (Breilmann et al 2019) (24 RCTs, n=3599) investigated the effectiveness and acceptability of benzodiazepines versus placebo for panic disorder. It concluded that benzodiazepines were possibly more effective than placebo in terms of failure to respond to treatment, but the evidence quality was assessed as low. The dropout rate was lower for

benzodiazepines but again the quality of evidence was assessed as low. Overall the quality of the included studies was low and none of the studies reported the long-term effects of benzodiazepines, including risk of dependency and withdrawal symptoms.

One RCT (Goddard et al. (2016)) (n=26) compared an SSRI supplemented with quetiapine extended release with SSRI alone in people with panic disorder and found no difference in response.

Psychological interventions

One Cochrane Review (Imai et al. 2016) (6 studies) in people with panic disorder, compared psychological therapies (not described in abstract) with antidepressants and benzodiazepines for short term remission, short term response and acceptability. The following results were noted:

- No difference between psychological therapies and SSRIs for any outcome based on evidence assessed by the authors as being low to very low quality.
- No difference between psychological therapies and TCAs based on evidence assessed by the authors as being low quality.
- No difference between psychological therapies and other antidepressants based on evidence assessed by the authors as being low quality.
- No difference between psychological therapies and benzodiazepines based on evidence assessed by the authors as being low quality.
- No difference between psychological therapies and antidepressants or antidepressants plus benzodiazepines based on evidence assessed by the authors as being very low quality.

A Cochrane Review (Pompoli et al. 2016) (54 studies) (n=3021) found that CBT was superior to WLC for short term remission, short term response and short term improvement in panic disorder symptoms. It noted there was little

evidence for other psychotherapies but the small amount of evidence for psychodynamic therapy showed promising results.

A systematic review (Pompoli et al. 2018) investigated whether specific components of CBT or combinations of specific components are superior to others in the treatment of panic disorder. It reported that interoceptive exposure and face-to-face setting were associated with better treatment efficacy and acceptability. Muscle relaxation and virtual-reality exposure were associated with significantly lower efficacy

Three RCTs investigated the impact of various CBT components or approaches.

Fogliati et al. 2016 (n=145) compared self-guided and clinician guided transdiagnostic and single disorder CBT with each other and with WLC. It reported superiority for all approaches over WLC and no difference between approaches for panic disorder symptoms. Nordgreen et al. 2016 (n=173) compared a stepped care approach comprising psychoeducation, guided internet treatment, and face-to-face CBT with face-to-face CBT and found no difference in recovery from panic disorder. However, it reported that most people who recovered in the stepped care group did so at the less therapist-demanding steps (75%). It also reported that the attrition rate was high in both groups but highest in stepped care compared with face-to-face (41% vs 27%). Gauditz et al. 2015 (n=47) compared CBT plus aerobic exercise with CBT plus low intensity exercise and found a significant difference in anxiety symptoms at 7 months' follow-up for the aerobic exercise group.

Intelligence gathering

Pharmacological interventions

No intelligence was identified for pharmacological treatments specifically for panic disorder.

Psychological interventions

One topic expert advised that new evidence was available for transdiagnostic approaches to psychological therapies for GAD and panic disorder. No other intelligence for CBT or other psychotherapies specifically for panic disorder was identified. No evidence was found in favour of either a transdiagnostic or single disorder approach to CBT for panic disorder or GAD.

Impact statement

Pharmacological treatments

Antidepressants

The guideline recommends SSRIs and TCAs only for the long-term treatment of panic disorder. SNRIs are not recommended for the treatment of panic disorder as no evidence has previously been identified for their effectiveness in this population. One Cochrane Review was found that supported the use of antidepressants for the treatment of panic disorder and supported the use of TCAs, SSRIs and SNRIs. The review reports that antidepressants of all classes produce greater treatment response than placebo (based on evidence assessed as low to moderate quality by the authors) and that fewer people taking antidepressants dropped out of studies for any cause when results were pooled for antidepressants. Analysis of study drop out for any reason by drug class found TCAs had a benefit over placebo and there was no difference between SSRIs and placebo and SNRIs and placebo based on evidence assessed as moderate quality by the authors.

TCAs and SSRIs produced more dropouts caused by adverse effects than placebo; results for SNRIs included the possibility of no difference compared with placebo.

The evidence for SNRI effectiveness is promising but evidence for an additional benefit over what is currently recommended is limited. Alone it is not enough to impact recommendations for step 3 pharmacological treatment of panic disorder. The effectiveness and tolerability of SNRIs will be reviewed at the next surveillance timepoint.

New evidence for antidepressants for panic disorder is unlikely to change recommendations

Benzodiazepines

Evidence from two Cochrane reviews reported that benzodiazepine is superior to placebo for treating panic disorder and may result in fewer treatment dropouts. There is limited evidence that benzodiazepines may be better tolerated than some antidepressants but evidence for benzodiazepines effectiveness compared with antidepressants is equivocal. The authors of these reviews assessed their included studies as being of low or very low quality. CG113 recommendation 1.4.21 states that benzodiazepines are associated with a poorer outcome in the long-term and should not be prescribed for the treatment of individuals with panic disorder. CCG113 currently recommends the antidepressant classes SSRI and TCA for step 3 treatment of panic disorder. New evidence found for benzodiazepine's effectiveness and tolerance compared with antidepressants is limited and is unlikely to change this recommendation.

New evidence for benzodiazepines for panic disorder is unlikely to change recommendations.

Psychological therapies

The guideline recommendation 1.4.15 recommends CBT for long-term treatment of panic disorder that should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols. Evidence found during 2019 surveillance and 2015 surveillance (see previous surveillance in stepped care for people with panic disorder – step 2 treatment in primary care) supports this recommendation.

The guideline recommendation 1.4.13 for step 3 care currently recommends psychological or pharmacological therapy for moderate to severe panic disorder and new evidence supports this recommendation. There is low quality evidence that psychological therapies have comparable effectiveness

with SSRIs, TCAs and benzodiazepines. This supports recommendation 1.4.13 which is taken from recommendation 1.4.3.6 from NICE guidance CG123 common mental health disorders. This recommends CBT or an antidepressant if the disorder is long standing or if the person has not benefitted or declined psychological interventions. New evidence compared only the short-term effects of CBT with those of antidepressants and further evidence would be required for CBT's long-term effects compared with antidepressants for this recommendation to be impacted.

There is also limited evidence that supplementation of CBT with muscle relaxation, with techniques to cope with fear of fear and exercise, can improve CBT outcomes. Further evidence for these techniques is required before recommendations can be made for specific supplementary techniques.

A single study comparing a single disorder with a transdiagnostic approach found they were both superior to placebo in reducing panic disorder symptoms but that there was no significant difference in panic disorder symptoms when approaches were compared with each other.

New evidence for psychological therapies for panic disorder is unlikely to change guideline recommendations.

Stepped care for people with panic disorder – step 4 review and referral to specialist mental health services

Surveillance proposal

No new information on stepped care for people with panic disorder – step 4 review and referral to specialist mental health services was identified at any surveillance review.

Stepped care for people with panic disorder – step 5 care in specialist mental health services

Surveillance proposal

No new information on stepped care for people with panic disorder – step 5 care in specialist mental health services was identified at any surveillance review.

Areas not currently covered in the guideline

Genotype testing and generalised anxiety disorder

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

Surveillance proposal

A section on genotype testing to predict treatment outcomes and adverse drug reactions in generalised anxiety disorder should not be added to the guideline.

2020 surveillance summary

Two systematic reviews (Lueken et al. 2016 and Zhu et al. 2017) were identified that investigated gene polymorphisms as predictors of tolerability and treatment response in people with anxiety disorders. Lueken et al. (60 studies) investigated the current evidence on the value of genetic, neuroimaging and physiological markers for predicting treatment response to pharmacological and psychological treatments. It reports preliminary evidence is available for the HTTLPR/rs25531 genotypes as modulators of treatment response. It also reports that included studies varied considerably in quality and greater methodological rigour is needed for this emerging area. Zhu et al. 2017 (40 studies) investigated two polymorphisms within the serotonin transporter gene, 5-HTTLPR and STin2, as predictors of SSRI efficacy and tolerability. It reported that the 5-HTTLPR S allele is generally associated with

adverse drug reaction during SSRI therapy but that studies sometimes report null or even opposite associations.

An ongoing pilot study Pharmacogenomic testing in primary care investigating the efficacy of a pharmacogenetic test kit to manage antidepressant use in people prescribed antidepressants , will complete in June 2020. No other interventional studies were identified.

Intelligence gathering

Independently of this surveillance review correspondence was received by NICE which highlighted the issue of adverse drug reactions (ADR) in people using psychotropic drugs such as antidepressants that can be attributed to their genetic makeup. It was suggested that the use of genotype testing before psychotropic medication prescription could enable identification of individuals at high risk of an ADR by identifying those with genetic variations that place them at high risk.

Impact statement

Pharmacogenetics and genotype testing is a burgeoning area of genetic predictive medicine. Evidence identified was non-interventional and characterizes pharmacogenetics as a discipline in its early stages that is yet to be widely adopted in clinical practice. Further evidence is needed before a full assessment of this emerging area on recommendations can be made.

New evidence is unlikely to impact on the guideline.

Research recommendations

2.1 A comparison of the clinical and cost effectiveness of sertraline and CBT in people with GAD that has not responded to guided self-help and psychoeducation

No evidence was found for this research recommendation

2.2 The clinical and cost effectiveness of two CBT-based low-intensity interventions (CCBT and guided bibliotherapy) compared with a waiting-list control for the treatment of GAD

No evidence was found for this research recommendation

2.3 The effectiveness of physical activity compared with waiting-list control for the treatment of GAD

Limited evidence partly addressing this recommendation is described in pharmacological and physical interventions section.

2.4 The effectiveness of chamomile and ginkgo biloba in the treatment of GAD

Limited evidence partly addressing this recommendation is described in the pharmacological and physical interventions section.

2.5 The clinical and cost effectiveness of a primary care-based collaborative care approach to improving the treatment of GAD compared with usual care

Limited evidence partly addressing this recommendation is described in the assessment and service delivery section

2.6 The clinical and cost effectiveness of two CBT-based low-intensity interventions (CCBT and guided bibliotherapy) compared with a waiting-list control for the treatment of panic disorder

See CCBT for panic disorder section

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Table 1 Studies comparing CBT to various controls in mixed disorder populations.

WLC=Waiting list control; SR-M=systematic review with meta analysis; CAU=Care as usual

Author	Year	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Primary outcome	Intervention or comparator more effective?
Carpenter	2018	SR-M	2843	41	Mixed	CBT	Placebo, pill	Target disorder symptoms Anxiety symptoms QoL Response rate	Intervention
Cuijpers	2016	SR-M	Not stated	144 (184 comparisons)	Mixed	CBT	WLC, CAU, placebo, pill	GAD symptoms	Intervention
Montero-Marin	2018	SR-M	2801	50	Mixed	CBT	Relaxation therapy	Anxiety	Intervention
Ori	2015	SR-C	788	21 (5 with panic disorder populations)	Mixed	CBT+d-cycloserine	CBT+placebo	Anxiety	Comparator
Watts	2015	SR-M	1318	48	Mixed	CBT	CAU	Anxiety	Intervention
Zhang	2019	SR-M	10701	57	Mixed	CBT, primary care	Controls, not specified	Anxiety	Intervention

Table 2 Studies comparing pharmacological interventions with various comparators in GAD and mixed disorder populations.

Author	Year	Study type	Sample size	Number of studies	Population	Intervention	Comparator	Primary outcome	Intervention or comparator more effective?
Baric	2018	SR-M	398	4	GAD	Kava kava	Placebo	HAMA	intervention
Batelaan	2014	SR-M	5233	28	Mixed	Discontinuing depressants	Continuing depressants	Relapse	Intervention
Chen	2019	SR-M	14812	91	GAD	norepinephrine-dopamine reuptake inhibitors	Placebo	Anxiety	intervention
Chen	2019	SR-M	14812	91	GAD	noradrenergic and specific serotonergic antidepressants	Placebo	Anxiety	intervention
Chen	2019	SR-M	14812	91	GAD	melatonergic receptor agonists	Placebo	Anxiety	intervention
Chen	2019	SR-M	14812	91	GAD	SSRIs	Placebo	Anxiety	intervention

Chen	2019	SR-M	14812	91	GAD	azapirones	Placebo	Anxiety	intervention
Chen	2019	SR-M	14812	91	GAD	anticonvulsants	Placebo	Anxiety	intervention
Chen	2019	SR-M	14812	91	GAD	SNRIs	Placebo	Anxiety	Intervention
Chen	2019	SR-M	14812	91	GAD	benzodiazepines	Placebo	Anxiety	Intervention
de Vries	2018	SR-M	1195	4	GAD, mild	SSRI	Placebo	GAD	Intervention
Durgam	2016	RCT	400	Not applicable	GAD	vilazodone, 20-40mg	Placebo	HARS	Intervention
de Vries	2018	SR-M	1195	4	GAD, severe	SSRI	Placebo	GAD	intervention
Fountoulakis	2019	RCT	50	Not applicable	GAD plus unipolar major depression	escitalopram plus pregabalin, 75-600mg/day	escitalopram plus placebo	STAI-S	No difference

Fu	2016	RCT	1843	4	GAD	vortioxetine, 2, 5, 10mg/d, multiple doses	placebo	Anxiety	No difference
de Vries	2018	SR-M	2151	10	Panic disorder, mild	SSRI	Placebo	Panic disorder	Intervention
Gommoll	2015	RCT	680	Not applicable	GAD	vilazodone 20 mg/day	Placebo	HAMA	No difference
de Vries	2018	SR-M	2151	10	Panic disorder, severe	SSRI	Placebo	Panic disorder	Intervention
Generoso	2017	SR-M	2299	8	GAD	pregabalin	Placebo	Anxiety symptoms	Intervention
Hieu	2019	SR-M		12	Mixed	Chamomile	Not described in abstract	GAD	Intervention
Li	2017	SR-M		14	GAD	venlafaxine XR (extended release)	Placebo	HAMA	Intervention
Gommoll	2015	RCT	680	Not applicable	GAD	vilazodone 40 mg/day	Placebo	HAMA	Intervention

Jafarnia	2017	RCT	40	Not applicable	GAD	sertraline plus saffron	sertraline plus placebo	HAMA	Intervention
Li	2017	SR-M		14	GAD	venlafaxine XR (extended release)	Placebo	Response to treatment	Intervention
Li	2017	SR-M		14	GAD	venlafaxine XR (extended release)	Placebo	Remission	Intervention
Li	2017	SR-M		14	GAD	venlafaxine XR (extended release)	Placebo	All-cause discontinuation	No difference
Li	2017	SR-M		14	GAD	venlafaxine XR (extended release)	Placebo	Adverse event discontinuation	Intervention
Li	2017	SR-M		14	GAD	venlafaxine XR (extended release)	Placebo	Inefficacy discontinuation	placebo
Li	2018	SR-M		8	GAD	duloxetine, short term treatment	Placebo	HADS anxiety subscale	Intervention
Keefe	2016	RCT	179	Not applicable	GAD	chamomile, 1,500 mg	Placebo	GAD-7	Intervention

Keefe	2016	RCT	179	Not applicable	GAD	chamomile, 1,500 mg	Placebo	clinical response	Intervention
Liu	2018	SR-M	1551	12	Mixed	Probiotics	placebo	Anxiety	no difference
Slee	2019	SR-M	25441	89	GAD	Duloxetine	Placebo	HAMA	Intervention
Slee	2019	SR-M	25441	89	GAD	pregabalin	Placebo	HAMA	Intervention
Slee	2019	SR-M	25441	89	GAD	venlafaxine	Placebo	HAMA	Intervention
Slee	2019	SR-M	25441	89	GAD	escitalopram	Placebo	HAMA	Intervention
Slee	2019	SR-M	25441	89	GAD	Quetiapine	Placebo	HAMA	Intervention
Syunyakov	2016	RCT	150	Not applicable	GAD (60) Adjustment disorder (90)	Afobazole	Diazepam	HAMA	Intervention

Syunyakov	2016	RCT	150	Not applicable	GAD (60) Adjustment disorder (90)	Afobazole	Diazepam	Withdrawal syndrome	Comparator
Zareifopoulos	2017	SR-M	844	3	GAD	vilazodone, 20-40mg	Placebo	HAMA	Intervention
Zareifopoulos	2017	SR-M	844	3	GAD	vilazodone, 20-40mg	Placebo	Response	Intervention
Zareifopoulos	2017	SR-M	844	3	GAD	vilazodone, 20-40mg	Placebo	Adverse effects	Placebo
Zhang	2016	SR-M	1975	6	GAD	Duloxetine	Placebo	Response	Intervention
Zhang	2016	SR-M	2399	6	GAD	Duloxetine	Placebo	Remission	Intervention
Zhang	2016	SR-M	1135	6	GAD	Duloxetine	Placebo	HAMA	Intervention
Zhang	2016	SR-M	1652	6	GAD	Duloxetine	Placebo	Sheehan disability score	Intervention

Mao	2016	RCT	179	Not applicable	GAD	chamomile, 1,500 mg, 12 weeks plus chamomile, 1500mg, 26 weeks	Chamomile, 1,500 mg, 12 weeks plus placebo, 26 weeks	Time to relapse	No difference
Sarris	2019	RCT	46	Not applicable	GAD	Antidepressant plus L-theanine, 450-900mg	Antidepressant plus placebo	HAMA	No difference
Stein	2017	RCT	412	Not applicable	GAD	Agomelatine, 10mg	Placebo	HAMA	Intervention
Stein	2017	RCT	412	Not applicable	GAD	Agomelatine, 25mg	Placebo	HAMA	Intervention