NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Surveillance review consultation document

4-year surveillance review of CG113: Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: Management in primary, secondary and community care

Background information

Guideline issue date: January 2011
4 year review: 2015

Surveillance review recommendation

Surveillance review proposal for consultation:

The Generalised anxiety disorder and panic disorder (with or without agoraphobia) guideline should not be considered for an update at this time.

Main findings of the current 4 year surveillance review

An Evidence Update was produced for the guideline in 2012 and was used as a source of evidence for the surveillance review. The Evidence Update considered new evidence from 1st July 2010 to 2nd April 2012. The Evidence Update indicated that there is currently insufficient new evidence to invalidate the guideline recommendations.

A literature search was conducted for systematic reviews and randomised controlled trials published between 2nd April 2012 (the end of the search period for the Evidence Update) and 15th January 2015 and relevant abstracts were assessed. Clinical feedback on the guideline was obtained from 4 members of the guideline development group (GDG) through a questionnaire survey.

One out of the 4 members of the GDG that responded to the questionnaire felt that the guideline requires an update in the area of low-intensity interventions for GAD, as CG113 evidence relied heavily on mixed anxiety populations rather than specifically GAD. The issue of whether therapist facilitation is required for low intensity interventions was also highlighted. The systematic review evidence provided to support the comments was retrieved in the literature search and is summarised as part of the overall evidence summary. The evidence on guided versus non-facilitated computerised CBT remains equivocal, with neither approach demonstrating clear superiority. This is consistent with CG113 recommendation 1.2.11 step 2 of the stepped care model, which recommends either or both approaches as treatment options, guided by the person's preference.

Clinical feedback also indicated that the recommended model of stepped care for panic disorder, with CBT to be offered as alternative first line treatment to self-help, is out of date and has been superseded by CG123 Common Mental Health Disorders. There may be a need to withdraw the recommended stepped care model and cross refer to the stepped care model recommended in NICE guidance CG123. This recommends self-help as a first line treatment for panic disorder, followed by CBT as a second line treatment (Section 1.2 Stepped care figure 1 and recommendations 1.4.2.5 and 1.4.3.6). It is proposed that CG113 cross refers to these recommendations for panic disorder. It is proposed that CG113 recommendation 1.4.9 be withdrawn.

Intelligence from the 4 year surveillance indicated that an amendment to a paragraph of text in CG113 was discussed and agreed with the GDG Chair and the National Collaborating Centre prior to its publication, in relation to the partial update of TA97. However, it was proposed that the amendment be postponed until the 4 year surveillance review. The following text should replace the final paragraph of the *From Evidence to Recommendations* section 9.4 (p.319 in the full version of the guideline):

a. This guideline was required to update the anxiety section of TA97 Computerised cognitive behaviour therapy for depression and anxiety (2006). During the evidence review for this work it became clear that the TA had considered the effectiveness of CCBT for treatments with a mixture of different anxiety disorders including agoraphobia and phobias and some patients also had panic with agoraphobia; it had not considered patients with a diagnosis of panic disorder without agoraphobia. This guideline has reviewed the evidence for CCBT for panic in patients with a diagnosis of panic disorder with or without agoraphobia. The CCBT packages that were included in this review are not available in this country. Due to this limited evidence a research recommendation has been made rather than a recommendation for clinical practice. This guideline has not reviewed the evidence for the specific treatment of agoraphobia or other phobias and the TA recommendation in respect of these treatments remains extant.

Clinical feedback highlighted an omission from CG113 recommendation 1.2.13 relating to self-help interventions. The following highlighted bullet point was omitted and requires inclusion in an amendment to this recommendation via NICE's process for dealing with post-publication changes:

Individual guided self-help for people with GAD should:

- be based on the treatment principles of cognitive behavioural therapy (CBT).
- include written or electronic materials of a suitable reading age (or alternative media)

- be supported by a trained practitioner, who facilitates the self-help programme and reviews progress and outcome
- usually consist of five to seven weekly or fortnightly face-to-face or telephone sessions, each lasting 20–30 minutes. [new 2011]

This was an unintended omission and came to light following a claim being made that a GAD guided self-help programme based on entirely different principles than CBT, and without any empirical evidence, was being advertised as in line with NICE recommendations.

New evidence was identified on quetiapine in the 4 year surveillance review, in addition to the NICE Evidence Summary (ESUOM12). Collectively the evidence on quetiapine, which is not licensed currently for the CG113 population, reinforces recommendation 1.2.26 which advises against the use of antipsychotics in primary care. However, the guideline should be read in conjunction with ESUOM12 because CG113 does not currently include quetiapine in its evidence review of antipsychotics. It is proposed that CG113 cross refers to ESUOM12.

New evidence was identified for the current 4 year surveillance review relating to the following clinical areas within the Anxiety guideline.

Clinical area: Experience of Care		
Q: For people who have GAD and their carers, what are their experiences of having problems with GAD, of access to services and of treatment?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new key evidence was found for this section. <u>4-year surveillance review (2015)</u> A secondary data analysis of an RCT[1] (n=124) found that coexisting pain was common in a sample of primary care patients with severe panic disorder or GAD, and appeared to negatively affect response to anxiety treatment. A systematic review[2] (40 studies) found that reported adherence levels to supported self-care interventions for depression and anxiety indicated a significant amount of patient involvement in these interventions. The proportion of people with panic disorder or GAD was not reported in the abstract. A systematic review[3] (6 studies) of help-seeking interventions for depression, anxiety and general psychological distress found that mental health literacy content was effective in improving help-seeking attitudes in the majority of studies at post-intervention, but had no effect on help-seeking behaviour. There was less evidence for other intervention types such as efforts to destigmatise or provide help-seeking source information. The proportion of people with GAD or panic disorder was not reported in the abstract. A systematic review[4] (9 studies) found that culturally adapted guideline driven depression and anxiety treatment was effective for USA minority patients from different cultural backgrounds. It should be noted that	No GDG feedback was provided through the GDG questionnaire.	New secondary RCT data analysis identified in the 4 year surveillance review indicates 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 reinforces 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. No conclusive evidence was found in the 4 year surveillance review for help seeking interventions, to improve help seeking attitudes, or for culturally adapted treatment.

the proportion of people with GAD or panic disorder was not reported in the abstract, and only a small number of USA based studies were identified, limiting the relevance of the findings to the UK population.		
Clinical area: Low intensity psychological interventions		
Q: In the treatment of GAD, do any of the following improve outcomes compared with other interventions (including treatment as usual): non-facilitated bibliotherapy, non-facilitated audiotherapy, non-facilitated computer therapy, guided bibliotherapy, guided computer therapy, psychoeducational groups and helplines? Q: What is the cost effectiveness of low-intensity interventions (non-facilitated bibliotherapy, non-facilitated audiotherapy, non-facilitated computer therapy, guided bibliotherapy, guided computer therapy, psychoeducational groups, and helplines) compared with other interventions in the treatment of GAD?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) An Australian study[5] (n=150) of an internet-based cognitive behavioural therapy (CBT) tool (the worry programme) that compared clinician assistance with technician assistance and with a delayed-treatment control group was included in the Evidence Update. The internet CBT programme consisted of 6 sessions to be completed within 10 weeks at a rate of 1 every 7–10 days. The primary outcome was change in the Penn State Worry Questionnaire (PSWQ) and the GAD-7 assessment tool. Significant differences were seen in PSWQ and GAD-7 scores at the end of treatment after controlling for the pre-treatment scores. The study provides some evidence that an internet-based method of CBT is effective with support from either clinicians or trained non-clinicians with clinician support. This particular method of internet-based CBT appears to be available only in Australia (via an organisation called 'This Way Up'), so the direct application of this method in UK practice was considered to be limited. However, the evidence was generally thought to be consistent with the option of individual guided self-help as recommended in CG113.	Clinical feedback indicated that the guideline requires an update in the area of low-intensity interventions for GAD, as CG113 evidence relied heavily on mixed anxiety populations rather than specifically GAD. The issue of whether therapist facilitation is required for low intensity interventions was also highlighted. The systematic review[10] evidence provided to support the comments was retrieved in the surveillance literature search and is summarised in the overall evidence summary. Clinical feedback was provided during the surveillance review to highlight an omission from CG113 recommendation 1.2.13. The following bullet point was omitted inadvertently and requires inclusion in an amendment to this recommendation: **Individual guided self-help for people with GAD should:** • **be based on the treatment principles of cognitive behavioural therapy**	**Meditative Therapies** The new RCT evidence indicates that mindfulness based therapy, with or without additional strategies, can improve outcomes in GAD diagnosed patients. However, in the absence of consistent higher quality research, the evidence remains inconclusive for this intervention. 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** Although a meta-analysis indicated that computerised CBT was equivalent to face-to-face CBT, a larger Cochrane review concluded that for people who can access it, face-to-face CBT is "probably clinically superior" and that the clinical results are not consistent with the stepped care model recommended in CG113. However, in view of the lack of high quality primary studies covered in the review, there is insufficient evidence to justify a change to the current recommendations on the stepped care transition from

4-year surveillance review (2015)
Meditative Therapies
An RCT[6] (n=81) found that acceptance-based behaviour therapy, combining mindfulness-and acceptance-based strategies with behavioural approaches, significantly improved outcomes in people with GAD.
 	
An RCT[7] (n=93) found that a Mindfulness-Based Stress Reduction programme (MBSR) compared to Stress Management Education (SME) was associated with a significantly greater reduction in anxiety as measured by the Clinical Global Impressions-Severity of Illness and -Improvement scales and the Beck Anxiety Inventory, but not the Hamilton Anxiety Rating Scale. MBSR was also associated with greater reductions than SME in anxiety and distress ratings in response to the TSST stress challenge and a greater increase in positive self-statements.
 	
An RCT[8] found that patients with depressive and anxiety symptoms receiving compassion-mindfulness therapy demonstrated significant decreases in anxiety. The Chinese medicine construct "stagnation" was found to mediate the effects of the intervention.
 	
An RCT[9] (n=105) compared MBSR versus CBT in patients with one or more DSM-IV anxiety disorders. CBT and adapted MBSR were both effective at reducing principal diagnosis severity. CBT outperformed adapted MBSR on anxious arousal outcomes at follow up whereas adapted MBSR reduced worry at a greater rate than CBT and resulted in greater reduction of comorbid emotional disorders. The adapted MBSR group evidenced greater mood disorders and worry at baseline, however. The groups showed equivalent treatment credibility, therapist adherence and competency, and reliable improvement. It should be noted that the proportion of people with
	(CBT)	low intensity to high intensity CBT.
		
		The collective systematic review and RCT evidence in the surveillance review indicates that computer based CBT is effective compared with no intervention, which is consistent with CG113.
		
		The evidence on guided versus non-facilitated computerised CBT is equivocal, with neither approach demonstrating clear superiority. This is consistent with CG113 recommendation 1.2.11 step 2 of the stepped care model, which does not advise one approach over the other:
		
		• For people with GAD whose symptoms have not improved after education and active monitoring in step 1, offer one or more of the following as a first-line intervention, guided by the person's preference:
		  • individual non-facilitated self-help
		  • individual guided self-help
		  • psychoeducational groups.
		
		Research recommendation 4.2 remains ongoing, as no RCTs comparing computerised CBT with bibliotherapy and wait list control were identified through the 4 year surveillance. However, the new evidence has added to the evidence base for computerised CBT as a low intensity intervention, and further evidence will be assessed at the next surveillance review point.
		
		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.
		
		Clinical feedback from the GDG has highlighted an omission from CG113 recommendation 1.2.13. The following bullet point was omitted and requires

GAD or panic disorder was not reported in the study abstract. **Media based (including computer based) treatments** It should be noted that the proportion of people with GAD and/or panic disorder was not reported in the abstract for the majority of studies identified. A systematic review[10] (101 studies, n=8403) assessed the effects of media-delivered behavioural and cognitive behavioural therapies (self-help) for anxiety disorders in adults. For the primary outcome of symptoms of anxiety, moderate-quality evidence showed medium effects compared with no intervention (72 studies, 4537 participants), and low-quality evidence of small effects favoured face-to-face therapy (24 studies, n=1360). An RCT[11] (n=103) (n=32 panic disorder) (GAD n=14) found that computerised CBT significantly improved both panic disorder and GAD in the secondary care setting on self-report measure of Work and social adjustment scale. However, effect sizes were described as moderate but were not reported in the study abstract. An RCT[12] (n=274) of patients with subclinical symptoms of GAD, but not meeting diagnostic criteria for GAD, Social Phobia or Panic Disorder showed that Web-based CBT targeting generalized anxiety was effective in reducing social anxiety symptoms but only for those without sleep disturbance, indicating that sleep disturbance interferes with CBT treatment. A meta analysis[13] (40 studies, n=2648) of computerised cognitive-behavioral therapy (cCBT) for the treatment of DSM-5 anxiety disorders found that cCBT was significantly more effective than wait-list		inclusion in an amendment to this recommendation: **Individual guided self-help for people with GAD should:** • **be based on the treatment principles of cognitive behavioural therapy (CBT)**

control in reducing symptoms. Moderator analyses also found that cCBT targeting specific anxiety disorders had greater efficacy than that targeting mixed anxiety symptoms. The efficacy of cCBT was equivalent to in-person CBT in studies that compared them head-to-head. However, the proportion of people with panic disorder was not reported in the abstract. A Meta-analysis[14] (59 studies n=3326) of CBT for anxiety disorders found that CBT was moderately effective for improving quality of life, especially in physical and psychological domains. Internet-delivered treatments were found to be less effective than face-to-face treatments in improving quality of life. An RCT[15] (n=100) found that internet delivered CBT, tailored to address comorbidities and preferences for primary-care patients with a principal anxiety disorder, was effective and cost-effective in the primary outcome (CORE-OM). The results were maintained at one year follow up. An RCT[16] (n=99) of patients diagnosed with Major Depressive Disorder (MDD), GAD or co-morbid GAD/MDD found that internet CBT was more effective than wait list control. Adherence was also high and gains were maintained at 3-month follow-up. In a second post hoc study in primary care (n=136), adherence to the iCBT programme was low yet effect sizes were large. An RCT[17] (n=257) found that automated emails increased rates of course completion for a transdiagnostic self-guided internet-delivered treatment, the Wellbeing Course, for people with depression and anxiety. Automated emails also improved outcomes in a subsample with elevated symptoms (PHQ-9 and GAD-7). It should be noted that the proportion of patients with GAD and/or panic		

disorder was not reported in the abstract. An RCT[18] (n=100) studied a 10-week, psychodynamic, internet delivered, guided self-help treatment based on affect-phobia therapy for depression and anxiety. A significant number of patients receiving the intervention recovered (had no diagnoses of depression and anxiety, and had less than 10 on both the PHQ-9 and the GAD-7). From post-treatment to follow-up, treatment gains were maintained on the PHQ-9, and significant improvements were seen on the GAD-7. An RCT[19] (n=91) evaluated the efficacy of a stand-alone, unguided, internet-based mindfulness treatment program for anxiety. Participants in the intervention group showed a larger decrease of symptoms of anxiety, depression, and insomnia from pre- to post-assessment than participants of the control group. However, the significance was not reported in the study abstract. An RCT[20] (n=123) of people diagnosed with panic disorder, GAD or social anxiety disorder found that internet-based tailored guided self-help treatments and internet-based standardised treatments were both effective in significant symptom reductions as compared with a wait-list control group on primary disorder-unspecific measures of anxiety, depression, and general symptomatology and on secondary anxiety disorder-specific measures. Neither treatment showed superiority over the other. An RCT[21] (n=26) found that CBT administered via videoconference was as effective as in-person therapy in significantly reducing symptoms of depression, anxiety, and stress and increasing quality of life in people with DSM-IV-TR diagnosis of a mood or anxiety disorder.		

Clinical area: High intensity psychological interventions		
Q: In the treatment of GAD, what are the risks and benefits associated with high intensity psychological interventions compared with other interventions (including treatment as usual)? For example: CBT, applied relaxation, psychodynamic therapy and non-directive therapies. Q: What is the cost effectiveness of high-intensity psychological interventions (such as CBT, applied relaxation, psychodynamic therapy and non-directive therapies) compared with other interventions in the treatment of GAD?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> A single-centre RCT[22] was conducted in people aged 18–65 years in the Netherlands with a primary diagnosis of GAD (n=126) as defined in the DSM-IV. The interventions assessed were meta-cognitive therapy (n=54), intolerance of uncertainty therapy (n=52) and delayed therapy (n=20). The primary outcome measures were the Penn State Worry Questionnaire (PSWQ) and the trait version of the State-Trait Anxiety Inventory (STAI-T). The intention-to-treat analysis showed significant reductions for both intervention groups compared with delayed treatment in both the PSWQ score and the State-Trait Anxiety Inventory (STAI-T). The results of this study suggest that psychological therapy is useful in GAD, which was considered to be consistent with recommendations in NICE CG113. A meta-analysis[23] of randomised controlled trials of CBT in anxiety disorders in people older than 55 years (including trials of wider age groups that reported age-specific results) was included in the Evidence Update. Anxiety disorders included GAD, panic disorder, agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder and 'anxiety not otherwise specified'. Overall, 12 studies were included in the meta-analysis (n=658). Immediately after the intervention compared with baseline, CBT was not significantly different from active controls. However, the difference between CBT and non-active controls	No GDG feedback was provided through the GDG questionnaire.	CG113 recommends a high-intensity psychological intervention as an option for treating GAD that has not improved after step 2 treatment. CBT and applied relaxation are particular alternative strategies recommended in the guideline (recommendation 1.2.17). However, the guideline does not make recommendations on choosing a particular method of CBT. Some new RCT evidence suggests that acceptance and commitment therapy, an adaptation of CBT, is as effective as CBT for GAD, although the largest of these trials studied a mixed anxiety population as distinct from GAD or panic diagnosed. This evidence is unlikely to impact on the recommendations. **Cognitive Behavioural Therapy** The evidence identified through the Evidence Update and 4 year surveillance was in favour of CBT which is consistent with CG113 recommendations 1.2.17 and 1.4.12 for both GAD and panic disorder. CG113 does not make specific recommendations for treatment of GAD in older people. The Evidence Update concluded that CBT may be more effective than non-active controls, but no better than active controls for treating anxiety in older people. However, additional evidence comparing outcomes of CBT in working age people versus older people is needed to address this uncertainty. The evidence from the 4 year surveillance suggests

was significant. At 3 months follow up, CBT was not significantly different from active control. A significant difference was seen at 6 months. However, at 12 months the difference was again non-significant. The authors stated that the effect size was 'small to moderate in older people compared with moderate to large in working-age adults'. However no data were given to quantify the effect sizes seen in working-age adults. The Evidence Update concluded that a direct comparison of outcomes of CBT in working age people versus older people is needed to address this uncertainty. A systematic review[24] was conducted on established interventions for the treatment of GAD (drugs, psychological, or lifestyle interventions) in older people and included in the Evidence Update. Studies were included if participants were older than 55 years with a mean or median age of 60 years or older and at least 75% were diagnosed with GAD as primary disorder. 25 articles reporting on a total of 27 trials were included (n= 2374). The results of this study suggest that both drug treatment and psychotherapy are effective for treating GAD in older people, so management strategies do not seem to need to differ between age groups. This evidence was considered to be consistent with the recommendations in CG113, which do not make specific recommendations for older people. However, this meta-analysis included benzodiazepines, which CG113 recommends for short-term use only in crises, because of associated tolerance and dependence. <u>4-year surveillance review (2015)</u> **Acceptance and commitment therapy (ACT)** An RCT[25] (n=128) was identified which compared CBT versus ACT for mixed anxiety disorders. Both treatments were found to be similar at post-treatment and 6- and 12-month follow-up measured by anxiety-		that telephone CBT may be superior to information only CBT for participants aged 60 and older in reducing general anxiety, but further evidence specific to GAD or panic disorder is required in order to assess the impact on the CG113 recommendations. New 4 year surveillance RCT evidence suggests that CBT improves the quality of life of participants with anxiety disorders and adjunctive Behavioural Marital Therapy (BMT) improves marital adjustment of couples where one partner has an anxiety disorder. However, the unknown sample size and proportion of GAD diagnosed patients limit the impact of this evidence on CG113, and further evidence is needed to assess any impact. New 4 year surveillance systematic review evidence indicates that there is no significant difference in effectiveness between psychotherapy and antidepressants for depression and anxiety disorders, but is limited in its impact due to being non-specific to GAD and panic disorder. **Psychodynamic therapies** The new 4 year systematic review evidence on psychodynamic therapies did not demonstrate effectiveness specifically for GAD and panic disorder. This is consistent with CG113, which does not recommend psychodynamic therapy for these populations.

specific and non-anxiety-specific outcomes. An RCT[26] (n=67) assessed the relationship between session-by-session putative mediators and treatment outcomes in traditional CBT and ACT for mixed anxiety disorders. Anxiety sensitivity and cognitive defusion both significantly mediated post-treatment worry; cognitive defusion more strongly predicted worry reductions in CBT than in ACT. In addition, cognitive defusion significantly mediated quality of life, behavioral avoidance, and (secondary) depression outcomes across both CBT and ACT, whereas anxiety sensitivity did not significantly mediate other outcomes. An RCT[27] (n=51) compared ACT versus CBT for people with GAD. The results showed that group ACT was as efficacious as group CBT. While participants in the ACT group maintained treatment gains at follow-up, participants in the CBT group continued to improve between post-assessment and follow-up. **Cognitive Behavioural Therapy** It should be noted that the proportion of people with GAD and/or panic disorder was not reported in the abstract for the majority of studies identified. An RCT[28] (n=60) found that telephone CBT was superior to information only CBT for participants age 60 and older in reducing general anxiety, anxiety symptoms, worry and insomnia, but the effects were not maintained at 6-month follow up, with the exception of worry. An RCT[29] (n=126) compared metacognitive therapy (MCT), intolerance of uncertainty therapy (IUT) and delayed treatment (DT) in GAD diagnosed outpatients. Both MCT and IUT, but not DT, produced significant reductions in GAD-specific symptoms with large effect sizes and high proportions of clinically significant		

change on various outcome measures, and the vast majority of the patients no longer fulfilled the diagnostic criteria for GAD. Results further indicated that MCT produced better results than IUT, although effect sizes were not reported in the abstract for this comparison. A meta-analysis[30] (41 studies with 2132 patients meeting diagnostic criteria for GAD) examined psychological therapies for GAD. The pooled effect of the 38 comparisons (from 28 studies) of psychotherapy versus a control group was large, with low to moderate heterogeneity. There were some indications that CBT was also effective at follow-up and that CBT was more effective than applied relaxation in the longer term. The statistical significance was not reported in the abstract. A meta-analysis[31] (12 studies) of psychological therapies in primary care for anxiety disorders found a moderate effect size for effectiveness in reducing symptoms. However, the quality of studies was not considered to be high and heterogeneity was significant. An RCT[32] found that CBT improved the quality of life of people with anxiety disorders and adjunctive Behavioural Marital Therapy (BMT) improved marital adjustment of couples where one partner had an anxiety disorder, relative to standard care of pharmacotherapy and psychoeducation. The sample size was not reported in the abstract. **Psychodynamic therapies** An updated systematic review[33] (33 studies, n=2173) of short term psychodynamic therapies for common mental health disorders examined primary outcomes of general, somatic, anxiety and depressive symptom reduction. Studies were of diverse conditions, and the proportion of patients with panic disorder and GAD was not reported in the abstract. Except for somatic		

measures in the short-term, all outcome categories suggested significantly greater improvement in the treatment versus the control groups in the short-term and medium-term. Effect sizes increased in long-term follow-up, but some of these effects did not reach statistical significance. A meta-analysis[34] (67 studies, n=5993) examined studies in which psychotherapy and antidepressant medication were directly compared in the treatment of depressive and anxiety disorders. The overall effect size indicating the difference between psychotherapy and pharmacotherapy after treatment in all disorders was not statistically significant. However, the proportion of patients with panic disorder or GAD was not reported in the abstract.		

Clinical area: Pharmacological and Physical Interventions

Q: In the treatment of GAD, which drugs improve outcomes compared with other drugs and with placebo?

Q: What is the cost effectiveness of pharmacological treatments compared with other interventions in the treatment of GAD?

Evidence summary	GDG/clinical perspective	Impact
<u>Evidence Update (2012)</u> The Evidence Update included a systematic review[24] of established interventions for the treatment of GAD (drugs, psychological, or lifestyle interventions) in older people. Studies were included if participants were older than 55 years with a mean or median age of 60 years or older and at least 75% were diagnosed with GAD as primary disorder. 25 articles reporting on a total of 27 trials were included (n= 2374). The results of this study suggest that both drug treatment and psychotherapy are effective for treating GAD in older people, so management strategies do not seem to need to differ between age groups. This evidence was considered to be consistent with the recommendations in CG113, which do not make specific	One respondent cited a study that suggests adding pregabalin to ineffective SSRI treatment can be helpful. This RCT[65] (n=356) found that adjunctive pregabalin was efficacious versus placebo for treatment of patients with GAD who had not optimally responded to previous or prospective monotherapies. Furthermore, one respondent stated that patent expiry and availability of generic drugs may affect economic modelling. Escitalopram (licensed for GAD treatment unlike Panel-recommended sertraline) was stated as having an expired patent but the respondent was unsure when/if a generic form will become	**Antipsychotics: Quetiapine** Currently CG113 recommends (1.2.26) against offering antipsychotics in primary care. New evidence was identified on Quetiapine in the 4 year surveillance review, in addition to the NICE evidence summary (ESUOM12). The evidence summary found only weak evidence for quetiapine monotherapy and limited evidence suggesting that it is no more effective than antidepressants, not effective as augmentation therapy together with antidepressants, and results in more patients discontinuing treatment due to adverse effects.

recommendations for older people. However, this meta-analysis included benzodiazepines, which CG113 recommends for short-term use only in crises, because of associated tolerance and dependence. An RCT[35] was conducted in the USA, of a collaborative care intervention compared with usual care in 1004 adults aged 18–75 years with various anxiety disorders (of whom 549 had GAD). Participants in the intervention group (including 270 people with GAD) could choose computer-assisted CBT designed to guide both the mental-health professional and the patient or pharmacotherapy (with drug treatment advice given by psychiatrists to the primary care doctor), or both. The CBT addressed the 4 most common anxiety disorders in primary care (GAD, panic disorder, social anxiety disorder and post-traumatic stress disorder). The outcome of the study was remission (defined as an overall anxiety severity impairment score of less than 5), improvement meaning the participant did not want further treatment or improvement with residual symptoms needing a type of treatment not offered in the study. For GAD, GAD Severity Scale (GADSS) scores were significantly lower in the intervention group than in the usual care group at 6 months, 12 months, and 18 months. The treatments used in this study span steps 3 and 4 of the care model recommended in CG113, and the interventions were reasonably comparable to those recommended in the guideline. The drug treatment algorithm used in the study resembled the drug treatment strategy of the guideline, with the notable difference that benzodiazepines were allowed as an add-on to antidepressant treatment whereas CG113 recommends that this class of drugs is used only during crises. <u>4-year surveillance review (2015)</u> **Antipsychotics: Quetiapine**	available in EU. The respondent also stated that the issue of QT prolongation with escitalopram may not have been considered in the guideline.	The additional RCT evidence identified in the 4 year surveillance review was consistent with ESUOM12. Collectively the evidence on quetiapine reinforces CG113 recommendation 1.2.26 which advises against the use of antipsychotics in primary care. However, the guideline should be read in conjunction with ESUOM12 as currently CG113 does not include quetiapine in its evidence review of antipsychotics. The limited RCT evidence on ziprasidone is also consistent with recommendation 1.2.26. **Combination treatment** Although combination treatment is recommended as a treatment option in the guideline for complex or treatment-refractory GAD, it also stated that evidence for combination treatments is lacking. The evidence retrieved in the Evidence Update was considered to be consistent with CG113, and provides some evidence of effectiveness of combination drug and psychological treatment. **Anticonvulsants: Pregabalin** There is some RCT evidence that adjunctive pregabalin can be effective for patients who have not optimally responded to previous or prospective antidepressant monotherapies. Further research is needed on monotherapy or adjunctive therapy before there is likely to be any significant impact on CG113 recommendation 1.2.24, which recommends pregabalin only if the person cannot tolerate SSRIs or SNRIs. **Benzodiazepines** New systematic review evidence identified at the 4 year surveillance review suggests that benzodiazepines are as effective as antidepressants for GAD and panic disorder with fewer side effects. However, CG113 recommendation 1.2.25 advises against

Quetiapine does not have UK marketing authorisation for treating GAD and so this is an off-label use of quetiapine. NICE Medicines and Prescribing Centre (MPC) has produced an evidence summary on Quetiapine for GAD: Generalised anxiety disorder: quetiapine (ESUOM12). Evidence relating to quetiapine in GAD was not assessed as part of the CG113 development because it was expected that this would be a subject of a NICE technology appraisal. The technology appraisal was suspended indefinitely after withdrawal of the licensing application by the manufacturer. The evidence summary found some RCT evidence that quetiapine monotherapy improves the symptoms of GAD compared with placebo, and limited evidence suggesting that it is not more effective than antidepressants. Other limited evidence suggests that adding quetiapine to an antidepressant does not improve symptoms in GAD that has not responded to the antidepressant alone. People taking quetiapine are more likely to discontinue treatment because of adverse effects compared with placebo or active treatment. A pilot RCT[36] (n=39) found that augmentation of antidepressant treatment with quetiapine XR did not result in clinical improvement according to the outcome measure of anxiety using the HAM-A and CGI-S scores at week 8, among the patients with either a primary anxiety disorder or a mood disorder with comorbid anxiety symptoms. However, treatment with quetiapine XR as an adjunct to antidepressant therapy appeared to provide a short-term benefit at 4 weeks. The proportion of patients with panic disorder or GAD was not reported in the abstract. A follow up RCT[37] (n=432) evaluated effects of quetiapine XR maintenance treatment on functioning		benzodiazepines for GAD in primary or secondary care except as a short-term measure during crises, due to the risk of dependence for patients requiring long-term treatment. No evidence was identified to impact on this recommendation. **Antidepressants** The evidence identified in the 4 year surveillance review was consistent with CG113 recommendation 1.2.23, which advises first line treatment with sertraline, based on cost effectiveness, followed by other selective serotonin reuptake inhibitors or serotonin–noradrenaline reuptake inhibitors. Further research is needed on Vortioxetine, as the current evidence on its efficacy is inconsistent and is unlikely to impact on CG113 recommendations. CG113 currently recommends sertraline on the basis of the lowest acquisition cost and cost effectiveness. The GDG expected the relative cost effectiveness of drugs for GAD to change with the availability of generics and lower acquisition costs. It was noted that the patent for escitalopram expired on 31st May 2014, which has enabled generic versions of the drug to be marketed in the UK and thereby impact on drug acquisition costs. However, as sertraline was considered to be more clinically effective than escitalopram, the cost reduction of escitalopram is unlikely to impact on recommendations 1.2.22 and 1.2.23. Further research on the clinical effectiveness escitalopram and other antidepressants will be considered at the next surveillance review. No conclusive evidence was found in the Evidence Update or 4 year surveillance review for physical or herbal interventions. Further research is needed on these alternative interventions before any potential impact on CG113 recommendations can be considered.

and sleep in patients with GAD. The risk of an anxiety event was significantly reduced for quetiapine XR vs. placebo, and improvements in functioning and sleep quality were maintained. The study was limited by the lack of active-comparator arm and exclusion of patients with comorbid depression. A secondary analysis[38] of one of the RCTs[39] (n=450) included in ESUOM12 found that in older people (aged >66 years) with GAD, extended-release quetiapine fumarate (quetiapine XR) significantly improved quality of life and sleep quality outcomes versus placebo, as measured by the enjoyment and satisfaction questionnaire Q-LES-Q-Short Form percentage maximum total score, and Pittsburgh Sleep Quality Index global score. An RCT[40] (n=409) assessed extended-release quetiapine fumarate (quetiapine XR) in patients with GAD and an inadequate response to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Adjunctive quetiapine XR did not show a statistically significant effect for the primary endpoint of Hamilton Anxiety Rating Scale (HAM-A) total score at week 8, although some secondary endpoints were statistically significant vs placebo. Quetiapine XR was generally well tolerated. **Antipsychotics: Ziprasidone** An RCT[41] (n=49) found that ziprasidone monotherapy in bipolar disorder with co-occurring lifetime panic or GAD was not associated with a clinically significant improvement in anxiety symptoms or improved function, and it was associated with a more negative side-effect profile relative to placebo. **Anticonvulsants: Pregabalin**		

An RCT[42] (n=106) found that pregabalin was effective in facilitating taper off chronic benzodiazepines for patients with GAD. An RCT[43] (n=615) examined long-term treatment and assessment of discontinuation of pregabalin in patients with GAD. Low levels of discontinuation symptoms were evident and rates of rebound anxiety were also low at both 12 and 24 weeks. **Antidepressants** An RCT[44] (n=151) found that duloxetine treatment was efficacious in the improvement of anxiety and functioning in older adult patients (aged >64 years) with GAD. Treatment-emergent adverse events occurred at twice the rate than with placebo including constipation, but the difference was only reported as significant for dry mouth. A systematic review[45] (22 studies) compared the efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders. No consistent evidence emerged supporting the advantage of using tricyclic antidepressants (TCA) over benzodiazepines (BDZ) in treating GAD, complex phobias and mixed anxiety-depressive disorders. BDZ showed fewer treatment withdrawals and adverse events than antidepressants. In panic disorder with and without agoraphobia the meta-analysis found BDZ treatments were more effective in reducing the number of panic attacks than TCA. BDZ medications were significantly better tolerated than TCA drugs, causing less discontinuation and side effects. As to newer antidepressants, BDZ trials resulted in comparable or greater improvements and fewer adverse events in patients suffering from GAD or panic disorder. An RCT[46] found that escitalopram was not significantly better than desvenlafaxine in Hamilton Depression		

Rating scale and Hamilton Anxiety Rating Scale scores, but escitalopram was better tolerated. **Vortioxetine** Three RCTs[47,48,49] were found on vortioxetine, one of which found it to be effective in reducing GAD symptoms, the other two found that it did not significantly improve symptoms, but was well tolerated. **Agomelatine** Two RCTs[50,51] were identified on agomelatine. One RCT[50] (n=139) found that agomelatine had at least similar efficacy to that of escitalopram for the short-term treatment of GAD with fewer adverse events. The other RCT[51] (n=227) found that the risk of relapse over time was significantly lower for patients who continued treatment with agomelatine than for those switched to placebo. **Pharmacological interventions: general** A systematic review[52] (27 trials, n=4344) found that pharmacological interventions effectively improved quality of life for patients with anxiety disorders from before to after treatment. However, the proportion of people with GAD or panic disorder was not reported in the abstract. **Other pharmacological treatments** A proof of concept RCT[53] found that L-759274, a novel neurokinin 1 (substance P) receptor antagonist, was not significantly superior to placebo and does not appear to be efficacious for the treatment of GAD. An RCT[54] (n=202) found that Yiqiyangxin, a Chinese medicine compound, combined with cognitive therapy was effective for people with GAD and significantly reduced recurrence after medicine withdrawal. A meta-analysis[55] (9 studies, n=273) found a		

significant benefit of D-cycloserine augmentation of behavioural therapy for the treatment of anxiety disorders. However, the proportion of patients with GAD or panic disorder was not reported in the abstract. An RCT[56] found that SSR149415, a vasopressin V(1b) receptor antagonist, was not significantly more effective than placebo for GAD, while paroxetine demonstrated efficacy on the Hamilton Anxiety Rating Scale. An RCT[57] (n=687) found that 5 or 10 mg/day Lu AA21004, a multimodal psychotropic agent, was efficacious in preventing relapse of GAD and was well tolerated in the maintenance treatment of GAD. **Herbal treatments** An RCT[58] (n=191) evaluated the effectiveness, safety, and tolerability of G. glauca, which is a herbal medicinal product, administered during 15 weeks in people with GAD. The results showed greater anxiolytic effectiveness from G. glauca than that obtained with lorazepam, and the tolerability analysis did not show any differences between treatments. An RCT[59] (n=539) found that silexan, a lavender oil preparation, was more efficacious than placebo for people with GAD. Adverse events rates for silexan were comparable to placebo and lower than for the active control paroxetine. An RCT[60] (n=114) found that sarasvata choorna for people with GAD did not provide better relief compared with placebo as measured by the Hamilton Anxiety Rating Scale. A systematic review[61] (5 studies) assessed the effectiveness of Withania somnifera (WS; common		

name, ashwagandha) for the treatment of anxiety. All 5 included studies concluded that WS resulted in greater score improvements (significantly in most cases) than placebo in outcomes on anxiety or stress scales. However, heterogenous methods and potential bias limited the strength of the findings. The proportion of people with either panic disorder or GAD were not reported in the abstract. An RCT[62] (n=75) of people with GAD found that Kava (Piper methysticum), a plant-based medicine, significantly reduced anxiety compared with placebo, with a moderate effect size. **Physical Interventions** An RCT[63] (n=50) of peri- and early postmenopausal women with anxiety found that auricular acupressure on the bilateral ear shenmen and subcortex points on alternating ears enabled significant tapering of medication (alprazolam and zolpidem). An RCT[64] (n=115) found that cranial electrotherapy stimulation significantly decreased anxiety and comorbid depression, without adverse events. The proportion of people with GAD or panic disorder was not reported in the abstract.		
Clinical area: Computerised cognitive behavioural therapy for panic disorder		
Q: In the treatment of panic disorder does CCBT improve outcomes?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new key evidence was found for this section. <u>4-year surveillance review (2015)</u> A meta analysis[13] (40 studies, n=2648) of computerised cognitive-behavioral therapy (cCBT) for the treatment of DSM-5 anxiety disorders found that cCBT was significantly more effective than wait-list	An amendment to the text of CG113 was discussed prior to its publication in 2011, in relation to the partial update of TA97. It was proposed that the following text be inserted but was postponed until the surveillance review (final paragraph of the Evidence to recommendations for chapter 9.4 p.319): **This guideline was required to update the**	Intelligence from the 4 year surveillance indicated that an amendment to a paragraph of text in CG113 was discussed and agreed with the GDG Chair and the National Collaborating Centre prior to its publication, in relation to the partial update of TA97. However, it was proposed that the amendment be postponed until the 4 year surveillance review. The agreed amended text should replace the final paragraph of the *From*

control in reducing symptoms. Moderator analyses also found that cCBT targeting specific anxiety disorders had greater efficacy than that targeting mixed anxiety symptoms. The efficacy of cCBT was equivalent to in-person CBT in studies that compared them head-to-head. However, the proportion of people with panic disorder was not reported in the abstract. An RCT[11] (n=103) (n=32 panic disorder) (GAD n=14) found that computerised CBT significantly improved both panic disorder and GAD in the secondary care setting on self-report measure of Work and social adjustment scale. However, effect sizes were described as moderate but were not reported in the abstract. An RCT[15] (n=100) found that internet delivered CBT, tailored to address comorbidities and preferences for primary-care patients with a principal anxiety disorder, was effective and cost-effective in the primary outcome (CORE-OM). The results were maintained at one year follow up. It should be noted that the proportion of people with panic disorder was not reported in the abstract. An RCT[20] (n=123) of people diagnosed with panic disorder, GAD or social anxiety disorder found that internet-based tailored guided self-help treatments and Internet-based standardised treatments were both effective in significant symptom reductions as compared with a wait-list control group on primary disorder-unspecific measures of anxiety, depression, and general symptomatology and on secondary anxiety disorder-specific measures. Neither treatment showed superiority over the other. It should be noted that the proportion of people with panic disorder was not reported in the abstract. A secondary analysis[66] of an RCT (n=104) found that	**anxiety section of TA97 Computerised cognitive behaviour therapy for depression and anxiety (2006). During the evidence review for this work it became clear that the TA had considered the effectiveness of CCBT for treatments with a mixture of different anxiety disorders including agoraphobia and phobias and some patients also had panic with agoraphobia. ; it had not considered patients with a diagnosis of panic disorder without agoraphobia.** **This guideline has reviewed the evidence for CCBT for panic in patients with a diagnosis of panic disorder with or without agoraphobia. The CCBT packages that were included in this review are not available in this country. Due to this limited evidence a research recommendation has been made rather than a recommendation for clinical practice.** **This guideline has not reviewed the evidence for the specific treatment of agoraphobia or other phobias and the TA recommendation in respect of these treatments remains extant.**	*Evidence to Recommendations* section 9.4 (p.319 in the full version of the guideline). This proposed amendment clarifies the scope of the partial update but has no impact on CG113 recommendations.

both Internet-based CBT and group CBT were effective treatment modalities for panic disorder. Predictors of positive treatment response for both modalities were having low levels of symptom severity and work impairment. In addition, anxiety sensitivity was found to have a small negative relationship with treatment outcome, suggesting that anxiety sensitivity may slightly enhance treatment response. An RCT[67] (n=149) investigated the effects of a tailored, therapist-guided, internet-based treatment for individuals with reoccurring panic attacks, and examined whether people in different age groups (18-30 years and 31-45 years) would respond differently to the treatment. All dependent measures improved significantly immediately following treatment and at the 12-month follow-up. Age group had no effect, indicating that age did not influence the outcome. An RCT[68] (n=126) evaluated the effectiveness of Don't Panic Online, an internet-based self-help course for mild panic symptoms, which is based on cognitive behavioural principles and includes guidance by email. Analyses of covariance (intention-to-treat) showed no significant differences in panic symptom reduction between intervention and wait list control groups. Analysis of intervention completers only showed a moderate effect size in favour of the intervention group.		
Clinical area: Stepped care for people with panic disorder		
Q: Step 1 – recognition and diagnosis		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new key evidence was found for this section. <u>4-year surveillance review (2015)</u> A systematic review[69] (10 unique studies) investigated the accuracy of self-report screening instruments in	No GDG feedback was provided through the GDG questionnaire.	New systematic review evidence identified through the 4 year surveillance indicates that the best performing test for panic disorder is the Patient Health Questionnaire. However, further validation of these instruments is needed to justify a change to CG113 Recommendation 1.4.3, which states:

diagnosing GAD and panic disorder in adults. The best-performing test for GAD was the Generalized Anxiety Disorder Scale 7 Item (GAD-7). The best-performing test for panic disorder was the Patient Health Questionnaire. However, further validation of these instruments is needed because neither instrument was replicated in more than 1 primary care population.		There is insufficient evidence on which to recommend a well-validated, self-reporting screening instrument to use in the diagnostic process, and so consultation skills should be relied upon to elicit all necessary information.
Clinical area: Stepped care for people with panic disorder		
Q: Step 2 – treatment in primary care		
Evidence Update (2012) No new key evidence was found for this section. 4-year surveillance review (2015) **Cognitive Behavioural Therapy** An RCT[70] (n=379) found that maintenance CBT for panic disorder patients with or without agoraphobia produced significantly lower relapse rates and reduced work and social impairment compared to the assessment only condition at a 21-month follow-up. An RCT[71] (n=84) found that therapist guided CBT for patients with panic disorder with agoraphobia increased activation of the hippocampus, which was positively correlated with treatment outcome, and a decreased connectivity between the left inferior frontal gyrus and the left hippocampus across time. An RCT[72] (n=36) found that group CBT was more effective than group physical exercise in the treatment of panic disorder, both immediately following treatment and at follow-up assessments. A post hoc analysis[73] of an RCT (n=369) examined whether co-occurring depression had negative effects on CBT outcomes in patients with panic disorder (PD) and agoraphobia (AG) and whether treatment for PD and AG (PD/AG) also reduces depressive	Clinical feedback indicated that the panic disorder section of the guideline incorporates a model of stepped care that is outdated (this section of the guideline has not been revised since 2004) and recommends a priority between first and second line treatments that is not cost-effective and is contrary to recommendations of CG123 Common Mental Health Disorders and the national Improving Access to Psychological Therapies programme in England. Specifically it recommends offering CBT as an alternative first line treatment to self-help, depending on the person's preference, which may no longer be justified.	**Cognitive Behavioural Therapy** The new RCT evidence identified through the 4 year surveillance on CBT indicated that group and maintenance CBT is effective for panic disorder and this is consistent with CG113 recommendations for panic disorder (1.4.9, 1.4.12-1.4.18 unchanged since CG22). However, clinical feedback indicates that the recommended model of stepped care, with CBT to be offered as an alternative first line treatment to self-help, is not cost effective. There is a potential need to withdraw the recommendations in order to align with CG123 Common Mental Health Disorders and other national recommendations (Improving Access to Psychological Therapies programme in England). CG123 recommends a stepped care model of self-help as a first line treatment for panic disorder, followed by CBT as a second line treatment (Section 1.2 Stepped care figure 1 and recommendations 1.4.25 and 1.4.36). It is proposed that CG113 cross refers to these recommendations for panic disorder, which has remained unchanged since 2004 (CG22). **Collaborative stepped care** New 4 year surveillance evidence indicates that a collaborative stepped care approach, comprising collaboration of psychiatric nurses (care managers),

symptomatology. Comorbid depression did not have a significant overall effect on anxiety outcomes at post-treatment and follow-up, except for slightly diminished post-treatment effect sizes for clinician-rated CGI and Hamilton Anxiety Rating Scale, when adjusting for baseline anxiety severity. **Collaborative stepped care** An RCT[74] (n=180) found that collaborative stepped care (CSC), with guided self-help as a first step, was more effective than care as usual for primary care patients with panic disorder or GAD, measured using the Beck Anxiety Inventory at baseline and after 3, 6, 9 and 12 months. CSC was provided by the psychiatric nurses (care managers) in collaboration with the general practitioner and a consultant psychiatrist. The intervention consisted of 3 steps, namely guided self-help, CBT and antidepressants. The trial was conducted in the Netherlands and the differing structure of the Dutch and UK health services may limit the impact on CG113. A cost utility analysis[75] of the same RCT (n=180) showed that CSC was a cost effective intervention for panic disorder and GAD, and was even dominant when a societal perspective was taken. **Other interventions** An RCT[76] (n=54) examined the effectiveness of manualised panic-focused psychodynamic psychotherapy (PFPP) for outpatients with panic disorder (with or without agoraphobia) in comparison with CBT. Both PFPP and a CBT were found to be effective, and emotional awareness was a strong moderator of treatment effectiveness in both treatments. A secondary analysis[77] of an RCT (Lambert) (15 GP practices) found that patients with panic disorder were		general practitioners and a consultant psychiatrist, is effective for both panic disorder and GAD. However, geographical specificity to the Netherlands may limit its applicability to the UK. Currently CG113 recommends a stepped care model but does not make specific recommendations for collaborative approach to this. Further evidence is required to justify a change to the recommendations. **Other interventions** The 4 year surveillance evidence on the following interventions was insufficient to impact on CG113 recommendations and further research is needed: • manualised panic-focused psychodynamic psychotherapy • occupational therapy-led lifestyle treatment azapirones

high healthcare resource users at baseline. Treatment with a lifestyle approach reduced resource use. This comprised occupational therapy-led lifestyle treatment comprising lifestyle review of fluid intake, diet pattern, exercise, caffeine, alcohol and nicotine. A systematic review[78] (3 studies, n=170) assessed the efficacy, acceptability and adverse effects of azapirones in alleviating symptoms of panic disorder. No study provided enough usable information on the primary efficacy outcome (response). For the primary acceptability outcome, moderate-quality evidence indicated that azapirones had lower acceptability than placebo. However, only trials of one azapirone (namely buspirone) were included in this review; this, combined with the small sample size, limits the impact on CG113.		
Clinical area: Stepped care for people with panic disorder		
Q: Step 3 – review and consideration of alternative treatments		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new key evidence was found for this section. <u>4-year surveillance review (2015)</u> An RCT[79] (n=20) found significant improvement in panic symptomatology among people with panic disorder following both the practice of yoga and the combination of yoga and psychotherapy. An RCT[80] (n=25) of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for people with panic disorder and major depression found significant improvements in panic disorder, major depression, clinical global impression, and social adjustment. Clinical improvement was sustained at 6-month follow-up.	No GDG feedback was provided through the GDG questionnaire.	No conclusive evidence which would impact on guideline recommendations was found in the 4 year surveillance review for the following interventions, due to small sample sizes or inconclusive results: • Yoga alone or yoga and psychotherapy • Repetitive transcranial magnetic stimulation • Breathing therapies

A systematic review[81] (2 studies, n=40) assessed the effects of repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults aged 18 to 65 years, either as a monotherapy or as an augmentation strategy. In both included studies the data for the primary outcome, panic symptoms as measured by the Panic Disorder Severity Scale (PDSS), were skewed and could not be pooled for a quantitative analysis. For this primary outcome one trial (Mantovani, described above) with 25 participants reported a superior effect of rTMS in reducing panic symptoms compared with sham rTMS, but this trial had a 16% dropout rate and so was deemed as having a high risk of attrition bias. The other trial found that all 15 participants exhibited a reduction in panic symptoms but there was no significant difference between rTMS and sham rTMS. An RCT[82] (n=74) of panic disorder patients found that two opposing breathing training methods effectively reduced the severity of panic disorder 1 month after treatment and that treatment effects were maintained at 6-month follow-up. Clinical improvement must have depended on elements common to both breathing therapies rather than on the effect of the therapies themselves on CO(2) levels.		
Clinical area: Research recommendation		
Q: 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?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new key evidence was found for this section. <u>4-year surveillance review (2015)</u> A systematic review[83] (7 studies, n=407) found that aerobic exercise demonstrated no significant effect for the treatment of anxiety disorders. The proportion of people with panic disorder or GAD was not reported in the abstract, but the authors stated that the result	No GDG feedback was provided through the GDG questionnaire.	New systematic review and RCT evidence on various exercise therapies is inconsistent in anxiety disorders, and this research recommendation remains ongoing.

remained the same when controlling for length of exercise sessions and type of anxiety disorder. AN RCT[84] (n=30) of women with GAD aged 18-37 years found that exercise training, including resistance and aerobic exercise training, reduced worry symptoms as measured by the Penn State Worry Questionnaire. A systematic review[85] (8 studies) found that exercise was as effective as an adjunctive treatment for anxiety disorders but was less effective than antidepressant treatment. Both aerobic and non-aerobic exercise reduced anxiety symptoms. The review reported that only 1 of the studies covered panic disorder, and did not report how many studies, or people, were GAD diagnosed. A systematic review[86] (12 studies) found that available evidence did not suggest a beneficial effect of qigong exercise on anxiety symptoms in anxiety and depression. The proportion of people in the studies with GAD was not reported in the abstract. An RCT[87] (n=32) found that adjunctive Tai Chi exercise significantly improved anxiety scores compared to drug treatment alone in people with an anxiety disorder. The proportion of people with panic disorder or GAD was not reported in the abstract.		
Clinical area: Research recommendation		
Q: What are the benefits of a primary care-based collaborative care approach to improving the treatment of GAD compared with usual care?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new key evidence was found for this section. <u>4-year surveillance review (2015)</u> An RCT[74] (n=180) found that collaborative stepped	No GDG feedback was provided through the GDG questionnaire.	New evidence identified through the 4 year surveillance review indicates that a collaborative stepped care approach, comprising collaboration of psychiatric nurses (care managers), general practitioners and a consultant psychiatrist, is effective for both panic

care (CSC), with guided self-help as a first step, was more effective than care as usual for primary care patients with panic disorder or GAD, measured using the Beck Anxiety Inventory at baseline and after 3, 6, 9 and 12 months. CSC was provided by the psychiatric nurses (care managers) in collaboration with the general practitioner and a consultant psychiatrist. The intervention consisted of 3 steps, namely guided self-help, CBT and antidepressants. The trial was conducted in the Netherlands and the differing structure of the Dutch and UK health services may limit the impact on CG113. A cost utility analysis[75] of the same RCT (n=180) showed that CSC was a cost effective intervention for panic disorder and GAD, and was even dominant when a societal perspective was taken. An RCT[88] (17 primary care clinics, n=1004) of people with anxiety disorder aged 18-75 years found that Coordinated Anxiety Learning and Management (CALM) significantly increased anxiety free days over 18 months, with modest increases in health-care expenditures. It should be noted that the study was conducted in the US setting and the proportion of people with panic disorder or GAD was not reported in the abstract. An RCT[89] (n=92) found that a telephone-based, low-intensity collaborative care model to concurrently manage cardiac patients with depression and/or anxiety disorders was effective for improving mental health-related quality of life over 24-weeks. The proportion of people with panic disorder or GAD was not reported in the abstract.		disorder and GAD. However, geographical specificity to the Netherlands may limit its applicability to the UK. RCT evidence on a collaborative approach, Coordinated Anxiety Learning and Management (CALM), suggested that this approach is effective in increasing anxiety free days, but geographical specificity to the USA may limit its applicability to the UK. Further research is needed on the telephone-based, low-intensity collaborative care model specific to the GAD population to add to the limited RCT evidence identified in the 4 year surveillance. Currently CG113 recommends a stepped care model but does not make specific recommendations for a collaborative approach to this. Further evidence is required to justify a change to the recommendations.

For the following areas of the guideline no new evidence was identified:

- Principles of care for people with panic disorder
    - General management for panic disorder
    - Shared decision-making and information provision
    - Language

- Stepped care for people with panic disorder
    - Step 4 – review and referral to specialist mental health services
    - Step 5 – care in specialist mental health services

- What is the relative effectiveness of sertraline compared with CBT in people with GAD that has not responded to guided self-help and psychoeducation in a stepped-care model?

- In well-defined GAD, what is the clinical and cost effectiveness of two CBT-based low-intensity interventions (CCBT and guided bibliotherapy) compared with a waiting-list control?

- 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?

- Is chamomile/ginkgo biloba more effective than placebo in increasing response and remission rates and decreasing anxiety ratings for people with GAD?

- In well-defined panic disorder, what is the clinical and cost effectiveness of two CBT-based low-intensity interventions (CCBT and guided bibliotherapy) compared with a waiting-list control?

Ongoing research

An ongoing RCT is comparing sertraline with CBT for people with GAD who have failed to respond to low intensity psychological interventions (http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0016/123361/PRO-13-28-02.pdf NCT02347033) estimated completion date unknown). This ongoing trial is relevant to the research recommendation 4.1:

- **What is the relative effectiveness of sertraline compared with CBT in people with GAD that has not responded to guided self-help and psychoeducation in a stepped-care model?**

Anti-discrimination and equalities considerations

None identified.

Conclusion

Through the 4 year surveillance review of CG113 no new evidence which may potentially change the direction of guideline recommendations was identified. The proposal is not to update the guideline at this time.

References

1. Morone NE, Belnap BH, He F et al. (2013) Pain adversely affects outcomes to a collaborative care intervention for anxiety in primary care. Journal of General Internal Medicine 28:58-66.

2. Simco R, McCusker J, and Sewitch M. (2014) Adherence to self-care interventions for depression or anxiety: A systematic review. Health Education Journal 73:714-730.

3. Gulliver A, Griffiths KM, Christensen H et al. (2012) A systematic review of help-seeking interventions for depression, anxiety and general psychological distress. BMC Psychiatry 12:81.

4. van LA, van SA, Dekker J et al. (2013) Bridging the gap for ethnic minority adult outpatients with depression and anxiety disorders by culturally adapted treatments. Journal of Affective Disorders 147:9-16.

5. Robinson E, Titov N, Andrews G et al. (3-6-2010) Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. PLoS ONE 5:e10942.

6. Hayes-Skelton SA, Roemer L, and Orsillo SM. (2013) A randomized clinical trial comparing an acceptance-based behavior therapy to applied relaxation for generalized anxiety disorder. Journal of Consulting & Clinical Psychology 81:761-773.

7. Hoge EA, Bui E, Marques L et al. (2013) Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects on anxiety and stress reactivity. Journal of Clinical Psychiatry 74:786-792.

8. Lo HHM, Ng SM, Chan CLW et al. (2013) The Chinese medicine construct "stagnation" in mind-body connection mediates the effects of mindfulness training on depression and anxiety. Complementary Therapies in Medicine 21:348-357.

9. Arch JJ, Ayers CR, Baker A et al. (2013) Randomized clinical trial of adapted mindfulness-based stress reduction versus group cognitive behavioral therapy for heterogeneous anxiety disorders. Behaviour Research & Therapy 51:185-196.

10. Mayo-Wilson E and Montgomery P. (2013) Media-delivered cognitive behavioural therapy and behavioural therapy (self-help) for anxiety disorders in adults. Cochrane Database of Systematic Reviews 9:CD005330.

11. Bell CJ, Colhoun HC, Carter FA et al. (2012) Effectiveness of computerised cognitive behaviour therapy for anxiety disorders in secondary care. Australian & New Zealand Journal of Psychiatry 46:630-640.

12. Gosling J, Batterham P, Christensen H et al. (2013) Sleep disturbance as a moderator of the effect of web-based anxiety treatment. Sleep and biological rhythms 11:66.

13. Adelman CB, Panza KE, Bartley CA et al. (2014) A meta-analysis of computerized cognitive-behavioral therapy for the treatment of DSM-5 anxiety disorders. Journal of Clinical Psychiatry 75:e695-e704.

14. Hofmann SG, Wu JQ, and Boettcher H. (2014) Effect of cognitive-behavioral therapy for anxiety disorders on quality of life: A meta-analysis. Journal of Consulting and Clinical Psychology 82: 375-391.

15. Nordgren LB, Hedman E, Etienne J et al. (2014) Effectiveness and cost-effectiveness of individually tailored Internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. Behaviour Research & Therapy 59:1-11.

16. Newby JM, Mackenzie A, Williams AD et al. (2013) Internet cognitive behavioural therapy for mixed anxiety and depression: a randomized controlled trial and evidence of effectiveness in primary care. Psychological Medicine 43:2635-2648.

17. Titov N, Dear BF, Johnston L et al. (2013) Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial. PLoS ONE [Electronic Resource] 8:e62873.

18. Johansson R, Bjorklund M, Hornborg C et al. (2013) Affect-focused psychodynamic psychotherapy for depression and anxiety through the Internet: a randomized controlled trial. PeerJ 1:e102.

19. Boettcher J, Astrom V, Pahlsson D et al. (2014) Internet-based mindfulness treatment for anxiety disorders: a randomized controlled trial. Behavior Therapy 45:241-253.

20. Berger T, Boettcher J, and Caspar F. (2014) Internet-based guided self-help for several anxiety disorders: a randomized controlled trial comparing a tailored with a standardized disorder-specific approach. Psychotherapy: Theory, Research, Practice, Training 51:207-219.

21. Stubbings DR, Rees CS, Roberts LD et al. (2013) Comparing in-person to videoconference-based cognitive behavioral therapy for mood and anxiety disorders: randomized controlled trial. Journal of Medical Internet Research 15:e258.

22. van der Heiden C, Muris P, and van der Molen HT. (2012) Randomized controlled trial on the effectiveness of metacognitive therapy and intolerance-of-uncertainty therapy for generalized anxiety disorder. Behaviour research and therapy 50:100-109.

23. Gould RL, Coulson MC, and Howard RJ. (2012) Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. Journal of the American Geriatrics Society 60:218-229.

24. Goncalves DC and Byrne GJ. (2012) Interventions for generalized anxiety disorder in older adults: Systematic review and meta-analysis. Journal of anxiety disorders 26:1-11.

25. Arch JJ, Eifert GH, Davies C et al. (2012) Randomized clinical trial of cognitive behavioral therapy (CBT) versus acceptance and commitment therapy (ACT) for mixed anxiety disorders. Journal of Consulting & Clinical Psychology 80:750-765.

26. Arch JJ, Wolitzky-Taylor KB, Eifert GH et al. (2012) Longitudinal treatment mediation of traditional cognitive behavioral therapy and acceptance and commitment therapy for anxiety disorders. Behaviour Research & Therapy 50:469-478.

27. Avdagic E, Morrissey SA, and Boschen MJ. (2014) A randomised controlled trial of acceptance and commitment therapy and cognitive-behaviour therapy for generalised anxiety disorder. Behaviour Change 31:110-130.

28. Brenes GA, Miller ME, Williamson JD et al. (2012) A randomized controlled trial of telephone-delivered cognitive-behavioral therapy for late-life anxiety disorders. American Journal of Geriatric Psychiatry 20:707-716.

29. Heiden C, Muris P, and Molen HT. (2012) Randomized controlled trial on the effectiveness of metacognitive therapy and intolerance-of-uncertainty therapy for generalized anxiety disorder. Behaviour research and therapy 50:100-109.

30. Cuijpers P, Sijbrandij M, Koole S et al. (2014) Psychological treatment of generalized anxiety disorder: a meta-analysis. Clinical Psychology Review 34:130-140.

31. Seekles W, Cuijpers P, Kok R et al. (2013) Psychological treatment of anxiety in primary care: a meta-analysis. Psychological Medicine 43:351-361.

32. Kavitha C, Rangan U, and Nirmalan PK. (2014) Quality of life and marital adjustment after cognitive behavioural therapy and behavioural marital therapy in couples with anxiety disorders. Journal of Clinical and Diagnostic Research JCDR 8:WC01-WC04.

33. Abbass AA, Kisely SR, Town JM et al. (2014) Short-term psychodynamic psychotherapies for common mental disorders. Cochrane Database of Systematic Reviews 7: CD004687.

34. Cuijpers P, Sijbrandij M, Koole SL et al. (2013) The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. World Psychiatry 12:137-148.

35. Craske MG, Stein MB, Sullivan G et al. (2011) Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. Archives of general psychiatry 68:378-388.

36. Chen YC, Chen CK, and Wang LJ. (2012) Quetiapine fumarate augmentation for patients with a primary anxiety disorder or a mood disorder: a pilot study. BMC Psychiatry 12:162.

37. Sheehan DV, Svedsater H, Locklear JC et al. (2013) Effects of extended-release quetiapine fumarate on long-term functioning and sleep quality in patients with Generalized Anxiety Disorder (GAD): data from a randomized-withdrawal, placebo-controlled maintenance study. Journal of Affective Disorders 151:906-913.

38. Datto C, Svedsater H, Locklear JC et al. (2013) Effect of extended-release quetiapine fumarate on quality of life and sleep in elderly patients with generalized anxiety disorder. Neuropsychiatry 3: 577-585.

39. Mezhebovsky I, Magi K, She F et al. (2013) Double-blind, randomized study of extended release quetiapine fumarate (quetiapine XR) monotherapy in older patients with generalized anxiety disorder. International Journal of Geriatric Psychiatry 28:615-625.

40. Khan A, Atkinson S, Mezhebovsky I et al. (2014) Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in patients with generalized anxiety disorder and a history of inadequate treatment response: a randomized, double-blind study. Annals of Clinical Psychiatry 26:3-18.

41. Suppes T, McElroy SL, Sheehan DV et al. (2014) A randomized, double-blind, placebo-controlled study of ziprasidone monotherapy in bipolar disorder with co-occurring lifetime panic or generalized anxiety disorder. Journal of Clinical Psychiatry 75:77-84.

42. Hadley SJ, Mandel FS, and Schweizer E. (2012) Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: a double-blind, placebo-controlled trial. Journal of Psychopharmacology 26:461-470.

43. Kasper S, Iglesias-Garcia C, Schweizer E et al. (2014) Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder. International Journal of Neuropsychopharmacology 17:685-695.

44. Alaka KJ, Noble W, Montejo A et al. (2014) Efficacy and safety of duloxetine in the treatment of older adult patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled trial. International Journal of Geriatric Psychiatry 29:978-986.

45. Offidani E, Guidi J, Tomba E et al. (2013) Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. Psychotherapy & Psychosomatics 82:355-362.

46. Maity N, Ghosal M, Gupta A et al. (2014) Clinical effectiveness and safety of escitalopram and desvenlafaxine in patients of depression with anxiety: A randomized, open-label controlled trial. Indian Journal of Pharmacology 46: 433-437.

47. Bidzan L, Mahableshwarkar AR, Jacobsen P et al. (2012) Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. European Neuropsychopharmacology 22:847-857.

48. Rothschild AJ, Mahableshwarkar AR, Jacobsen P et al. (2012) Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. European Neuropsychopharmacology 22:858-866.

49. Mahableshwarkar AR, Jacobsen PL, Serenko M et al. (2014) A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10mg in acute treatment of adults with generalized anxiety disorder. Human Psychopharmacology 29:64-72.

50. Stein DJ, Ahokas A, Marquez MS et al. (2014) Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. Journal of Clinical Psychiatry 75:362-368.

51. Stein DJ, Ahokas A, Albarran C et al. (2012) Agomelatine prevents relapse in generalized anxiety disorder: a 6-month randomized, double-blind, placebo-controlled discontinuation study. Journal of Clinical Psychiatry 73:1002-1008.

52. Hofmann SG, Wu JQ, Boettcher H et al. (2014) Effect of pharmacotherapy for anxiety disorders on quality of life: a meta-analysis. [Review]. Quality of Life Research 23:1141-1153.

53. Michelson D, Hargreaves R, Alexander R et al. (2013) Lack of efficacy of L-759274, a novel neurokinin 1 (substance P) receptor antagonist, for the treatment of generalized anxiety disorder. International Journal of Neuropsychopharmacology 16:1-11.

54. Wang T, Ding JY, Xu GX et al. (2012) Efficacy of Yiqiyangxin Chinese medicine compound combined with cognitive therapy in the treatment of generalized anxiety disorders. Asian Pacific Journal of Tropical Medicine 5:818-822.

55. Bontempo A, Panza KE, and Bloch MH. (2012) D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders: a meta-analysis. Journal of Clinical Psychiatry 73:533-537.

56. Griebel G, Beeske S, and Stahl SM. (2012) The vasopressin V(1b) receptor antagonist SSR149415 in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies. Journal of Clinical Psychiatry 73:1403-1411.

57. Baldwin DS, Loft H, and Florea I. (2012) Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. International Clinical Psychopharmacology 27:197-207.

58. Herrera-Arellano A, Jimenez-Ferrer JE, Zamilpa A et al. (2012) Therapeutic effectiveness of Galphimia glauca vs. lorazepam in generalized anxiety disorder. A controlled 15-week clinical trial. Planta Medica 78:1529-1535.

59. Kasper S, Gastpar M, Muller WE et al. (2014) Lavender oil preparation Silexan is effective in generalized anxiety disorder--a randomized, double-blind comparison to placebo and paroxetine. International Journal of Neuropsychopharmacology 17:859-869.

60. Gupta K, Mamidi P, and Thakar AB. (2014) Randomised placebo controlled study on Sarasvata choorna in generalised anxiety disorder. International Journal of Green Pharmacy 8: 231-236.

61. Pratte MA, Nanavati KB, Young V et al. (2014) An alternative treatment for anxiety: A systematic review of human trial results reported for the Ayurvedic Herb Ashwagandha (Withania somnifera). Journal of Alternative and Complementary Medicine 20: 901-908.

62. Sarris J, Stough C, Bousman CA et al. (2013) Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. Journal of Clinical Psychopharmacology 33:643-648.

63. Kao C-L, Chen C-H, Lin W-Y et al. (2012) Effect of auricular acupressure on peri- and early postmenopausal women with anxiety: A double-blinded, randomized, and controlled pilot study. Evidence-based Complementary and Alternative Medicine 2012: 567639.

64. Barclay TH and Barclay RD. (2014) A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. Journal of Affective Disorders 164:171-177.

65. Rickels K, Shiovitz TM, Ramey TS et al. (2012) Adjunctive therapy with pregabalin in generalized anxiety disorder patients with partial response to SSRI or SNRI treatment. International Clinical Psychopharmacology 27:142-150.

66. Alaoui SE, Hedman E, Ljotsson B et al. (2013) Predictors and moderators of internet- and group-based cognitive behaviour therapy for panic disorder. PLoS ONE 8: e79024.

67. Silfvernagel K, Carlbring P, Kabo J et al. (2012) Individually tailored internet-based treatment for young adults and adults with panic attacks: randomized controlled trial. Journal of Medical Internet Research 14:e65.

68. van BW, Riper H, Klein B et al. (2013) An Internet-based guided self-help intervention for panic symptoms: randomized controlled trial. Journal of Medical Internet Research 15:e154.

69. Herr NR, Williams JW, Jr., Benjamin S et al. (2-7-2014) Does this patient have generalized anxiety or panic disorder?: The Rational Clinical Examination systematic review. JAMA 312:78-84.

70. White KS, Payne LA, Gorman JM et al. (2013) Does maintenance CBT contribute to long-term treatment response of panic disorder with or without agoraphobia? A randomized controlled clinical trial. Journal of Consulting & Clinical Psychology 81:47-57.

71. Straube B, Lueken U, Jansen A et al. (2014) Neural correlates of procedural variants in cognitive-behavioral therapy: a randomized, controlled multicenter FMRI study. Psychotherapy & Psychosomatics 83:222-233.

72. Hovland A, Nordhus IH, Sjobo T et al. (2013) Comparing physical exercise in groups to group cognitive behaviour therapy for the treatment of panic disorder in a randomized controlled trial. Behavioural & Cognitive Psychotherapy 41:408-432.

73. Emmrich A, Beesdo-Baum K, Gloster AT et al. (2012) Depression does not affect the treatment outcome of CBT for panic and agoraphobia: results from a multicenter randomized trial. Psychotherapy & Psychosomatics 81:161-172.

74. Muntingh A, Feltz-Cornelis C, van MH et al. (2014) Effectiveness of collaborative stepped care for anxiety disorders in primary care: a pragmatic cluster randomised controlled trial. Psychotherapy & Psychosomatics 83:37-44.

75. Goorden M, Muntingh A, van MH et al. (2014) Cost utility analysis of a collaborative stepped care intervention for panic and generalized anxiety disorders in primary care. Journal of Psychosomatic Research 77:57-63.

76. Beutel ME, Scheurich V, Knebel A et al. (2013) Implementing panic-focused psychodynamic psychotherapy into clinical practice. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 58:326-334.

77. Lambert RA. (26-7-2012) Routine general practice care for panic disorder within the lifestyle approach to managing panic study. Mental Illness 4:e18.

78. Imai H, Tajika A, Chen P et al. (2014) Azapirones versus placebo for panic disorder in adults. Cochrane Database of Systematic Reviews 9:CD010828.

79. Vorkapic CF and Range B. (2014) Reducing the symptomatology of panic disorder: the effects of a yoga program alone and in combination with cognitive-behavioral therapy. Frontiers in psychiatry Frontiers Research Foundation 5:177.

80. Mantovani A, Aly M, Dagan Y et al. (10-1-2013) Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. Journal of Affective Disorders 144:153-159.

81. Li H, Wang J, Li C et al. (2014) Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. Cochrane Database of Systematic Reviews 9:CD009083.

82. Kim S, Wollburg E, and Roth WT. (2012) Opposing breathing therapies for panic disorder: a randomized controlled trial of lowering vs raising end-tidal P(CO2). Journal of Clinical Psychiatry 73:931-939.

83. Bartley CA, Hay M, and Bloch MH. (1-8-2013) Meta-analysis: aerobic exercise for the treatment of anxiety disorders. Progress in Neuro-Psychopharmacology & Biological Psychiatry 45:34-39.

84. Herring MP, Jacob ML, Suveg C et al. (2012) Feasibility of exercise training for the short-term treatment of generalized anxiety disorder: a randomized controlled trial. Psychotherapy & Psychosomatics 81:21-28.

85. Jayakody K, Gunadasa S, and Hosker C. (2014) Exercise for anxiety disorders: systematic review. British Journal of Sports Medicine 48:187-196.

86. Wang C-W, Chan CLW, Ho RTH et al. (2013) The effect of qigong on depressive and anxiety symptoms: A systematic review and meta-analysis of randomized controlled trials. Evidence-based Complementary and Alternative Medicine 2013: 716094.

87. Song Q-H, Shen G-Q, Xu R-M et al. (2014) Effect of Tai Chi exercise on the physical and mental health of the elder patients suffered from anxiety disorder. International journal of physiology, pathophysiology and pharmacology 6:55-60.

88. Joesch JM, Sherbourne CD, Sullivan G et al. (2012) Incremental benefits and cost of coordinated anxiety learning and management for anxiety treatment in primary care. Psychological Medicine 42:1937-1948.

89. Huffman JC, Mastromauro CA, Beach SR et al. (2014) Collaborative care for depression and anxiety disorders in patients with recent cardiac events: the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized clinical trial.[Erratum appears in JAMA Intern Med. 2014 Aug;174(8):1419]. JAMA Internal Medicine 174:927-935.