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[Intervention Protocol]

Pharmacological treatments in panic disorder in adults: a network meta-analysis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

1. To compare individual active drugs (antidepressants and benzodiazepines) and placebo in terms of efficacy and acceptability in the acute treatment of panic disorder, with or without agoraphobia.
2. To rank individual active drugs for panic disorder (antidepressants, benzodiazepines and placebo) according to their effectiveness and acceptability.
3. To explore heterogeneity and inconsistency between direct and indirect evidence in the network meta-analyses.

BACKGROUND

Description of the condition

A panic attack is a discrete period of fear or anxiety that has a rapid onset and reaches a peak within 10 minutes (APA 2013a). The main symptoms involve bodily systems, such as racing heart, chest pain, sweating, shaking, dizziness, flushing, churning stomach, faintness and breathlessness. Other recognised panic attack symptoms involve fearful cognitions, such as the fear of collapse, going mad or dying, and derealisation (sensation that the world is unreal) (APA 2013a).

Panic disorder first entered diagnostic classification systems in 1980 with the publication of the *Diagnostic and Statistical Manual of Mental Disorders - 3rd edition* (DSM-III), following observations that patients with panic attacks responded to treatment with imipramine, which is a tricyclic antidepressant (TCA) (Klein 1964). To diagnose panic disorder, further conditions must be met relating to the frequency of attacks, the need for some attacks to come on 'out of the blue' rather than in a predictable, externally-triggered situation, and exclusions where attacks are attributable solely to medical causes or panic-inducing substances, notably caffeine. DSM-IV also requires that at least one attack has been followed by: a) persistent concern about having additional attacks; b) worry about the implications of the attack or its consequences; or c) a significant change in behaviour related to the attacks (APA 1994). The core features of panic attacks remained unchanged in DSM-5 (APA 2013a), but in DSM-5 panic disorder and agoraphobia are no longer linked and are now coded in two diagnoses (APA 2013b).

Panic disorder is common in the general population; it occurs in 1% to 4% of people (lifetime prevalence) (Eaton 1994; Bijl 1998; Kessler 2012). In primary care settings, panic has been reported to have a prevalence of around 10% (King 2008). This is because common mental disorders are more often dealt with in primary care (King 2008). Its cause is not fully understood and probably there are several reasons why panic occurs. Biological theories incorporate the faulty triggering of an inbuilt anxiety response, possibly a suffocation alarm. Evidence for this comes from biological challenge tests (lactate and carbon dioxide trigger panic in those with the disorder) and from animal experiments and neuroimaging studies in humans that show activation of fear circuits in the brain, such as that involving a part of the brain called periaqueductal grey matter (Gorman 2000).

About one quarter of people with panic disorder also have agoraphobia (Kessler 2006). Agoraphobia is defined as anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help may not be available in the event of having a panic attack (APA 2013a). The presence of agoraphobia is associated with increased severity and worse outcome (Kessler 2006). There are several risk factors that predict the development of agoraphobia in people with panic disorder: female gender, more intense dizziness during a panic attack, cognitive factors, dependent personality traits and social anxiety disorder (Starcevic 2009).

Panic disorder, with or without agoraphobia, co-occurs very frequently with other psychiatric disorders, such as drug dependence, major depression, bipolar I disorder, social phobia, specific phobia, and generalised anxiety disorder (Grant 2006). It is estimated that generalised anxiety disorder co-occurs in 68% of people with panic disorder, whilst 24% to 88% of people with panic disorder have major depression (Starcevic 2009).

Description of the intervention

This review is focused on antidepressants and benzodiazepines, two pharmacological interventions. The treatment of panic disorder includes psychological and pharmacological interventions, often used in combination (Furukawa 2007; Watanabe 2009). The main pharmacological treatments used in panic disorder are antidepressants and benzodiazepines (BDZs). Azapirones, gabapentinoids, anticonvulsants, beta-blockers and inositol have also been studied but are not a focus of this review.

Historically, pharmacological interventions for panic disorder have been based on the use of older antidepressants, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) (Bruce 2003). MAOIs and TCAs are, however, burdened by severe adverse effects, such as dietary restrictions (to avoid hypertensive crisis) for MAOIs; and anticholinergic (e.g. memory problems and confusion), arrhythmogenic (heart rhythm problems) and overall poor tolerability for TCAs (Wade 1999). Benzodiazepines (BDZs), particularly high potency ones, have been used as a safer alternative in panic disorder (Stein 2010), although they may work less effectively in the long term (NICE 2011). Recent guidelines—for example APA 2009, NICE 2011, BAP 2014 and Katzman 2014—consider newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) and the serotonin noradrenaline reuptake inhibitor venlafaxine, as first-line treatment for panic disorder, due in part to their more favourable adverse effect profile over older antidepressant groups, MAOIs and TCAs. A meta-analysis comparing SSRIs and TCAs in panic disorder showed that SSRIs are as effective as TCAs, and are better tolerated (Bakker 2002), although other studies showed a possible overestimation of the efficacy of SSRIs over older antidepressants in panic disorder (Anderson 2000; Otto 2001).

BDZs have higher incidence of dependence and withdrawal reaction when compared to antidepressants (Wade 1999); and they may not be effective in treating panic disorder that occur together with depression (Ballenger 1998). In spite of these caveats, it appears that BDZs continue to be widely prescribed for the treatment of panic disorder (Bruce 2003).

How the intervention might work

Antidepressant drugs augment the function of the monoamines serotonin and noradrenaline. Serotonergic antidepressants (SSRIs) promote the transmission of the neurotransmitter serotonin across brain synapses. They most notably do it in the part of the brain called dorsal raphe nucleus (Briley 1993). They prevent reuptake of serotonin into nerve terminals by inhibiting serotonin transporters, thus allowing more serotonin to be available for neurotransmission. In panic disorder, imaging studies have revealed reduced expression of the 5H1A serotonin receptor (Nash 2008), which has an inhibitory function, so the increased serotonin throughput may in part serve to overcome this deficit of inhibition. Noradrenergic antidepressants can similarly increase transmission of the catecholamine noradrenaline. Some antidepressants, such as the serotonin-norepinephrine reuptake inhibitor (SNRI) drugs (e.g. venlafaxine, duloxetine) and TCAs, can enhance both serotonin and noradrenaline transmission by inhibiting both transporters.

BDZs moderate the gamma-Aminobutyric acid (GABA) neurotransmitter system, which is the brain's main inhibitory neurotransmitter. They activate the GABA-A BDZ receptor. This receptor complex contains a chloride channel, opened by agonists, which ultimately reduce anxiety and create sedation. The BDZ binding site communicates only indirectly with the channel, meaning that BDZs are safer than their predecessors, the barbiturates. It is known through imaging studies that the inhibitory GABA system is deficient in panic disorder (Malizia 1998; Cameron 2007); thus BDZs' ability to activate the GABA-A BDZ receptor can counteract this. It is likely that both monoamine-based systems and GABA-based systems converge, allowing both antidepressants and BDZs to have efficacy in panic disorder despite their differing actions on neurotransmitter systems. One possibility is via serotonergic neurons that modulate GABA input to the part of the brain called periaqueductal grey matter.

Why it is important to do this review

People with panic disorder are profoundly impacted by this condition often experiencing challenges engaging with work, education and social or family life. These challenges not only impact people with panic disorder but also have substantial social and economic costs (Batelaan 2007). Similarly, a recent German study (Brettschneider 2019) found that 60% of societal costs associated with panic disorder were due to productivity losses and absences from work. Therefore further information on the safety and effectiveness of pharmacological interventions have the potential to benefit both people with panic disorder and society.

Pharmacological treatments are widely used in clinical practice to treat panic disorder; however, no network meta-analysis has been conducted recently. To our knowledge, the last meta-analysis specifically focused on benzodiazepines for panic disorder was published in 1991 (Wilkinson 1991); and the last two meta-analyses focusing on antidepressants for this condition were published more than 10 years ago and 7 years ago (Bakker 2002 and Andrisano 2013 respectively). Standard pair-wise meta-analyses of psychopharmacological interventions in panic disorder have been published within Cochrane (Imai 2014; Bighelli 2016; Bighelli 2018; Breilmann 2019). Other reviews have been published on combined psychotherapy and pharmacotherapy in panic disorder (Furukawa 2007; Watanabe 2009). However, given the complexity of the condition it is very important to carry out a comprehensive and comparative evaluation of the main pharmacological treatment options within the framework of a network meta-analysis (NMA). NMAs produce estimates of the relative effects between any pair of interventions in the network, and usually yields more precise estimates than a single direct or indirect estimate (Higgins 2019).

We want to evaluate which treatments, if any, are the most effective and safe. In particular, we aim to assess if the NMA findings are of sufficient validity to help patients, mental health professionals and policy makers identify the best pharmacological treatments for panic disorder, in order to improve clinical practice and patient care. These analyses will also generate suggestions for future research to reduce key uncertainties in the evidence base.

OBJECTIVES

1. To compare individual active drugs (antidepressants and benzodiazepines) and placebo in terms of efficacy and acceptability in the acute treatment of panic disorder, with or without agoraphobia.
2. To rank individual active drugs for panic disorder (antidepressants, benzodiazepines and placebo) according to their effectiveness and acceptability.
3. To explore heterogeneity and inconsistency between direct and indirect evidence in the network meta-analyses.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include double-blind randomised controlled trials (RCTs) comparing with each other, one of the following drugs (see the list below) or placebo, in the acute treatment of panic disorder. We will exclude trials in which drugs are used as an augmentation strategy to any other psychotropic drugs. For trials that have a cross-over design, we will only consider results from the first randomisation period. Cluster-randomised trials will be included only if intracluster correlation coefficients are reported.

We will exclude:

- relapse prevention trials;
- studies in patients with a diagnosis of panic disorder where the effects of treatments are measured after panic attacks have been induced (for example with CO_2 inhalations or lactate infusions);
- studies administering psychosocial therapies targeted at panic disorder concurrently;
- studies comparing psychosocial interventions; and
- quasi-randomised trials.

Types of participants

The fundamental assumption underpinning a network meta-analysis is that of consistency/transitivity (Caldwell 2005; Cipriani 2013). We assume that any patient who meets the inclusion criteria below is, in principle, equally likely to have been randomised to any of the eligible interventions examined in this review—that is, that they are 'jointly randomisable' (Salanti 2012).

Participant characteristics

Patients aged 18 or older, of either sex, with a primary diagnosis of panic disorder, with or without agoraphobia.

Diagnosis

Diagnosis will be according to any of the following criteria: DSM-III-R; DSM-IV or the *International Classification of Diseases, 10 edition* (ICD-10); DSM-5. We will not adopt studies using operationalised criteria before DSM-III-R because their conceptualisation of panic disorder is substantively different.

Comorbidities

When the study eligibility focuses on agoraphobia rather than panic disorder, and is operationally diagnosed according to the above-named criteria, and when we can safely assume that at least some of the patients experience panic disorder as defined by the above criteria, we will include the study. Considering that over 95% of patients with agoraphobia seen clinically suffer from panic disorder as well (Goisman 1995), the effect of their inclusion will be

examined in a subgroup analysis. We will exclude trials in which all participants have a concurrent primary diagnosis of any psychiatric disorder other than panic disorder or agoraphobia if the focus is not the treatment of panic disorder. We will exclude trials in which participants have a serious concomitant medical illness.

Setting

Inpatient, outpatient and primary care.

Subset data

We will not include trials that provide data on a relevant subset of their participants (e.g. a study that includes a subset of participants meeting criteria for panic disorder).

Types of interventions

We will include only studies where medications were used at therapeutic dosage. We define therapeutic doses as doses that are indicated for panic disorder by any of the North American, European or Japanese regulatory agencies. Where such are not available, we will follow the same dose ranges as for major depression (for antidepressants) and generalised anxiety disorder (for benzodiazepines).

Antidepressants

- TCAs and related antidepressants: amitriptyline, clomipramine, desipramine, dosulepin/dothiepin, doxepin, imipramine, lofepramine, protriptyline, maprotiline, nortriptyline, trimipramine, amitriptylineoxide, butriptyline, cianopramine, demexiptilline, dibenzepin, dimetacrine, fluotracen, iprindole, imipraminoxide, melitracen, metapramine, nitroxazepine, noxiptiline, opipramol, pipofezine, propizepine, quinupramine
- Selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, femoxetine, indalpine, zimelidine
- Monoamine-oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, brofaromine, triRima™, befloxatone, benmoxin, caroxazone, cimoxatone, clorgyline, deprenyl, iproclozide, mebanazine, minaprine, nialamide, octamoxin, pheniprazine, phenoxypropazine, pirlindole, pivhydrazine, safrazine, selegiline, toloxatone.
- Serotonin-noradrenaline reuptake inhibitors: desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine.
- Noradrenergic and specific serotonergic antidepressants: mirtazapine, setiptiline
- Noradrenergic and dopaminergic reuptake inhibitors: bupropion, cilobamin, diclofensine, nomifensine
- Noradrenergic reuptake inhibitors: reboxetine, viloxazine.
- Others: agomelatine, amineptine, trazodone, nefazodone, mianserin, vortioxetine and non-conventional herbal products (e.g. Hypericum), viqualine, tianeptine, etoperidone, medifoxamine, pizotifen, benacytine ritanserin, tedatioxetine, thozalinone

Benzodiazepines (BDZs)

Alprazolam, bretazenil, bromazepam, chlordiazepoxide, cinolazepam, clonazepam, cloxazolam, clorazepate, delorazepam, diazepam, estazolam, etizolam, fludiazepam, flunitrazepam, flurazepam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, lormatezepam, medazepam, nimatazepam, nitrazepam, nodazepam, oxazepam, phenazepam, pinazepam, prazepam, premazepam, quazepam, temazepam, tetrazepam, triazolam and any other drug belonging to the BDZ class.

Placebo

Placebo can be active (i.e. mimicking side effects) or inactive (completely inert). We will include studies using active and inactive placebo. This could be a potential source of heterogeneity or inconsistency (or both).

Types of outcome measures

We will include studies that meet the above inclusion criteria regardless of whether they report on the following primary and secondary outcomes.

Primary outcomes

1. Response to treatment (i.e. substantial improvement from baseline as defined by the original investigators). We will consider as response the following definitions: “much or very much improved” according to the Clinical Global Impression Change Scale; more than 40% reduction in the Panic Disorder Severity Scale score; or more than 50% reduction in the Fear Questionnaire Agoraphobia Subscale. When multiple measures are used, we will give preference to the most global measure.

2. Total number of dropouts due to any reason (as a proxy measure of treatment acceptability).

Secondary outcomes

3. Remission (i.e. satisfactory end-state as defined by global judgment of the original investigators). Examples would be “panic free” and “no or minimal symptoms” according to the Clinical Global Impression Severity Scale. When multiple measures are used, we will give preference to the most global measure.

4. Panic symptom scales and global judgment on a continuous scale. Examples include Panic Disorder Severity Scale total score (0 to 28), Clinical Global Impression Severity Scale (1 to 7), and Clinical Global Impression Change Scale (1 to 7).

5. Frequency of panic attacks (as recorded, for example, by a panic diary).

6. Agoraphobia (as measured, for example, by the Fear Questionnaire, Mobility Inventory, or behavioural avoidance test).

When more than one scale is available in the paper, preference will be given in the following order.

- Panic Disorder Severity Scale (PDSS) > Panic and Agoraphobia Scale (PAS) > Anxiety Sensitivity index- Revised (ASI-R) > Anxiety Sensitivity index (ASI) > Anxiety Control Questionnaire (ACQ) > Body Sensations Questionnaire (BSQ) > other scales specific for panic disorder;
- Clinical Global Impression - Severity (CGI-S) > Clinical Global Impression- Improvement (CGI-I) > Global Assessment Scale (GAS) > Global Assessment of Functioning (GAF) > other global scales;
- Fear Questionnaire - Agoraphobia subscale (FQ-ag) > Fear Questionnaire - Global (FQ-global) > Mobile Inventory for Agoraphobia- Avoidance-Alone (MI-AAL) > MI-Avoidance-

Accompanied (MI-AAC) > other scales specific for agoraphobia only; and
- Panic frequency > panic severity > other scales specific for panic attacks only.

Once the scale has been chosen, if both self- and observer-rated assessments are available, we will give preference to the latter. The actual measure entered into the meta-analysis is indicated at the top of the listings in the table 'Characteristics of included studies'.

Timing of outcome assessment

All outcomes are short term: we define this as acute phase treatment, which normally would last two to six months. When studies report more response rates at different time points within two to six months, we will give preference to the time point closest to three months (i.e. 12 weeks).

Hierarchy of outcome measures

When several possible outcome measures are reported for the same outcome, we will use the primary outcome according to the original study.

Search methods for identification of studies

Trials which include at least two of the interventions are eligible for inclusion in the review. We will search for all possible comparisons formed by the interventions of interest, as defined above.

Electronic searches

We will search the following databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

- Cochrane Common Mental Disorders Specialised Register (all available years) (Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library;
- Ovid MEDLINE databases (2014 onwards) (Appendix 2);
- Ovid Embase (2014 onwards);
- Ovid PsycINFO (2014 onwards);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; all available years);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; all available years).

Date restrictions have been applied to MEDLINE, Embase and PsycINFO for the following reason. The Cochrane Common Mental Disorders Group relocated to the University of York in 2016 and the group's specialised register (which previously included RCTs from these databases) fell out of date at this time. We will conduct additional searches to account for this period from 2014 onwards.

We will apply no further restrictions on date, language or publication status to the searches.

We will search for retraction statements and errata once we have selected the included studies and will rerun all searches close to publication if more than 12 months have elapsed since the initial search date.

Searching other resources

Two review authors will check independently the reference lists of all included studies, non-Cochrane systematic reviews and major textbooks of affective disorders (written in English), for published reports and citations of unpublished research. We will also conduct a citation search via the Web of Science (included studies only) to identify additional works; and we will contact experts in the field.

Data collection and analysis

Selection of studies

At least two review authors will independently screen titles and abstracts for inclusion of all the studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publications and two review authors will independently screen them and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. The two review authors will resolve any disagreement through discussion or, if required, they will consult a third member of the review team. We will identify and exclude duplicate records and we will collate multiple reports that relate to the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form, piloted on at least one study in the review, to extract study characteristics and outcome data. Two authors from the review team will extract study characteristics and outcome data from included studies.

From each included study we will extract data on the following study, intervention and population characteristics that may act as effect modifiers.

1. Methods: study design, randomisation (individual or cluster), total duration of study, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, setting, sex, diagnostic criteria, presence or absence of medical and psychiatric comorbidities, presence or absence of elderly participants, percentage of patients with agoraphobia, percentage of patients with baseline depression, inclusion criteria, and exclusion criteria.
3. Interventions: medication dose, medication dose range, use of rescue medication.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. Where possible we will extract data at the arm level, not summary effects.
5. Notes: sponsorship/funding for trial, and notable conflicts of interest of trial authors.

We plan to compile a table of important trial and patient characteristics and visually inspect the similarity of factors we consider likely to modify treatment effect.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person. One review author will transfer data into the Review Manager 5 file

(Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

To assess risk of bias in RCTs, we will use the Cochrane risk of bias tool (Higgins 2011).

Two review authors will independently assess risk of bias for each included study. We will resolve any disagreements by discussion or by involving another author.

For each trial, we will assess the following domains:

- sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessors;
- incomplete outcome data;
- selective reporting.

We will judge each domain as being at a low, high or unclear risk of bias. We will also extract relevant text which underpins our judgement and this will be presented in the 'Risk of bias' tables.

Measures of treatment effect

Dichotomous data

For binary outcomes we will estimate the risk ratio (RR) and its 95% confidence interval (CI) using a random-effects model. It has been shown that a random-effects model has good generalisability (Furukawa 2002); and that RR is more intuitive than odds ratio (OR) (Boissel 1999). Furthermore, ORs tend to be interpreted as RR by clinicians (Deeks 2000). This may lead to an overestimation of the impression of the effect (Higgins 2019). For all primary outcomes we will calculate the number needed to treat for an additional beneficial or harmful outcome (NNTB or NNTH) and its 95% CI using Visual Rx (www.nntonline.net), taking account of the event rate in the control group.

Continuous data

(1) Summary statistics

It is likely that different studies have used varied panic rating scales; therefore we will use standardised mean difference (SMD). We will interpret the magnitude of SMDs using standard rules of thumb (Cohen 1992). If all included studies have used the same instrument, we will use mean difference (MD).

(2) Endpoint versus change data

Trials usually report results either using endpoint means and standard deviation (SD) of scales or using change in mean values from baseline of assessment rating scales. We prefer to use scale endpoint data, which typically cannot have negative values and are easier to interpret from a clinical point of view. If endpoint data are unavailable, we will use the change data in separate analyses. If we use MD, we will pool results based on change data and endpoint data in the same analysis.

Considering that clinical trials for panic disorder are usually small and that data distribution is difficult to assess for studies with small samples, in this review we will give priority to the use and analysis of dichotomous variables both for efficacy and acceptability. Where outcome data or SDs are not recorded, we will ask authors to supply the data. When only the standard error (SE) or t-statistics or P values are reported, we will calculate SDs according to Altman 1996. In the absence of data from the authors, we will calculate the mean value of known SDs from the group of included studies according to Furukawa 2006. We will check that the original SDs are properly distributed, so that the imputed SD represents the average.

Relative treatment rankings

We will estimate the ranking probabilities (and their 95% CrIs) for all treatments of being at each possible rank.

Cluster-randomised trials

In cluster-randomised trials groups of individuals rather than individuals are randomised to different interventions. If we identify cluster placebo-controlled randomised trials, we will use the generic inverse variance technique, if such trials have been appropriately analysed taking into account intraclass correlation coefficients to adjust for cluster effects. Where trialists have not adjusted for the effects of clustering, we will attempt to do this by obtaining an intracluster correlation coefficient and then following the guidance given in chapter 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Cross-over trials

Cross-over trials are trials in which all participants receive both the control and intervention treatment but in a different order. The major problem is a carry-over effect from the first phase to the second phase of the study, especially if the condition of interest is unstable (Elbourne 2002). As this is the case with panic disorder, we will include randomised cross-over studies but will use only data up to the point of first cross-over.

Studies with multiple treatment groups

Multi-arm studies where the same medication at different doses is compared will remain intact with no adjustments to the numerator or denominator of the shared intervention group. We will account for the correlation between the effect sizes from multi-arm studies using the approach suggested in Higgins 1996 and Dias 2013a.

Dose-ranging studies

We will also include dose-ranging studies—where different doses of the same medication are compared to each other—and we will pool the different dose arms and consider them to be one so long as they are within the standard range (see above).

Dealing with missing data

We will try to contact the study authors for all relevant missing data.

(1) Dichotomous outcomes

We will calculate response, or remission on treatment, using an intention-to-treat analysis (ITT). We will follow the principle 'once randomised always analysed'. Where participants left the study before the intended endpoint, we will assume that they would have experienced the negative outcome. We will test the validity of the above assumption by sensitivity analysis, applying worst- and best-case scenarios. When dichotomous outcomes are not reported but the baseline mean and SD on a panic disorder scale are reported,

we will calculate the number of responding or remitted participants according to a validated imputation method (Furukawa 2005). We will analyse the validity of the above approach by sensitivity analysis. If necessary, authors of studies will be contacted to obtain data or clarification (or both).

(2) Continuous outcomes

Concerning continuous data, the *Handbook* recommends avoiding imputation of continuous data and suggests using the data as presented by the original authors. Where ITT data are available, we will prefer them to 'per-protocol analysis'. If necessary, we will contact authors of studies to obtain data or clarification (or both).

(3) Skewed or qualitative data

We will present skewed and qualitative data descriptively.

We will consider several strategies for skewed data. If papers report a mean and SD and there is also an absolute minimum possible value for the outcome, we will divide the mean by the SD. If this is less than 2, then we will conclude that there is some indication of skewness. If it is less than 1 (that is the SD is bigger than the mean) then there is almost certainly skewness. If papers have not reported the skewness and simply report means, SDs and sample sizes, we will use these numbers. Because there is a possibility that these data may not have been properly analysed, and can also be misleading, we will conduct analyses with and without these studies. If the data have been log-transformed for analysis, and the geometric means are reported, skewness will be reduced. This is the recommended method of analysis of skewed data (Higgins 2019). If papers use non-parametric tests and describe averages using medians, they cannot be formally pooled in the analysis. We will follow the recommendation made in the *Handbook* that results of these studies be reported in a table in our review, along with all other papers. This means that the data will not be lost from the review and the results can be considered when drawing conclusions, even if they cannot be formally pooled in the analyses.

(4) Missing statistics

When only P or SE values are reported, we will calculate SDs (Altman 1996). In the absence of supplementary data after requests to the authors, the SDs will be calculated according to a validated imputation method (Furukawa 2006). We will examine the validity of these imputations in the sensitivity analyses.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in Section 10 of the *Handbook* (Higgins 2019). We will examine small-study effects in the network, including publication bias, through network meta-regression (Chaimani 2012); see Sensitivity analysis section below for further details.

Assessment of transitivity across treatment comparisons

Transitivity characterises a network of interventions when the distributions of potential effect modifiers (as described above) are balanced across all pair-wise comparisons. Transitivity can be interpreted as the extension of the clinical and methodological heterogeneity across the network of different comparisons, and is necessary to ensure a valid network meta-analysis. We will evaluate transitivity in this review as follows.

(1) We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; for example, whether antidepressants are administered in the same way in studies comparing antidepressants to placebo and in those comparing antidepressants to benzodiazepines.

(2) We will compare the distribution of the potential effect modifiers across the different pair-wise comparisons.

Data synthesis

We will conduct random-effects network meta-analyses (NMAs) that compare three or more interventions across a network of studies. NMAs combine together both direct (interventions compared in trials) and indirect evidence (interventions not compared directly in trials but part of the network) (Higgins 2019). We will conduct all NMAs in a Bayesian framework, and take into account the correlations induced by multi-arm trials, using WinBUGS 1.4.3 (Winbugs 2012) or OpenBUGS (Lunn 2009). We will use standard non-informative priors based on published WinBUGS code (Dias 2013a).

There are three possible models that could be fitted.

1. A class (lumped) model (i.e. antidepressants (ADs) and benzodiazepines (BDZs) will be compared with each other and with placebo).
2. An individual treatment model (i.e. all ADs and BDZs listed in the 'Types of Intervention' section will be compared with each other and with placebo).
3. A hierarchical model where we include both class and treatments.

We will investigate models depending on the available data and use network plots to illustrate the structure of these networks.

We will measure the goodness of fit of the model to the data by the posterior mean of the residual deviance. This is defined as the difference between the deviance for the fitted model and the deviance for the saturated model, where deviance measures the fit of the model to the data points using the likelihood function. Where necessary we will examine leverage plots to help identify any specific data points (trial arms) that were fitting poorly in each model. A leverage plot displays the leverage (a measure of influence equal to the contribution of each trial arm to P_D, the effective number of parameters) versus the signed, square root of the residual deviance (a measure of fit) for each data point. Points with a high leverage are influential, which means that they have a strong influence on the model parameters that generate their fitted values.

Given the complexity of the models, we have not prespecified burn in and number of iterations. These will be determined as part of a model-fitting process. Convergence will be assessed using two chains and based on the Brooks-Gelman-Rubin diagnostic tool in WinBUGS.

Assessment of statistical heterogeneity

We will assume a homogeneous between-study variability across studies (Lu 2004).

We will base the statistical assessment of heterogeneity in the entire network on the magnitude of the heterogeneity standard

deviation parameter, Tau^2, estimated from the model and the 95% prediction interval for the relative treatment effects.

Inconsistency can be considered an additional layer of heterogeneity which can occur in networks of evidence. It can occur when there is a discrepancy between a direct and indirect estimate of treatment effect.

We will also use global goodness-of-fit statistics to compare a model assuming consistency with a model that does not. In case of considerable inconsistency we will investigate possible sources of it (e.g. mistakes in data extraction or in data entry).

We will conduct node-splitting analyses to identify in greater detail inconsistencies in the network (van Valkenhoef 2016). We will conduct these analyses on the two primary outcomes: response to treatment and total dropouts for any reason.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are often exploratory in nature and should be interpreted cautiously: firstly, because they often involve multiple analyses leading to false positive results; and secondly, because these analyses lack power and are more likely to result in false negative results. Therefore, we will explore heterogeneity using the following covariates in the network meta-analyses for the two primary outcomes.

- People with panic disorder without agoraphobia versus people with panic disorder and agoraphobia.
- Date: we will include the publication year as a continuous variable, centred on the mean date. An earlier review noted evidence of attrition bias in earlier studies of benzodiazepines (Breilmann 2019). Design and statistical analyses of clinical trials have changed over time; we will therefore assess if this is a source of heterogeneity.
- Placebo response: related to the earlier point, Breilmann 2019 found that trials of benzodiazepines may underestimate placebo response rates. In addition, the onset of action differs between interventions (e.g. SSRIs, TCAs, benzodiazepines) included in the network. Therefore, this may be a source of heterogeneity in placebo response that may impact on the network. We propose to include placebo response as a random effect, allowing response rates to differ by intervention.

Sensitivity analysis

The following sensitivity analyses have been planned a priori. We will examine if the results change and check for the robustness of the observed findings by:

1. excluding trials with imputed response rate;
2. excluding studies using ad hoc outcome scale versus studies using a validated scale such as the Panic Disorder Severity Scale (PDSS) Panic Disorder Severity Scale, Clinical Global Impression Severity Scale, and Clinical Global Impression Change Scale (for responses and remission outcomes only);
3. including, where doses vary between trials, these different doses for each treatment as separate nodes in the network;
4. conducting bias-adjustment models for the two primary outcomes (Dias 2013b). The following models will be fitted.

a) Bias adjustment: an initial exploration of the data suggests there may be differences between small and large studies. To estimate the influence of small-study effects on the network meta-analyses we will examine the association between effect estimates and their variance (small studies usually have larger variances). We will also investigate the impact of high risk of bias for each of the domains of the Cochrane 'Risk of bias' tool.

Analyses will be conducted on the primary outcomes using WinBUGS. We will assess the magnitude of the bias parameter along with its 95% credible intervals (CrIs). The impact on relative effects estimates and between-trial standard deviation will also be examined.

b) Bias arising from missing data: as we've noted above, trial analyses of missing data may have resulted in bias. Therefore, we will estimate the magnitude of "informative missing parameters" and assess the impact of adjusting for these effects in the network meta-analyses. We propose to conduct sensitivity analyses for the two primary outcomes.

Our routine comparisons of random-effects and fixed-effect models, as well as our secondary outcomes of remission rates and continuous severity measures, may be considered additional forms of sensitivity analyses.

'Summary of findings' table

We will create a 'Summary of findings' table including the primary outcomes: response and total number of dropouts.

Currently, two methods for evaluating confidence in the results of an NMA have been recommended in the *Handbook*: CINeMA (CINeMA 2017; Nikolakopoulou 2019); and GRADE working group approaches (Puhan 2014).

However, only frequentist NMA estimates are compatible with CINeMA software. The complexity of our analyses requires modelling to be conducted in a Bayesian framework. Therefore, we are unable to use the CINeMA approach in our review.

There are also potential limitations with the Puhan 2014 approach noted in a recent paper (Phillippo 2019). Since confidence ratings are based on individual pairwise comparisons, rather than the network as a whole, applying this method could potentially generate logically incoherent judgements in some contexts.

We therefore plan to use threshold analyses to explore the impact of potential biases and evaluate the confidence in our NMA estimates (Phillippo 2018; Phillippo 2019).

We will conduct threshold analyses at the study and contrast level (Phillippo 2019). We will judge a clinically important effect to consist of OR = 0.67 or OR = 1.50 compared with placebo for both primary outcomes. Some concerns with imprecision will be indicated by a 95% CrI exceeding 0.67 or 1.50. Major concerns with imprecision will be indicated by a 95% CrI exceeding both 0.67 and 1.50. We will estimate invariant intervals where any changes (at the study or contrast level) within this threshold would not impact our conclusions on the precision of our NMA estimates.

To assess the impact of risk of bias and reporting bias (or small-study effects) we will compare these identified thresholds with published estimates (e.g. Savovic 2018) and parameters estimated

in our bias adjustment models. We will assess whether the conclusions are likely to be robust given the estimated magnitude of bias.

To assess the impact of heterogeneity we will re-run the threshold analyses based on 95% prediction intervals (which capture heterogeneity not taken into account by CrIs) and compare with the findings using 95% CrIs.

In terms of incoherence, where inconsistency between direct and indirect evidence has been identified in our analyses we will assess the extent to which the conclusions are likely to be robust to these data issues.

Similarly, if indirectness has been identified we will assess the likely impact on our conclusions based on the estimated invariant intervals.

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APPENDICES

Appendix 1. Cochrane Specialized Register

The Cochrane Common Mental Disorders Group (CCMD) maintains an archived controlled trials register known as the CCMDCTR. This specialized register contains over 40,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm, and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register with more than 50% of reference records tagged to around 12,500 individually PICO-coded study records. Reports of studies for inclusion in the register were collated from (weekly) generic searches of key bibliographic databases to June 2016, which included: MEDLINE (1950 onwards), Embase (1974 onwards), PsycINFO (1967 onwards), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and review-specific searches of additional databases. Reports of studies were also sourced from international trials registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) are on the Group's website, with an example of the core MEDLINE search displayed below.

[MeSH Headings]: eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/ OR *[Title/ Author Keywords]:* (eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).tw,kf. AND *[RCT filter]:* (controlled clinical trial.pt. or randomised controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomised controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs were tagged to the appropriate study record.

The CCMDCTR-Studies Register will be searched for this review on condition alone.
Condition = panic
Records will be manually screened for drug therapy trials.

The CCMDCTR-References Register will be searched using a more sensitive set of free-text terms to identify additional untagged/uncoded reports of RCTs. A further search will be conducted to identify drug therapy trials for 'Anxiety Disorders Not Otherwise Specified' (ADNOS), which may include a subset of participants with panic disorder

CCDANCTR-Refs Search 1 (panic):
#1. panic or agoraphobi*
#2. (antidepress* or anti-depress* or "anti depress*" or MAOI* or RIMA* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) NEAR (uptake or reuptake or re-uptake or "re uptake")) or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or pharmacotherap* or psychotropic* or "drug therapy")
#3. (agomelatine or alaproclate or amoxapine or amineptine or amitriptylin* or amitriptylinoxide or atomoxetine or befloxatone or benactyzine or binospirone or brofaromine or (buproprion or amfebutamone) or butriptyline or caroxazone or cianopramine or cilobamine or cimoxatone or citalopram or (chlorimipramin* or clomipramin* or chlomipramin* or clomipramine) or clorgyline or clovoxamine or (cx157 or tyrima) or demexiptiline or deprenyl or (desipramine* or pertofrane) or desvenlafaxine or dibenzepin or diclofensine or dimetacrin* or dosulepin or dothiepin or doxepin or duloxetine or desvenlafaxine or dvs-233 or escitalopram or etoperidone or femoxetine or fluotracen or fluoxetine or fluvoxamine or (hyperforin or hypericum or "st john*") or imipramin* or iprindole or iproniazid* or ipsapirone or isocarboxazid* or levomilnacipran or lofepramine* or ("lu aa21004" or vortioxetine) or "lu aa24530" or (ly2216684 or edivoxetine) or maprotiline or melitracen or metapramine or mianserin or milnacipran or minaprine or mirtazapine or moclobemide or nefazodone or nialamide or nitroxazepine or nomifensine or norfenfluramine or nortriptylin* or noxiptilin* or opipramol or oxaflozane or paroxetine or phenelzine or pheniprazine or pipofezine or pirlindole or pivagabine or pizotyline or propizepine or protriptylin* or quinupramine or reboxetine or rolipram or scopolamine or selegiline or sertraline or setiptiline or teciptiline or thozalinone or tianeptin* or toloxatone or tranylcypromin* or trazodone or trimipramine or venlafaxine or viloxazine or vilazodone or viqualine or zalospirone)
#4. (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or "ethyl loflazepate" or "cm 6912" or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or "wy 3498" or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or (zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or "z drugs") or *pam or *lam or nonbenzo*)
#5. (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or *piron* or or gabapentin* or pregabalin or mirogabalin or imagabalin)
#6. (#1 and (#2 or #3 or #4 or #5))
CCDANCTR-Refs Search 2 (ADNOS) :
#7. ((anxiety or anxious or ADNOS) and not (agoraphobi* or panic or (social NEAR (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or "post trauma*" or posttrauma*))
#8. (#7 and (#2 or #3 or #4 or #5))

Appendix 2. Other database searches

Biomedical database update searches will be restricted from 2014 to present.

Cochrane Central Register of Controlled Trials (CENTRAL)

Current Issue

#1MeSH descriptor: [Panic] this term only
#2MeSH descriptor: [Panic Disorder] this term only
#3MeSH descriptor: [Agoraphobia] this term only
#4(panic or agoraphobi*)
#5#1 or #2 or #3 or #4
#6MeSH descriptor: [Antidepressive Agents] explode all trees
#7MeSH descriptor: [Neurotransmitter Uptake Inhibitors] explode all trees
#8MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees
#9(antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*)

#10(Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone)
#11MeSH descriptor: [Benzodiazepines] explode all trees
#12(benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs or nonbenzo*)
#13(azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or gabapentin* or pregabalin or mirogabalin or imagabalin)
#14(placebo* or dummy or "sugar pill*")
#15#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16#5 and #15
#17(2014* or 2015* or 2016* or 2017*)
#18#16 and #17

Ovid MEDLINE databases

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 (panic or agoraphobi*).mp.
2 exp Antidepressive Agents/
3 exp Neurotransmitter Uptake Inhibitors/
4 exp Monoamine Oxidase Inhibitors/
5 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp.
6 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.
7 exp Benzodiazepines/
8 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or

midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs or nonbenzo*).mp.
9 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or gabapentin* or pregabalin or mirogabalin or imagabalin).mp.
10 (placebo* or dummy or sugar pill).mp.
11 or/2-10
12 randomized controlled trial.pt.
13 randomi#ed.ti,ab,kf.
14 controlled clinical trial.pt.
15 Double-Blind Method/
16 clinical trials as topic.sh.
17 randomly.ab.
18 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,kf.
19 trial.ti,kf.
20 (animals not (humans and animals)).sh.
21 or/12-19
22 21 not 20
23 1 and 11 and 22
24 (NLM or HSR).ro.
25 23 and 24
26 (2014* or 2015* or 2016*).yr,ed.
27 25 and 26
28 remove duplicates from 27

Ovid Embase

1980 to present
1 Panic/
2 Agoraphobia/
3 (panic or agoraphobi*).mp.
4 or/1-3
5 exp antidepressant agent/
6 exp serotonin uptake inhibitor/
7 exp serotonin noradrenalin reuptake inhibitor/
8 exp noradrenalin uptake inhibitor/
9 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or
Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.
10 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp.
11 exp Benzodiazepine derivative/
12 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or

propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs or nonbenzo*).mp.
13 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or gabapentin* or pregabalin or mirogabalin or imagabalin).mp.
14 (placebo* or dummy or sugar pill*).mp.
15 or/5-14
16 major clinical study/
17 Randomized controlled trial/
18 Controlled clinical study/
19 double blind procedure/
20 randomization/
21 (RCT or randomi#ed).ti,ab,kw.
22 ((at random or random*) adj2 (allocat* or assign* or divide* or division or number)).ti,ab,kw.
23 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw.
24 or/16-23
25 ((animal or nonhuman) not (human and (animal or nonhuman))).de.
26 24 not 25
27 4 and 15 and 26
28 elsevier.cr.
29 27 and 28
30 (random* adj sampl* adj7 ("cross section*" or questionnaire*1 or survey* or database*1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
31 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.
32 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
33 (Systematic review not (trial or study)).ti.
34 (review.ab. and review.pt.) not trial.ti.
35 or/30-34
36 29 not 35
37 (2014* or 2015* or 2016*).yr,dd.
38 36 and 37

Ovid PsycINFO

1987 to present
1 Panic Attack/ or Panic/ or Panic Disorder/
2 Agoraphobia/
3 (panic or agoraphobi*).mp.
4 adnos.ti,ab,id.
5 (anxiety disorder* adj2 otherwise specified).ti,ab,id.
6 or/1-5
7 exp Antidepressant Drugs/
8 Neurotransmitter Uptake Inhibitors/ or exp serotonin norepinephrine reuptake inhibitors/ or exp serotonin reuptake inhibitors/
9 exp Monoamine Oxidase Inhibitors/
10 exp Tricyclic Antidepressant Drugs/
11 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp.
12 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.
13 exp benzodiazepines/

14 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs or nonbenzo*).mp.
15 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or gabapentin* or pregabalin or mirogabalin or imagabalin).mp.
16 (placebo* or dummy or sugar pill*).mp.
17 or/7-16
18 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,id.
19 trial.ti,id.
20 randomi#ed.ti,ab,id.
21 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).ti,ab,id.
22 (placebo* or dummy or sugar pill*).mp.
23 or/18-22
24 6 and 17 and 23
25 (2014* or 2015* or 2016*).yr,an.
26 24 and 25
27 ((anxiety or ADNOS) not (agoraphobi* or panic or (social adj3 (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or post trauma* or posttrauma*)).ti,id,hw.
28 17 and 23 and 27
29 25 and 28
30 26 or 29

WHAT'S NEW

Date	Event	Description
27 October 2020	New citation required and major changes	Protocol updated from earlier published version (Guaiana 2017)

HISTORY

Protocol first published: Issue 7, 2017

CONTRIBUTIONS OF AUTHORS

GG, CB, MK, TAF and AC conceived the review. GG, DC and AC wrote the draft of the protocol. NM, SD and DC contributed to the methodology and all authors critically commented on the protocol. HI, AT, AC, IB and AC will select the studies, appraise their quality and extract data.

DECLARATIONS OF INTEREST

GG: is a diplomate of the Academy of Cognitive Therapy.
CB: no conflicts of interest.
NM: no conflicts of interest.
SJD: no conflicts of interest.
TAF: has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Otsuka, Pfizer, Shionogi and Mitsubishi-Tanabe, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha publishers. He has received grant or research support from the Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, the Japan Foundation for Neuroscience and Mental Health, Mitsubishi-Tanabe and Mochida. He is diplomate of the Academy of Cognitive Therapy. TAF has a patent 2018-177688 pending.
HI: no conflicts of interest.
SD: no conflicts of interest.
DC: no conflicts of interest.

MK: no conflicts of interest.
AT: has received honoraria for speaking at a meeting sponsored by Eli Lilly and Tanabe-Mitsubishi.
IB: no conflicts of interest.
AP: no conflicts of interest.
AC: was expert witness for Accord Healthcare in a patent issue about quetiapine extended release. Outside the submitted work, AC has received consultancy fees from INCiPiT (Italian Network for Paediatric Trials), and educational and consultancy from Angelini Pharma.

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Internal sources

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  Salary and protected research time for GG
- University of Verona, Italy

  Salary for CB, IB
- University of Bristol, UK

  Salary for DC
- University of Toronto, Canada

  Salary and protected time for SJD
- Kyoto University, Japan

  Salary for TAF, HI, AT
- University of Oxford, UK

  Salary for AC

External sources

- No sources of support supplied