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[Intervention Review]

Benzodiazepines versus placebo for panic disorder in adults

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ABSTRACT

Background

Panic disorder is characterised by recurrent unexpected panic attacks consisting of a wave of intense fear that reaches a peak within a few minutes. Panic disorder is a common disorder, with an estimated lifetime prevalence of 1% to 5% in the general population and a 7% to 10% prevalence in primary care settings. Its aetiology is not fully understood and is probably heterogeneous.

Panic disorder is treated with psychological and pharmacological interventions, often used in combination. Although benzodiazepines are frequently used in the treatment of panic disorder, guidelines recommend antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), as first-line treatment for panic disorder, particularly due to their lower incidence of dependence and withdrawal reaction when compared to benzodiazepines. Despite these recommendations, benzodiazepines are widely used in the treatment of panic disorder, probably because of their rapid onset of action.

Objectives

To assess the efficacy and acceptability of benzodiazepines versus placebo in the treatment of panic disorder with or without agoraphobia in adults.

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR Studies and References), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950-), Embase (1974-), and PsycINFO (1967-) up to 29 May 2018. We handsearched reference lists of relevant papers and previous systematic reviews. We contacted experts in the field for supplemental data.

Selection criteria

All double-blind (blinding of patients and personnel) controlled trials randomising adults with panic disorder with or without agoraphobia to benzodiazepine or placebo.

Data collection and analysis

Two review authors independently checked the eligibility of studies and extracted data using a standardised form. Data were then entered into Review Manager 5 using a double-check procedure. Information extracted included study characteristics, participant characteristics, intervention details, settings, and outcome measures in terms of efficacy, acceptability, and tolerability.

Main results

We included 24 studies in the review with a total of 4233 participants, of which 2124 were randomised to benzodiazepines and 1475 to placebo. The remaining 634 participants were randomised to other active treatments in three-arm trials. We assessed the overall methodological quality of the included studies as poor. We rated all studies as at unclear risk of bias in at least three domains. In addition, we judged 20 of the 24 included studies as having a high risk of bias in at least one domain.

Two primary outcomes of efficacy and acceptability showed a possible advantage of benzodiazepines over placebo. The estimated risk ratio (RR) for a response to treatment was 1.65 (95% confidence interval (CI) 1.39 to 1.96) in favour of benzodiazepines, which corresponds to an estimated number needed to treat for an additional beneficial outcome (NNTB) of 4 (95% CI 3 to 7). The dropout rate was lower among participants treated with benzodiazepines (RR 0.50, 95% CI 0.39 to 0.64); the estimated NNTB was 6 (95% CI 5 to 9). We rated the quality of the evidence as low for both primary outcomes. The possible advantage of benzodiazepine was also seen for remission (RR 1.61, 95% CI 1.38 to 1.88) and the endpoint data for social functioning (standardised mean difference (SMD) -0.53, 95% CI -0.65 to -0.42), both with low-quality evidence. We assessed the evidence for the other secondary outcomes as of very low quality. With the exception of the analyses of the change score data for depression (SMD -0.22, 95% CI -0.48 to 0.04) and social functioning (SMD -0.32, 95% CI -0.88 to 0.24), all secondary outcome analyses showed an effect in favour of benzodiazepines compared to placebo. However, the number of dropouts due to adverse effects was higher with benzodiazepines than with placebo (RR 1.58, 95% CI 1.16 to 2.15; low-quality evidence). Furthermore, our analyses of adverse events showed that a higher proportion of participants experienced at least one adverse effect when treated with benzodiazepines (RR 1.18, 95% CI 1.02 to 1.37; low-quality evidence).

Authors' conclusions

Low-quality evidence shows a possible superiority of benzodiazepine over placebo in the short-term treatment of panic disorders. The validity of the included studies is questionable due to possible unmasking of allocated treatments, high dropout rates, and probable publication bias. Moreover, the included studies were only short-term studies and did not examine the long-term efficacy nor the risks of dependency and withdrawal symptoms. Due to these limitations, our results regarding the efficacy of benzodiazepines versus placebo provide only limited guidance for clinical practice. Furthermore, the clinician's choice is not between benzodiazepines and placebo, but between benzodiazepines and other agents, notably SSRIs, both in terms of efficacy and adverse effects. The choice of treatment should therefore be guided by the patient's preference and should balance benefits and harms from treatment in a long-term perspective.

PLAIN LANGUAGE SUMMARY

Benzodiazepines for panic disorder in adults

Why is this review important?

Panic disorder is common in the general population and is characterised by recurrent unexpected panic attacks consisting of a wave of intense fear that reaches a peak within a few minutes. Agoraphobia often develops after one or more panic attacks and is a fear of being in situations where escape may be difficult or help would not be available if needed. Panic disorder is treated with psychological interventions and medication, often used in combination. Although not usually recommended as first-line treatment, benzodiazepines are frequently used in the treatment of panic disorder. Benzodiazepines show a rapid onset of action, but they also have a high risk of dependency and withdrawal symptoms.

Who will be interested in this review?

Patients and general practitioners.

What questions does this review aim to answer?

How effective is treatment with benzodiazepine compared to placebo (a sham treatment) in treating panic disorder with or without agoraphobia?

How acceptable are benzodiazepines compared to placebo in treating panic disorder with or without agoraphobia?

How many people with panic disorder with or without agoraphobia who are treated with benzodiazepines experience side effects compared to placebo?

Which studies were included in the review?

We searched electronic databases and study registers to find all relevant studies. We only included randomised controlled trials (a type of study in which participants are assigned to a treatment group using a random method) that compared treatment with benzodiazepine and placebo in adults with a diagnosis of panic disorder with or without agoraphobia. We only included studies in which patients and the clinicians did not know which treatment they received. We included 24 studies with a total of 4233 participants in our review.

What does the evidence from the review tell us?

We found consistent evidence for a possible advantage of benzodiazepines in the improvement of panic symptoms and in the number of participants dropping out of treatment. Furthermore, benzodiazepines may improve social functioning more than placebo. However, there may be more dropouts due to side effects and more participants who experience at least one side effect when treated with benzodiazepines. We found several severe limitations in the design of the included studies. For example, it seems that at least in some studies participants and physicians were able to guess to which treatment arm the participants were allocated, thus it is possible that some trials were not really blinded. These limitations may have led to an overestimation of the treatment effect. Another major limitation is that our included studies were only short-term studies and did not reflect the risks of dependency and withdrawal symptoms. Furthermore, it is unclear if the effect is maintained after the end of treatment.

What should happen next?

High-quality long-term studies should be carried out to establish whether the benefits of treatment can be maintained and to put the benefits in context of withdrawal effects and the risk of dependency. However, it is unlikely that the general conclusions regarding the short-term efficacy and the dependency potential of benzodiazepines will change. Comparisons with other active treatment including psychotherapy, for example in multiple-treatment meta-analyses, may thus be more suitable to inform clinical practise.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Benzodiazepines compared to placebo for adults with panic disorder

Benzodiazepines compared to placebo for adults with panic disorder

Patient or population: adults with panic disorder

Intervention: Benzodiazepines

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Benzodiazepines			
Response follow up: range 3 weeks to 15 weeks	Study population		RR 1.65 (1.39 to 1.96)	2476 (16 RCTs)	⊕⊕⊕⊕ LOW 1 2 3 4
	412 per 1.000	679 per 1.000 (572 to 807)			
Total number of dropouts follow up: range 4 weeks to 15 weeks	Study population		RR 0.50 (0.39 to 0.64)	3558 (21 RCTs)	⊕⊕⊕⊕ LOW 1 2 3 4
	346 per 1.000	173 per 1.000 (135 to 222)			
Remission follow up: range 5 weeks to 15 weeks	Study population		RR 1.61 (1.38 to 1.88)	2907 (15 RCTs)	⊕⊕⊕⊕ LOW 1 2 3 4
	404 per 1.000	651 per 1.000 (558 to 760)			
Panic symptoms - endpoint score assessed with: CGI-S, CGI-I, PGI Scale from: 1 to 7 follow up: range 4 weeks to 8 weeks	The mean panic symptoms - endpoint score was 0 SD	SMD 0.92 SD lower (1.22 lower to 0.61 lower)	-	1489 (7 RCTs)	⊕⊕⊕⊕ VERY LOW 1 2 3 4 5
Panic symptoms - mean change assessed with: CGI-S, CGI-I, PGI Scale from: 1 to 7 follow up: range 4 weeks to 10 weeks	The mean panic symptoms - mean change was 0	SMD 0.5 lower (0.87 lower to 0.13 lower)	-	719 (4 RCTs)	⊕⊕⊕⊕ VERY LOW 1 2 3 4 5
Number of dropouts due to adverse effects follow up: range 4 weeks to 15 weeks	Study population		RR 1.58 (1.16 to 2.15)	3263 (14 RCTs)	⊕⊕⊕⊕ LOW 1 2 3 4
	41 per 1.000	65 per 1.000			

(47 to 88)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CGI-I: Clinical Global Impression - Improvement; **CGI-S:** Clinical Global Impression - Severity; **CI:** Confidence interval; **PGI:** Patient's Global Impression; **RCT:** randomised controlled trial; **RR:** Risk ratio; **SD:** standard deviation; **SMD:** standardised mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- ¹ Downgraded one point due to study limitations (unclear allocation concealment, possibly broken blinded assessment, and high dropout rates (>20%)).
- ² Despite the high statistical heterogeneity not downgraded for inconsistency, because the direction of the effects is consistent.
- ³ Not downgraded for indirectness, because we do not have evidence supporting that the effect will differ significantly in comorbid patients.
- ⁴ Downgraded one point due to publication bias.
- ⁵ Downgraded one point due to wide confidence intervals.

BACKGROUND

Description of the condition

A panic attack is a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes, and in which at least 4 of 13 characteristic symptoms are experienced (APA 2013b). Many of these symptoms involve bodily systems, such as racing heart, chest pain, sweating, shaking, dizziness, flushing, stomach churning, faintness, and breathlessness. Further recognised panic attack symptoms involve cognitive symptoms, such as the fear of losing control or going crazy, fear of dying, and derealisation (APA 2013b).

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 the tricyclic antidepressant imipramine (Klein 1964). To diagnose panic disorder, further conditions must be met relating to the frequency of attacks, the need for some 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-5 requires additionally that at least one attack has been followed by either 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 2013b).

In DSM-5, panic disorder and agoraphobia are no longer linked and are now coded in two diagnoses, while the core features of panic attacks remain unchanged (APA 2013a).

Panic disorder is common in the general population with a lifetime prevalence of 1% to 5% (Bandelow 2015; de Jonge 2016). In primary care settings panic disorder have been reported to have a prevalence of around 7% to 10% (King 2008; Serrano-Blanco 2010). Its aetiology is not fully understood and is probably heterogeneous as it is neither exclusively biological nor exclusively psychological induced (Dresler 2013). Cognitive theories hypothesise that panic disorder occurs due to catastrophic misinterpretations of bodily sensations, mainly those involved in normal anxiety reactions (e.g. palpitations, breathlessness) (Clark 1993). 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, such as that involving the periaqueductal gray matter (Dresler 2013; Gorman 2000). The periaqueductal gray matter is, for example, involved in ascending and descending pain modulation and contributes to defensive behaviours and postural freezing (Gorman 2000; Hemington 2015).

Agoraphobia is 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 1994). Even though agoraphobia can be diagnosed separately from panic disorder since DSM-5, it often occurs with panic disorder (APA 2013b). About one-fourth of people suffering from panic disorder also have agoraphobia (Kessler 2006). The presence of agoraphobia in conjunction with panic disorder is associated with increased severity and impairment (Kessler 2006). There are several risk

factors that predict the development of agoraphobia in people suffering from panic disorder: female gender, more severe dizziness during panic attacks, cognitive factors, dependent personality traits, and social anxiety disorder (Starcevic 2009).

Panic disorder, with or without agoraphobia, is highly comorbid 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 major depression has a prevalence of 24% to 88% among people with panic disorder (Starcevic 2009).

Description of the intervention

The treatment of panic disorder includes psychological and pharmacological interventions, often used in combination (Bandelow 2017; Watanabe 2009). Historically, pharmacological interventions for panic disorder have been based on the use of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) (Bruce 2003). However, MAOIs and TCAs are burdened by severe adverse effects, such as dietary restrictions (to avoid hypertensive crisis) for MAOIs, and anticholinergic side effects (e.g. dry mouth, sedation) or orthostatic hypotension, which may result in falls in elderly patients and overall poor tolerability for TCAs (Batelaan 2012; Wade 1999). Benzodiazepines, particularly high-potency ones, have been used as a safer alternative in panic disorder (Stein 2010). However, guidelines (American Psychiatric Association guideline: APA 2009; British Association for Psychopharmacology guideline: Baldwin 2014; National Institute for Health and Care Excellence guideline: NICE 2011) consider antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), as first-line treatment for panic disorder, due to their more favourable adverse effect profile over MAOIs and TCAs, and the lower incidence of dependence and withdrawal reaction when compared to benzodiazepines (Bandelow 2012). Moreover, benzodiazepines alone may not be effective in treating panic disorder comorbid with depression (Ballenger 1998; Dell'osso 2013), and have a less good long-term outcome (NICE 2011). In spite of these caveats, it appears that benzodiazepines continue to be widely prescribed for the treatment of panic disorder (Bruce 2003; Olsson 2015).

How the intervention might work

Benzodiazepines moderate the gamma-Aminobutyric acid (GABA) neurotransmitter system, which is the brain's main inhibitory neurotransmitter. They act as agonists at the GABA-A benzodiazepine receptor. This complex contains a chloride channel which can be opened by agonists which ultimately produce anxiolysis and sedation. The benzodiazepine binding site communicates only indirectly with the channel, meaning that benzodiazepines are safer than their predecessors, the barbiturates. It is known through imaging studies that the inhibitory GABA system is deficient in panic disorder (Cameron 2007; Malizia 1998), and thus benzodiazepines' ability to act as agonists at the GABA-A benzodiazepine receptor can counteract this. It is likely that both monoamine-based systems and GABA-based systems converge, allowing both antidepressants and benzodiazepines 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 periaqueductal gray matter.

Why it is important to do this review

Benzodiazepines are widely used in panic disorder. Published randomised controlled trials show some evidence of efficacy (Batelaan 2012). Two meta-analyses concerning the effects of benzodiazepines in comparison to placebo for the treatment of panic disorder were published in 1991 and 1993. In these meta-analyses, the authors compared the effectiveness of psychological and pharmacological treatments (Clum 1993), and the effect of antidepressants and benzodiazepines compared with placebo (Wilkinson 1991). Both reviews showed superiority of benzodiazepines to placebo in the treatment of panic disorder in adults. However, no systematic review on all benzodiazepines in panic disorder has been conducted in recent years. An up-to-date review was needed to help prescribers identify the effect size of active treatment compared to placebo in panic disorder for short- and long-term treatment, in order to be better guided in the choice of the pharmacological agent.

OBJECTIVES

To assess the effects of benzodiazepines for panic disorder in adults, specifically to:

1. determine the efficacy of benzodiazepines in alleviating symptoms of panic disorder with or without agoraphobia in comparison to placebo;
2. review the acceptability of benzodiazepines in panic disorder with or without agoraphobia in comparison with placebo; and
3. investigate the adverse effects of benzodiazepines in panic disorder with or without agoraphobia, including the general prevalence of adverse effects, compared to placebo.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind (blinding of patients and personnel) randomised controlled trials (RCTs) using a parallel-group design that compare benzodiazepines with placebo as monotherapy. We included cross-over trials, RCTs with more than two arms, and cluster RCTs.

We excluded quasi-randomised trials, such as those allocated by using alternate days of the week. We only included double-blind studies because of the subjectivity of the endpoints and a substantial placebo response in panic disorder patients (Rosenberg 1994).

Types of participants

Participants

People aged 18 years or older.

Diagnosis

People with primary diagnosis of panic disorder, with or without agoraphobia, diagnosed according to any of the following criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, or International Statistical Classification of Diseases and Related Health Problems (ICD-10). In case study eligibility focused on agoraphobia, rather than panic disorder, we included studies if operationally diagnosed according to the above-named

criteria and when it was possible to safely assume that at least 30% of the participants were suffering from panic disorder as defined by the above criteria. There is evidence that over 95% of participants with agoraphobia suffer from panic disorder as well (Goisman 1995). However, we planned to examine the effect of the inclusion of these studies, for example in a subgroup analysis.

Comorbidities

We excluded studies in which all participants had a serious comorbid physical disorders (e.g. myocardial infarction, chronic obstructive pulmonary disorder, uncontrolled diabetes, electrolyte disturbances), as they may confound treatment effectiveness and tolerability. We excluded studies where panic was induced.

We included participants with comorbid mental disorders, but examined the effect of including these participants in subgroup analyses.

Settings

We included all types of settings (inpatient, outpatient, primary care).

Types of interventions

Any trial comparing a benzodiazepine as monotherapy (alprazolam, bretazenil, bromazepam, chlordiazepoxide, cinolazepam, clonazepam, clobazepam, clorazepate, diazepam, estazolam, fludiazepam, flunitrazepam, flurazepam, flutoprazepam, halazepam, ketazolam, lorazepam, lorazepam, medazepam, nimatazepam, nitrazepam, nodazepam, oxazepam, phenazepam, pinazepam, prazepam, premarazepam, quazepam, temazepam, tetrazepam, and triazolam) with placebo in the treatment of panic disorder, with or without agoraphobia.

We included acute treatment studies treating participants for less than six months. We excluded long-term and relapse prevention studies, as these might cause heterogeneity and limit the validity of our results.

We applied no restriction on dose, frequency, intensity, route of administration, or duration.

We excluded studies administering psychosocial therapies targeted at panic disorder concurrently.

Types of outcome measures

Primary outcomes

1. Rate of response, i.e. substantial improvement from baseline as defined by the original investigators. Examples would be 'very much or much improved' according to the Clinical Global Impression Change Scale; more than 40% reduction in the Panic Disorder Severity Scale score (which is considered as equivalent to 'very much or much improved' on the Clinical Global Impression of Improvement Scale (CGI-I)) (Furukawa 2009); and more than 50% reduction in the Fear Questionnaire Agoraphobia Subscale (which is considered as an appropriate rate of response according to Bandelow 2006).
2. Total number of dropouts for any reason as a proxy measure of treatment acceptability.

Secondary outcomes

1. Remission, i.e. satisfactory end-state as defined by global judgement of the original investigators. Examples would be 'panic free' and 'no or minimal symptom' according to the Clinical Global Impression - Severity Scale (CGI-S).
2. Panic symptom scales and global judgement on a continuous scale. Examples include Panic Disorder Severity Scale total score (0 to 28), CGI-S (1 to 7), and Clinical Global Impression Change Scale (1 to 7). When multiple measures were used, we gave preference according to the order above with preference given to panic symptoms scales. The measurements used in the meta-analyses are listed in the 'Description of studies' section (see 'Outcomes').
3. Frequency of panic attacks, e.g. as recorded by a panic diary.
4. Agoraphobia, e.g. as measured by Fear Questionnaire, Mobility Inventory, behavioural avoidance test.
5. General anxiety, e.g. as measured by Hamilton Rating Scale for Anxiety, Beck Anxiety Inventory, State-Trait Anxiety Index, Sheehan Patient-Rated Anxiety Scale, Anxiety Subscale of Symptom Checklist-90-Revised (SCL-90-R).
6. Depression, e.g. as measured by Hamilton Rating Scale for Depression, Beck Depression Inventory, Depression Subscale of SCL-90-R.
7. Social functioning, e.g. as measured by Sheehan Disability Scale, Global Assessment Scale, Social Adjustment Scale-Self Report.
8. Quality of life, e.g. as measured by 36-item Short Form Health Survey (SF-36), SF-12.
9. Patient satisfaction with treatment.
10. Economic costs.
11. Number of dropouts due to adverse effects.
12. Number of participants experiencing at least one adverse effect.

Timing of outcome assessment

All outcomes were short term, which we defined as acute-phase treatment that would normally last two to six months.

When studies reported response rates at different time points within two to six months, we gave the time point closest to 12 weeks preference.

Search methods for identification of studies

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

The Cochrane Common Mental Disorders Group (CCMD) maintained a comprehensive, specialised register of RCTs, the CCMDCTR (to June 2016). The 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 c12,500 individually PICO coded study records. Reports of trials for inclusion in the register were collated from (weekly) generic searches of MEDLINE (1950-), Embase (1974-), and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and review-specific searches of additional databases. Reports of trials were also sourced from international trial 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) can be found on the Group's website with an example of the core MEDLINE search displayed in [Appendix 1](#).

Electronic searches

Searches for this review have been through a number of iterations. We initially ran a broad search of CCMDCTR using the following terms for a suite of panic reviews registered with the Group (1 January 2013):

CCMDCTR-Studies

Diagnosis = "panic disorder" and Age Group = (adult or aged or unclear or "not stated")

We manually screened all records for placebo-controlled benzodiazepine trials.

CCMDCTR-References

We searched the References Register using the free-text term 'panic*' to identify additional untagged, uncoded references. We screened abstracts for benzodiazepine trials and checked full-text articles where necessary to check for placebo controls.

In March 2014 and September 2015, we updated the search across three panic reviews simultaneously (BZDs vs PBO; ADs vs PBO; ADs vs BZDs), using the following combination of search terms: ((ADs or BZDs) and (Panic or ADNOS)) ([Appendix 2](#)).

Other database searches

Prior to publication we ran a cross-search of Ovid MEDLINE, Embase, and PsycINFO (3 May 2017 and 29 May 2018) using terms for 'Panic + BZDs + RCT filter' (only) ([Appendix 3](#)). We also searched CENTRAL, the international trial registers, and the CCMDCTR at this time (although the latter was only up-to-date as of 30 June 2016 due to staff changes within the Group). We limited the update search to results published since 2014.

Searching other resources

We checked 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 contacted experts in the field.

Data collection and analysis

Selection of studies

Two review authors (FG (clinical expertise), MK (methodological expertise)) independently selected trials for inclusion in the review.

FG and MK inspected the search hits by reading the titles and the abstracts to see if they met the inclusion criteria. Disagreements were resolved by consultation with the coauthors. We obtained the full articles of each study deemed potentially relevant, and the two review authors independently assessed the full-texts for inclusion in the review. In case of discordance, consensus was sought by discussion between the review authors. Where it was not possible to evaluate a study because of the language or missing information, we categorised the study as 'awaiting classification' until a translation or further information can be obtained. We reported the reasons for the exclusions of trials in the 'Characteristics of excluded studies' table.

All decisions made during the selection process, with numbers of studies and references, were recorded and presented in a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two review authors (FG, MK) used a data extraction form to independently extract the following data from the included studies: participant characteristics (age, sex, severity of panic disorder, study setting), intervention details (dosage, duration of study, sponsorship), study characteristics (blinding, allocation, etc.), and outcome measures of interest. We first piloted the extraction sheet on a sample of 10% of the included studies. Any disagreements were resolved by discussion or by consulting a third review author (CB). If necessary, we contacted the authors of the studies to obtain clarification.

Main comparison

1. Benzodiazepines (as defined in [Types of interventions](#)) versus placebo.

Assessment of risk of bias in included studies

Two review authors (FG, MK) independently assessed the risk of bias using the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This tool encourages consideration of how the randomisation sequence was generated, how allocation was concealed, the integrity of blinding of participants, personnel, and outcome assessment, the completeness of outcome data, selective reporting, and other biases. We also considered sponsorship bias.

We assessed and categorised risk of bias, in each domain and overall, into:

1. low risk of bias; plausible bias unlikely to seriously alter the results;
2. high risk of bias; plausible bias that seriously weakens confidence in the results; and
3. unclear risk of bias; plausible bias that raises some doubt about the results.

In case of disagreement between the assessors, the final rating was made by consensus or with the involvement of a third review author (CB). Where details of randomisation and other characteristics of trials were inadequate, we contacted the study authors to obtain further information.

Measures of treatment effect

The main outcome was reduction of severity of panic and agoraphobia symptoms. Clinical improvement was usually presented as a change in a panic disorder scale(s) (mean and standard deviation (SD)) or as a dichotomous outcome (responder or non-responder, remitted or not-remitted), or both.

Binary or dichotomous data

For binary outcomes, we calculated a standard estimation of the random-effects model risk ratio (RR) and its 95% confidence interval (CI). It has been shown that a random-effects model has good generalisability (Furukawa 2002), and that RR is more intuitive than odds ratio (Boissel 1999). Furthermore, odds ratios tend to be interpreted as RR by clinicians (Deeks 2000), which may lead to an

overestimation of the impression of the effect (Higgins 2011). For all primary outcomes we calculated the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) statistic and its 95% CI using Visual Rx (Cates 2018), taking into account the event rate in the control group.

Continuous data

Summary statistics

In accordance with the protocol, we summarised continuous data from different scales as standardised mean difference (SMD). If all included studies used the same instrument, we used the mean difference (MD) as effect size.

Endpoint versus change data

Trials usually report results either using endpoint means and SD of scales or using change in mean values from baseline of assessment rating scales. We preferred 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 were unavailable, we used the change data in separate analyses. In case we calculated MD, we pooled results based on change data and endpoint data in the same analysis.

Unit of analysis issues

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 the possibility of 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, randomised cross-over studies were eligible for inclusion, but we planned to use only data up to the point of first cross-over.

Studies with multiple treatment groups

If a study had more than two treatment arms, especially two appropriate dose groups of the same drug, the different dose arms were pooled and considered to be one using the procedures described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cluster-randomised trials

In cluster-randomised trials, groups of individuals rather than individuals are randomised to different interventions. If we identified cluster placebo-controlled randomised trials, we planned to use the generic inverse variance technique if such trials had been appropriately analysed taking into account intraclass correlation coefficients to adjust for cluster effects. Where trialists had not adjusted for the effects of clustering, we planned to attempt to follow the guidance in Section 16.3.4 of the *Cochrane Handbook* (Higgins 2011).

Dealing with missing data

We attempted to contact study authors for all relevant missing data. We used the following strategies only if the missing information was not available or if we received no response from the authors.

Dichotomous outcomes

We calculated response, or remission on treatment, using an intention-to-treat analysis following the principle 'once randomised always analysed'. Where participants left the study before the intended endpoint, it was assumed that they would have experienced the negative outcome. We planned to test the validity of the above assumption by sensitivity analysis, applying worst- and best-case scenarios. When dichotomous outcomes were not reported, but the baseline mean and SD on a panic disorder scale were reported, we calculated the number of responding or remitted participants according to a validated imputation method (Furukawa 2005). We tested the validity of the above approach by sensitivity analysis. If necessary, we contacted authors of studies to obtain data or clarification or both.

Continuous outcomes

The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) recommends avoiding imputations of continuous data and suggests using the data as presented by the original authors. Where intention-to-treat data were available, they have been preferred to 'per-protocol' analysis.

Skewed or qualitative data

We planned to present skewed and qualitative data descriptively.

We considered several strategies for skewed data. If papers reported a mean and SD, and there was also an absolute minimum possible value for the outcome, we planned to divide the mean by the SD. If this quotient was less than two, we concluded that there was some indication of skewness. If it was less than one (i.e. the SD is bigger than the mean), then there was almost certainly skewness. If papers did not report the skewness and simply reported means, SDs, and sample sizes, these numbers were used. Because there was a possibility that these data may not have been properly analysed and could also be misleading, we conducted analyses with and without these studies. If the data had been log-transformed for analysis, and the geometric means were reported, skewness was reduced. This is the recommended method of analysis of skewed data (Higgins 2011). If studies used non-parametric tests and described averages using medians, they could not be formally pooled in the analysis. We followed the recommendation of the *Cochrane Handbook* that results of these studies should be reported in a table in our review, along with all other papers. This means that the data were not lost from the review, and their results could be considered when drawing conclusions, even if they could not be formally pooled in the analyses.

Missing statistics

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

Assessment of heterogeneity

Following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, heterogeneity was quantified by the I^2 statistic. Section 9.5.2 of the *Cochrane Handbook*

recommends overlapping intervals for I^2 interpretation (Higgins 2011), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

We used the χ^2 test and its P value as a statistical test for heterogeneity. In a meta-analysis of few trials, χ^2 will be underpowered to detect heterogeneity, if it exists. We used a P value of 0.10 as a threshold of statistical significance for the χ^2 test. We also visually assessed the forest plots for evidence of heterogeneity.

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 Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A funnel plot is usually used to investigate publication bias, although it is limited if there are only few studies of similar size. In addition, asymmetry in a funnel plot does not always reflect publication bias. We used visual inspection of funnel plots to assess publication bias as well as the statistical test for funnel plot asymmetry proposed by Eggers or Rücker (Higgins 2011). We did not use funnel plots for outcomes if there were 10 or fewer studies, or if all studies were of similar size.

Data synthesis

We used random-effects models to calculate the treatment effects. We preferred the random-effects model, as it takes into account differences between studies even when there is no evidence of statistical heterogeneity. Due to a wider confidence interval, it is usually a more conservative estimate than the fixed-effect model. We note that the random-effects model gives added weight to small studies, which can either increase or decrease the effect size. We applied a fixed-effect model on primary outcomes only to see whether it markedly changed the effect size.

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 and lead to false positive results; and secondly, these analyses lack power and are more likely to result in false-positive results. Keeping in mind the above reservations, we planned to perform the following subgroup analyses.

1. For participants with agoraphobia and for participants without agoraphobia, because the same treatment may have differential effects with regard to panic and agoraphobia.
2. If groups within any of the subgroups were found to be significantly different from one another, we ran meta-regression for exploratory analyses of additive or multiplicative influences of the variables in question.
3. We compared acute-phase treatment studies that lasted for less than four months versus acute-phase treatment studies that last for four months or more.
4. We conducted a post hoc subgroup analysis for individual medications to investigate differences between benzodiazepines.

5. We conducted post hoc meta-regression analyses to investigate the influence of trial duration on the primary outcomes.

We explored subgroup differences by examining the overlap of the confidence intervals and the formal test for heterogeneity across subgroup implemented in Review Manager 5 ([Review Manager 2014](#)). We conducted meta-regressions with the 'metafor' package in R using a random-effects model ([Viechtbauer 2010](#)).

Sensitivity analysis

We examined the robustness of our observed findings by excluding studies:

1. at high risk of bias in at least one domain (i.e. trials with inadequate allocation concealment and blinding, with incomplete data reporting, and/or with high probability of selective outcome reporting);
2. with dropout rates greater than 20%;
3. funded by the pharmaceutical company marketing each benzodiazepine. This sensitivity analysis is particularly important in view of the repeated findings that funding strongly affects outcomes of research studies ([Als-Nielsen 2003](#); [Bhandari 2004](#); [Lexchin 2003](#)), and because industry sponsorship and authorship of clinical trial reports have increased over the last 20 years ([Buchkowsky 2004](#)); and

4. whose participants clearly had significant psychiatric comorbidities including primary or secondary depressive disorders.

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

'Summary of findings' table

We summarised the findings using a 'Summary of findings' table, according to the GRADE approach ([Higgins 2011](#)).

RESULTS

Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#), and [Characteristics of studies awaiting classification](#).

Results of the search

The searches (last update May 2018) identified 1828 references, of which 1744 remained after de-duplication. We excluded 1564 references after assessment of titles and abstracts. We retrieved 180 full-text papers for full inspection, of which 156 were excluded. Twenty-four studies fulfilled our inclusion criteria and were included in the review. See [Figure 1](#) for a PRISMA flow diagram depicting the study selection process ([Moher 2009](#)).

Figure 1. Study flow diagram.

Included studies

We included 24 studies in this review (Baker 2003; Beauclair 1994; Carter 1995; CNCPS 2° phase 1992; Davidson 1994; Garvey 1989; GSK 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Munjack 1989a; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Savoldi 1990; Schweizer 1992; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Tesar 1991; Uhlenhuth 1989; Valenca 2000). One study fulfilling the inclusion criteria contained no usable data, but was included in the review (Garvey 1989). Study characteristics are listed as follows (see also [Characteristics of included studies](#)).

Design

All included studies were randomised trials and applied double-blind methodology. Nine studies randomised their participants into three or more treatment arms with one or more benzodiazepine groups, an active comparator group, and a placebo group (CNCPS 2° phase 1992; GSK 1994; Klosko 1990; Munjack 1989a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Uhlenhuth 1989). The remaining 15 studies compared one or more benzodiazepines to placebo (Baker 2003; Beauclair 1994; Carter 1995; Davidson 1994; Garvey 1989; Lydiard 1992; Moroz 1999; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Savoldi 1990; Schweizer 1992; Schweizer 1993a; Tesar 1991; Valenca 2000). One study used a cross-over design (Schweizer 1992). We did not identify relevant cluster-randomised trials.

Trial duration

The treatment in two studies lasted 3 weeks (Garvey 1989; Schweizer 1992), in 5 studies 4 weeks (Baker 2003; Beauclair 1994; Carter 1995; Davidson 1994; Savoldi 1990), 1 study 5 weeks (Munjack 1989a), in 6 studies 6 weeks (Lydiard 1992; Moroz 1999; Pecknold 1994; Schweizer 1993a; Tesar 1991; Valenca 2000), in 7 studies 8 weeks (CNCPS 2° phase 1992; Noyes 1996; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Uhlenhuth 1989), and in 3 other studies the treatment lasted 9, Rosenbaum 1997, 10, GSK 1994, or 15, Klosko 1990, weeks. All studies used the end of the treatment as final follow up time for the acute treatment phase.

Five studies extended the acute phase to evaluate the effects of discontinuation of benzodiazepines, which lasted from five weeks, Schweizer 1993a, to six, Carter 1995, or seven weeks (Moroz 1999; Rosenbaum 1997). One study did not report the length of the discontinuation follow-up (CNCPS 2° phase 1992).

Sample sizes

The included studies involved a total of 4233 participants. Of these, 2124 were randomised to benzodiazepines. Of the remaining 2109 participants, 1475 were randomised to placebo, 482 to imipramine, 77 to paroxetine, 34 to buspirone, 23 to propranolol, and 18 to behaviour therapy. The mean sample size per arm was 77 participants (range 2 to 391). We did not include one study in this summary because the sample size was inconsistently reported (Garvey 1989).

Setting

Eight studies were multicentre trials (Carter 1995; CNCPS 2° phase 1992; Davidson 1994; GSK 1994; Moroz 1999; Noyes 1996; Pecknold 1994; Rosenbaum 1997). The remaining 16 studies did not state the number of centres. Twenty-one studies were conducted in

a single nation, namely the USA (Carter 1995; Davidson 1994; Garvey 1989; GSK 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Munjack 1989a; Rosenbaum 1997; Schweizer 1992; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Tesar 1991; Uhlenhuth 1989), Canada (Baker 2003; Beauclair 1994), Brazil (Valenca 2000), and Italy (Savoldi 1990). One study was conducted in two nations: the USA and Canada (Pecknold 1994). Two studies recruited participants across continents: one study included 15 countries in Europe and North and South America (CNCPS 2° phase 1992), and one study was conducted in North America and Australia (Noyes 1996).

Four studies enrolled outpatients (Beauclair 1994; Moroz 1999; Rosenbaum 1997; Uhlenhuth 1989). The remaining 20 studies did not explicitly report the setting.

Participants

With the exception of two studies (Baker 2003; GSK 1994), all included studies involved participants with a diagnosis of panic disorder with agoraphobia or phobic avoidance. The remaining two studies included people with panic disorder, but did not explicitly include people with agoraphobia or phobic avoidance. Eight studies enrolled people with secondary depressive disorders (CNCPS 2° phase 1992; GSK 1994; Klosko 1990; Lydiard 1992; Noyes 1996; Pecknold 1994; Sheehan 1993; Tesar 1991).

Thirteen studies recruited participants between the ages of 18 and 65 years (Baker 2003; Beauclair 1994; Carter 1995; CNCPS 2° phase 1992; Davidson 1994; Garvey 1989; Klosko 1990; Lydiard 1992; Munjack 1989a; Pecknold 1994; Schweizer 1993a; Schweizer 1993b; Sheehan 1993). Four studies recruited participants in the following age ranges: 18 to 64 years (Tesar 1991), 18 to 55 years (Valenca 2000), 20 to 50 years (Savoldi 1990), and 55 to 73 years (Sheikh 1999). Three studies reported inclusion of participants 18 years or older, GSK 1994; Rosenbaum 1997, or "over the legal age of consent", Moroz 1999. Four studies did not report the age range. The mean age (SD) in these four studies was: 36.6 (10.5) (Noyes 1996), 35 (Schweizer 1992), 34.7 (Taylor 1990), and 31.5 (7.12) (Uhlenhuth 1989).

Interventions and comparators

All included studies compared benzodiazepines to placebo: 12 studies examined alprazolam (CNCPS 2° phase 1992; GSK 1994; Klosko 1990; Lydiard 1992; Munjack 1989a; Pecknold 1994; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Uhlenhuth 1989), five studies clonazepam (Baker 2003; Beauclair 1994; Moroz 1999; Rosenbaum 1997; Valenca 2000), two studies adinazolam (Carter 1995; Davidson 1994), one study etizolam (Savoldi 1990), and one study midazolam (Schweizer 1992). Three studies compared two benzodiazepines to placebo: alprazolam and diazepam, Garvey 1989; Noyes 1996, and alprazolam and clonazepam, Tesar 1991. Additional active comparators were: imipramine (CNCPS 2° phase 1992; Schweizer 1993b; Sheikh 1999; Taylor 1990; Uhlenhuth 1989), paroxetine (GSK 1994), propranolol (Munjack 1989a), buspirone (Sheehan 1993), and behaviour therapy (Klosko 1990).

Outcomes

The included studies used the following outcome measures, and were used in our meta-analyses.

1. Panic symptoms and global judgement: CGI-S (Beauclair 1994; Carter 1995; Davidson 1994; GSK 1994; Moroz 1999; Pecknold 1994; Rosenbaum 1997; Schweizer 1993a; Tesar 1991; Valenca 2000), CGI-I (Noyes 1996), Physician's Global Improvement Rating (CNCPS 2° phase 1992), Physician's Global Impression (Sheikh 1999).
2. Frequency of panic attacks: panic attack diary (Davidson 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Noyes 1996; Pecknold 1994; Schweizer 1992; Schweizer 1993a; Schweizer 1993b; Sheikh 1999; Taylor 1990; Tesar 1991; Uhlenhuth 1989); Panic Attack Index, 10-point scale (Beauclair 1994), Panic and Anxiety Attack Scale (Carter 1995).
3. Agoraphobia: Overall/Global Phobia Scale (CNCPS 2° phase 1992; GSK 1994; Noyes 1996; Pecknold 1994; Schweizer 1993a; Sheehan 1993; Taylor 1990; Tesar 1991; Uhlenhuth 1989), SCL-90 Phobia Scale (Davidson 1994; Carter 1995), Assessor Phobia Avoidance Scale (Munjack 1989a), Level of Fear (Schweizer 1993b).
4. General anxiety: Hamilton Anxiety Rating Scale (HAMA) (Beauclair 1994; CNCPS 2° phase 1992; Davidson 1994; GSK 1994; Klosko 1990; Moroz 1999; Munjack 1989a; Noyes 1996; Pecknold 1994; Savoldi 1990; Schweizer 1992; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Uhlenhuth 1989).
5. Depression: Hamilton Depression Rating Scale (Beauclair 1994; CNCPS 2° phase 1992; Munjack 1989a; Pecknold 1994; Savoldi 1990; Schweizer 1993a; Sheehan 1993; Sheikh 1999; Taylor 1990; Uhlenhuth 1989), Montgomery-Åsberg Depression Rating Scale (GSK 1994), Beck Depression Inventory (Tesar 1991).
6. Social functioning: Five-point Work and Social Disability Scale (CNCPS 2° phase 1992; Noyes 1996; Schweizer 1993b; Taylor 1990; Tesar 1991; Uhlenhuth 1989), Three-factor Disability Scale (Sheehan 1993), Social Adjustment Self-Report Questionnaire (GSK 1994).

Sixteen studies reported response rates (Baker 2003; Beauclair 1994; Carter 1995; Davidson 1994; GSK 1994; Klosko 1990; Moroz 1999; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Savoldi 1990; Schweizer 1992; Schweizer 1993a; Sheehan 1993; Uhlenhuth 1989; Valenca 2000). The studies used varying definitions of response: receiving a score of 1 or 2 on CGI-I (Carter 1995; Davidson 1994; Rosenbaum 1997; Schweizer 1992), $\geq 50\%$ decrease from baseline in number of panic attacks (GSK 1994; Schweizer 1993a), number of panic attacks per wk < 3 (Uhlenhuth 1989), $\geq 50\%$ decrease from baseline in scores (Baker 2003), $\geq 50\%$ decrease from baseline on the CGI-S (Beauclair 1994), "much" or "very much" improved in CGI-S score panic disorder rating (Moroz 1999), rating of non-clinical severity (Klosko 1990), ≥ 8 on Clinical Global Impression-

Improvement (Noyes 1996), much improved or better (Pecknold 1994), "excellent" or "good" at clinician's rating of improvement (Savoldi 1990), score 4 to 10 on CGI-21 (Sheehan 1993), $\geq 50\%$ decrease from baseline in HAMA (Valenca 2000).

All but three studies reported the total number of dropouts (Baker 2003; Garvey 1989; Schweizer 1992). Fifteen studies reported dropouts due to adverse effects (Beauclair 1994; Carter 1995; CNCPS 2° phase 1992; Davidson 1994; GSK 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Savoldi 1990; Schweizer 1993a; Schweizer 1993b; Tesar 1991). Four studies reported the total number of participants experiencing side effects (GSK 1994; Moroz 1999; Savoldi 1990; Valenca 2000).

Fifteen studies reported remission rates (CNCPS 2° phase 1992; GSK 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Munjack 1989a; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Taylor 1990; Tesar 1991; Valenca 2000). All 15 studies defined remission rate as the proportion of participants who were free of panic attacks.

No study reported data on quality of life, patient satisfaction with treatment, or economic outcomes.

Excluded studies

Overall, we excluded 85 studies from the review because of the inclusion criteria. The main reasons for exclusion were the lack of a relevant comparators (no placebo group) or a wrong diagnosis (e.g. other anxiety disorder; psychoneurotic participants; healthy participants). Further reasons were: a wrong intervention, a wrong study design, and the lack of relevant data (see also Figure 1 and Characteristics of excluded studies). For one study we received information that the data were from a subsample of a larger study, but the author could not remember of which study (Fava 1989). To avoid double inclusion, the study was excluded.

Ongoing studies

We did not identify any ongoing studies.

Studies awaiting classification

We were unable to assess nine studies, which are awaiting classification (see Characteristics of studies awaiting classification).

Risk of bias in included studies

For graphical representations of the 'Risk of bias' assessment, please refer to Figure 2 and Figure 3. Details and justification for the 'Risk of bias' ratings of each included study are presented in the 'Risk of bias' tables in Characteristics of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baker 2003	?	?	?	?	?	-	?
Beauchair 1994	?	?	+	+	-	+	?
Carter 1995	?	?	+	?	?	-	?
CNCPS 2* phase 1992	+	?	+	?	-	-	?
Davidson 1994	?	?	?	?	+	-	?
Garvey 1989	?	?	?	?	?	?	?
GSK 1994	?	?	?	?	?	?	?
Klosko 1990	?	?	+	+	-	-	?
Lydiard 1992	?	?	+	?	-	-	?
Moroz 1999	?	?	+	?	-	-	?
Munjack 1989a	?	?	-	?	-	-	?
Noyes 1996	?	?	?	?	-	-	?
Pecknold 1994	?	?	?	?	-	-	?
Rosenbaum 1997	+	?	+	?	?	-	?
Savoldi 1990	?	?	?	?	-	?	?
Schweizer 1992	?	?	?	?	+	?	?
Schweizer 1993a	?	?	+	?	-	+	?
Schweizer 1993b	?	?	+	?	-	+	?
Sheehan 1993	?	?	+	?	-	-	?
Sheikh 1999	?	?	+	?	-	?	?

Figure 3. (Continued)

Sheikh 1999	?	?	+	?	-	?	?
Taylor 1990	?	?	-	-	-	-	?
Tesar 1991	?	?	+	?	-	+	?
Uhlenhuth 1989	?	?	+	?	+	+	?
Valenca 2000	?	?	?	?	?	-	?

The overall methodological quality of the studies was poor. We rated all studies as having an unclear risk of bias in at least three domains. In addition, we judged 20 of the 24 included studies as having a high risk of bias in at least one domain.

Allocation

Twenty-two studies did not report details on the sequence generation and were judged as having an unclear risk of bias (Baker 2003; Beauclair 1994; Carter 1995; Davidson 1994; Garvey 1989; GSK 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Munjack 1989a; Noyes 1996; Pecknold 1994; Savoldi 1990; Schweizer 1992; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Taylor 1990; Tesar 1991; Uhlenhuth 1989; Valenca 2000). Two studies provided sufficient information on sequence generation (CNCPS 2° phase 1992; Rosenbaum 1997).

None of the included studies provided sufficient information on allocation concealment, therefore we rated all trials as having an unclear risk of bias for this domain.

Blinding

Performance bias

All of the included studies were declared as “double-blind”. In nine trials, the authors provided no further information concerning the mechanism of blinding and were judged as being at unclear risk of performance bias (Baker 2003; Davidson 1994; Garvey 1989; GSK 1994; Noyes 1996; Pecknold 1994; Savoldi 1990; Schweizer 1992; Valenca 2000). Thirteen studies provided information on blinding methods (e.g. use of identical tablets) and were judged as having a low risk of bias for this domain (Beauclair 1994; Carter 1995; CNCPS 2° phase 1992; Klosko 1990; Lydiard 1992; Moroz 1999; Rosenbaum 1997; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Tesar 1991; Uhlenhuth 1989). We rated two studies as having a high risk of bias (Munjack 1989a; Taylor 1990), because additional analysis of these samples showed that physicians, Munjack 1989b, or participants and physicians, Margraf 1991, were able to guess the assignment with high accuracy.

Detection bias

We rated two trials as having a low risk of detection bias (Beauclair 1994; Klosko 1990). We rated one trial as having a high risk of detection bias (Taylor 1990), because data were collected from participants and physicians, and both were able to guess the participants' group assignment (Margraf 1991). The remaining trials did not provide details on the blinding of the assessors, therefore we judged the risk of bias to be unclear.

Incomplete outcome data

We rated three trials to be adequate in terms of addressing incomplete outcome data (Davidson 1994; Schweizer 1992; Uhlenhuth 1989). We classified six studies as at unclear risk of bias for this domain (Baker 2003; Carter 1995; Garvey 1989; GSK 1994; Rosenbaum 1997; Valenca 2000), and the remaining 15 studies as at high risk of bias. Most studies at high risk of attrition bias reported unequal dropout rates between the treatment groups, with higher rates in the placebo groups.

Selective reporting

For almost all studies the study protocol was not available, hindering our judgement of outcome reporting bias. However, in five studies the results were consistent with the outcomes prespecified in the methods section (Beauclair 1994; Schweizer 1993a; Schweizer 1993b; Tesar 1991; Uhlenhuth 1989), therefore we judged the risk of bias for these studies as low. Using the same criterion, we judged five studies as having an unclear risk of bias (Garvey 1989; GSK 1994; Savoldi 1990; Schweizer 1992; Sheikh 1999), and 14 as having a high risk of bias for this domain (Baker 2003; Carter 1995; CNCPS 2° phase 1992; Davidson 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Munjack 1989a; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Sheehan 1993; Taylor 1990; Valenca 2000).

Other potential sources of bias

We assessed all but one study, Baker 2003, as having an unclear risk of bias for this domain, because they were sponsored or supported by pharmaceutical companies marketing benzodiazepines (Hoffmann-La Roche; Upjohn, Bristol-Myers Squibb), or there was no information on study sponsoring.

Effects of interventions

See: [Summary of findings for the main comparison Benzodiazepines compared to placebo for adults with panic disorder](#)

COMPARISON 1: Benzodiazepines versus placebo

This comparison comprises 14 outcomes. See also: Summary of findings table 1.

Primary outcomes

1.1 Treatment response

Sixteen studies provided data on treatment response, including a total of 2476 participants. We found a difference between benzodiazepines and placebo (risk ratio (RR) 1.65, confidence

interval (CI) 1.39 to 1.96; $P < 0.001$) in favour of benzodiazepines (Analysis 1.1, Figure 4). The outcome showed substantial levels of heterogeneity ($I^2 = 67\%$; $P < 0.001$). The magnitude of effect

corresponds to a number needed to treat for an additional beneficial outcome (NNTB) of 4 (95% CI 3 to 7).

Figure 4. Forest plot of comparison: 1 Benzodiazepines versus placebo, outcome: 1.1 Treatment response.

1.2 Total number of dropouts

We were able to extract data on treatment dropout from 21 studies involving a total of 3558 participants (Analysis 1.2, Figure 5). Fewer participants dropped out when treated with benzodiazepines

compared to placebo (RR 0.50, CI 0.39 to 0.64; $P < 0.001$). Heterogeneity of study effects was substantial ($I^2 = 63\%$; $P < 0.001$). The magnitude of the effect corresponds to an NNTB of 6 (95% CI 5 to 9); treating six people with benzodiazepines will result in one person fewer dropping out.

Figure 5. Forest plot of comparison: 1 Benzodiazepines versus placebo, outcome: 1.2 Total number of dropouts.

Secondary outcomes

1.3 Treatment remission

Data on remission were available from 15 studies, including a total of 2907 participants. More participants were panic-free after treatment with benzodiazepines compared to participants treated with placebo (RR 1.61, CI 1.38 to 1.88; $P < 0.001$) (Analysis 1.3). Heterogeneity of remission rates was substantial ($I^2 = 62\%$; $P < 0.001$).

1.4 Panic symptom scales and global judgement on a continuous scale

Eleven studies reported data on endpoint or change scores. In accordance with our protocol, we have presented endpoint and change score data independently.

1.4.1 Endpoint data

Seven trials (1489 participants) reported endpoint data on a panic symptom scale.

We found evidence for better symptomatic improvement with benzodiazepine compared to placebo (standardised mean difference (SMD) -0.92, CI -1.22 to -0.61; $P < 0.001$). The heterogeneity was considerable ($I^2 = 80\%$; $P < 0.001$) (Analysis 1.4). For two studies included in this analysis we found some indication of skewness (Sheikh 1999; Valenca 2000). The exclusion of these studies changed the result only marginally (data not shown).

1.4.2 Change score data

Four trials (719 participants) reported change scores. Benzodiazepines were more effective than placebo in reducing panic symptoms (SMD -0.50, CI -0.87 to -0.13; $P = 0.007$). The heterogeneity was considerable ($I^2 = 80\%$; $P = 0.002$) (Analysis 1.4).

1.5 Frequency of panic attacks

Sixteen studies including 2129 participants reported frequency of panic attacks. Three of these studies did not report SDs and were not included in the meta-analysis (Moroz 1999; Sheikh 1999; Uhlenhuth 1989). The SDs could not be imputed due to the heterogeneity of the outcomes. The analysis showed an advantage favouring the treatment of benzodiazepines over placebo (mean difference (MD) -2.12, CI -3.07 to -1.17; $P < 0.001$). Heterogeneity of the effect was substantial ($I^2 = 75\%$; $P < 0.001$) (Analysis 1.5). For 12 of 13 studies included in this analysis, we found some indication of certain skewness (Carter 1995; Davidson 1994; GSK 1994; Klosko 1990; Lydiard 1992; Noyes 1996; Pecknold 1994; Schweizer 1992; Schweizer 1993a; Schweizer 1993b; Taylor 1990; Tesar 1991). The remaining study also showed an advantage of benzodiazepines in reducing the frequency of panic attacks (MD -8.40, 95% CI -11.99 to -4.81; $P < 0.001$) (Beauclair 1994).

1.6 Agoraphobia

1.6.1 Endpoint data

Eight trials (1654 participants) reported endpoint data on agoraphobic symptoms. We found evidence of lower endpoint scores in participants treated with benzodiazepines compared to placebo (SMD -0.38, CI -0.59 to -0.17; $P < 0.001$). Heterogeneity was substantial for this outcome ($I^2 = 68\%$; $P = 0.003$) (Analysis 1.6). For two studies included in this analysis, we found some indication of certain skewness (CNCPS 2° phase 1992; Sheehan 1993). The exclusion of these studies changed the results only marginally (data not shown).

1.6.2 Change score data

Five trials (717 participants) reported change scores. Participants treated with benzodiazepines showed a better improvement than participants receiving placebo (SMD -0.32, CI -0.55 to -0.08; $P = 0.008$). This subgroup had moderate levels of heterogeneity ($I^2 = 46\%$; $P = 0.12$) (Analysis 1.6).

1.7 General anxiety (Hamilton Rating Scale for Anxiety)

Seventeen studies including 2549 participants reported data on the HAMA. We found an MD of -5.24 (CI -6.59 to -3.90; $P < 0.001$) in favour of benzodiazepine. Heterogeneity was substantial ($I^2 = 68\%$; $P < 0.001$) (Analysis 1.7). For four studies included in this analysis, we found some indication of certain skewness (GSK 1994; Schweizer 1993a; Schweizer 1993b; Sheikh 1999). The exclusion of these studies changed the results only marginally (data not shown).

1.8 Depression

1.8.1 Endpoint data

Eight trials (968 participants) reported depression scale endpoint data. We found evidence for lower depression scores after treatment with benzodiazepines compared to placebo (SMD -0.7, CI -1.08 to -0.32; $P < 0.001$). Heterogeneity of the effects was considerable ($I^2 = 78\%$; $P < 0.001$) (Analysis 1.8). For two studies included in this analysis, we found some indication of certain skewness (CNCPS 2° phase 1992; Sheikh 1999). The exclusion of these studies changed the results only marginally (data not shown).

1.8.2 Change score data

We included four trials (441 participants) in this analysis. We found no evidence of a difference between benzodiazepines and placebo (SMD -0.22, CI -0.48 to 0.04; $P = 0.09$). Heterogeneity was moderate ($I^2 = 40\%$; $P = 0.17$) (Analysis 1.8).

1.9 Social functioning

1.9.1 Endpoint data

Five trials (1207 participants) were relevant to this analysis. One of these studies did not report SDs and was not included in the meta-analysis (Uhlenhuth 1989). The SDs could not be imputed because no other study used the same scale. The analysis revealed a difference in social symptom scores in favour of benzodiazepine-treated participants (SMD -0.53, CI -0.65 to -0.42; $P < 0.001$). We found no important heterogeneity ($I^2 = 0\%$; $P = 0.85$) (Analysis 1.9). For one study included in this analysis, we found some indication of certain skewness (Schweizer 1993b). The exclusion of this study changed the results only marginally (data not shown).

1.9.2 Change score data

Three trials (246 participants) reported sufficient data to be included in the analysis. One of these studies did not report SDs and was not included in the meta-analysis (Taylor 1990). The SDs could not be imputed because it was not clear which scale was used. We found no evidence of a statistically significant difference between benzodiazepines and placebo (SMD -0.32, CI -0.88 to 0.24; $P = 0.26$). Heterogeneity was substantial ($I^2 = 70\%$; $P = 0.07$) (Analysis 1.9).

1.10 Number of dropouts due to adverse effects

Fourteen studies involving 3263 participants reported the dropout due to adverse effects. More participants dropped out due to adverse events in the benzodiazepine group (RR 1.58, CI 1.16 to

2.15; $P < 0.001$). Heterogeneity was not important ($I^2 = 0\%$; $P = 0.97$) (Analysis 1.10). The magnitude of effect corresponds to a number needed to treat for an additional harmful outcome (NNTH) of 41 (95% CI 21 to 146).

1.11 Number of participants experiencing at least one adverse effect

Four studies involving 658 participants reported the number of participants with at least one adverse event. The analysis showed an increased number of participants with at least one adverse event in the benzodiazepine group (RR 1.18, CI 1.02 to 1.37; $P = 0.02$). The heterogeneity of findings across studies was moderate ($I^2 = 42\%$; $P = 0.16$) (Analysis 1.11). The magnitude of effect corresponds to an NNTH of 8 (95% CI 4 to 71).

Quality of life

None of the included studies reported data on quality of life outcomes.

Patient satisfaction with treatment

We identified no study relevant to this outcome.

Economic costs

None of the included studies reported economic data.

Subgroup analyses

Participants with agoraphobia versus participants without agoraphobia

We planned a priori to conduct two subgroup analyses for participants with and without agoraphobia (subgroup analysis 1 and 2). Most trials included participants with or without agoraphobia, and no study explicitly stated the exclusion of people with agoraphobia, thus it was not possible to conduct these subgroup analyses.

Treatment duration: less than four months versus four months and more

All of the included studies lasted less than four months, thus this subgroup analysis was not possible.

Investigated benzodiazepines

We conducted a post hoc subgroup analysis of individual medications to explore differences within the group of benzodiazepines.

We identified six different benzodiazepines in the included studies: adinazolam, alprazolam, clonazepam, diazepam, etizolam, and midazolam. The subgroup analysis did not reveal substantial differences between the subgroups in terms of treatment response (test for subgroup differences: $\text{Chi}^2 = 3.00$, $\text{df} = 5$, $P = 0.70$, $I^2 = 0\%$; Analysis 1.12). The subgroup analysis indicates that there may be differences between the benzodiazepines for number of total dropouts ($\text{Chi}^2 = 9.37$, $\text{df} = 4$, $P = 0.05$, $I^2 = 57.3\%$; Analysis 1.13).

Meta-regression

We conducted post hoc meta-regression analyses to investigate the influence of trial duration on the primary outcomes.

The analyses were not indicative of an influence of treatment duration on response rates ($b = -0.008$, $R^2 = 0.0\%$, $P = 0.829$, $I^2 = 66\%$) or dropout rates ($b = -0.052$, $R^2 = 0.0\%$, $P = 0.443$, $I^2 = 66\%$).

Sensitivity analyses

We defined the following sensitivity analyses a priori.

Exclusion of trials at high risk of bias

Thirteen of the 16 studies included in the treatment response analysis were judged as having a high risk of bias and were excluded. The high risk occurred in the following domains: incomplete outcome data (Beauclair 1994; Klosko 1990; Moroz 1999; Noyes 1996; Pecknold 1994; Savoldi 1990; Schweizer 1993a; Sheehan 1993) and selective reporting (Baker 2003; Carter 1995; Davidson 1994; Rosenbaum 1997; Valenca 2000). Accordingly, 19 of the 21 studies included in the analysis of total number of dropouts were judged as having a high risk of bias and were excluded. The high risk occurred in the following domains: blinding (Munjack 1989a; Taylor 1990), incomplete outcome data (Beauclair 1994; CNCPS 2° phase 1992; Klosko 1990; Lydiard 1992; Moroz 1999; Noyes 1996; Pecknold 1994; Savoldi 1990; Schweizer 1993a; Schweizer 1993b; Sheehan 1993; Sheikh 1999; Tesar 1991), and selective reporting (Carter 1995; Davidson 1994; Rosenbaum 1997; Valenca 2000). The exclusion of these studies did not substantially change the results from the original analysis concerning response rates and total number of dropouts (Analysis 1.14; Analysis 1.15).

Exclusion of trials with dropout rates > 20%

Ten of the 16 studies included in the treatment response analysis reported overall dropout rates of more than 20% and were excluded (Beauclair 1994; GSK 1994; Klosko 1990; Moroz 1999; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Savoldi 1990; Schweizer 1993a; Uhlenhuth 1989). The exclusion of these trials did not substantially change the results concerning response rates (Analysis 1.16).

Regarding the total number of dropouts, 17 of the 21 studies included in the analysis of total number of dropouts reported overall dropout rates of more than 20% and were excluded (Beauclair 1994; CNCPS 2° phase 1992; GSK 1994; Klosko 1990; Lydiard 1992; Moroz 1999; Munjack 1989a; Noyes 1996; Pecknold 1994; Rosenbaum 1997; Savoldi 1990; Schweizer 1993a; Schweizer 1993b; Sheikh 1999; Taylor 1990; Tesar 1991; Uhlenhuth 1989). Concerning the total number of dropouts, we no longer found evidence of a difference between benzodiazepines and placebo (Analysis 1.17).

Exclusion of trials sponsored by the manufacturer of each benzodiazepine

All studies but one, Baker 2003, were sponsored by the manufacturer or did not provide information on study sponsoring. It is likely that at least some of the studies not reporting funding were also sponsored by the manufacturer, therefore we considered the planned analyses not to be meaningful.

Exclusion of studies with subsets of participants with significant psychiatric comorbidities

Five of the 16 studies in the treatment response analysis included participants with psychiatric comorbidities and were excluded in the sensitivity analysis (GSK 1994; Klosko 1990; Noyes 1996; Pecknold 1994; Sheehan 1993). In the analysis of dropout rates, 8 of the 21 studies included participants with psychiatric comorbidities and were excluded in the sensitivity analysis (CNCPS 2° phase 1992; GSK 1994; Klosko 1990; Lydiard 1992; Noyes 1996; Pecknold 1994; Sheehan 1993; Tesar 1991). The exclusion of these studies did not substantially change the results for response and number of

dropouts compared to the original analysis ([Analysis 1.18](#); [Analysis 1.19](#)).

Exclusion of studies with imputed values

We did not use imputed values for our primary efficacy outcome 'response' or the secondary outcome 'remission'. We used few imputed SDs in our analysis of secondary outcomes ('agoraphobia', 'general anxiety', 'depression'). Details on which data were imputed can be found in the footnotes of these analysis ([Analysis 1.6](#); [Analysis 1.7](#); [Analysis 1.8](#)). The exclusion of these studies changed the results only marginally (data not shown).

Reporting bias

We visually inspected the funnel plots for the primary outcomes (see [Figure 6](#); [Figure 7](#)). Both funnel plots show an asymmetry, and thus may indicate the presence of a publication bias. We tested the asymmetry with Begg's regression test and found a statistically significant asymmetry of the effect sizes for response ($P = 0.002$) and dropout rates ($P = 0.006$). The review included one unpublished trial ([GSK 1994](#)).

Figure 6. Funnel plot of comparison: 1 Benzodiazepines versus placebo, outcome: 1.1 Treatment response.

Figure 7. Funnel plot of comparison: 1 Benzodiazepines versus placebo, outcome: 1.2 Total number of dropouts.

DISCUSSION

Summary of main results

We included 24 studies involving a total of 4233 participants in this review.

We found low-quality evidence of an advantage of benzodiazepines over placebo in terms of both primary outcomes, namely treatment response (efficacy) and total number of participants dropping out of treatment (acceptability). The estimated RR for response was 1.65, which corresponds to an estimated NNTB of 4 (95% CI 3 to 7). For total number of dropouts, the estimated RR was 0.50, and the estimated NNTB was 6 (95% CI 5 to 9). We also saw the possible advantage of benzodiazepine for remission and improvement of social functioning (endpoint data) (low-quality evidence). The evidence for the other secondary outcomes was of very low quality. With the exception of the analyses of the change score data for depression and social functioning, all secondary outcome analyses showed an effect in favour of benzodiazepines compared to placebo. Furthermore, we found low-quality evidence that the number of dropouts due to adverse effects was higher with benzodiazepines than with placebo and that a higher proportion of participants experienced at least one adverse effect when treated with benzodiazepines compared with placebo.

We rated the quality of the evidence for both primary outcomes as low due to high and unbalanced dropout rates and the substantial heterogeneity across trials (see Summary of findings table 1). For the same reasons we rated the quality of evidence for the

outcome of remission as low. We rated the evidence for the panic symptoms scales outcomes as very low quality, and the evidence for the outcome of number of dropouts due to adverse effects as low quality (see Summary of findings table 1). Our subgroup and sensitivity analyses did not indicate that the examined factors had a significant impact on the results.

Overall completeness and applicability of evidence

We conducted a comprehensive search to identify all available published and unpublished articles fulfilling our inclusion criteria, but the completeness and applicability may have been limited by various factors. Firstly, the patient populations of the included studies were highly selected. For example, most studies excluded patients with psychiatric comorbidities or patients with intake of other drugs, although panic disorder is highly comorbid with other psychiatric disorders (e.g. drug dependence, major depression, bipolar I disorder, social phobia, specific phobia, and generalised anxiety disorder) (Grant 2006; Preti 2016). The analysed population is therefore probably not fully representative of patients usually seen in routine practice, and the results of this review may not automatically apply to the general population. Secondly, although the studies included in the review were carried out in different countries from several continents, the majority of studies were conducted in the USA and Europe and thus may be not transferable to Asia, Africa, and other regions. Thirdly, we were unable to assess quality of life, patient satisfaction with treatment, and economic costs, as we found no studies reporting on these outcomes. Lastly, some analyses were underpowered (e.g. number of participants experiencing at least one adverse effect) because only a few studies

provided appropriate data for these outcomes. Finally, the validity of the outcome used to measure severity of panic disorder may be a further limitation. Panic disorder is a multifaceted disorder, typically characterised by panic attacks and avoidance, both of which deteriorate the afflicted person's functioning, but the two may be compensatory of each other (e.g. when one is completely agoraphobic, one may be free of panic attacks). More recent measures of panic disorder severity (e.g. Panic Disorder Severity Scale) take into account all of these aspects, but older studies often focused on one aspect of the disorder and thus may have neglected the other aspects. Our review was able to synthesise what was measured in the original studies only.

Quality of the evidence

Using the Cochrane 'Risk of bias' tool, we assessed the overall methodological quality of the included studies as poor. We rated all studies as having an unclear risk of bias in at least three domains. In addition, we judged 20 of the 24 included studies as having a high risk of bias in at least one domain. Among these, 15 studies showed a high risk of attrition bias, and two further studies showed a high risk of bias for blinding of participants and physicians. These potential biases are a major threat to the validity of the studies included in this review. Most studies with high risk of attrition bias reported unequal dropout rates between the treatment groups, with higher rates in the placebo groups. Furthermore, participants in the placebo group dropped out early in trials comparing benzodiazepines and placebo (Lavori 1992). The missings are thus clearly not completely random, resulting in a high risk of an underestimation of the placebo effect and therefore of an overestimation of the treatment effect, because in the last observation carried forward analyses participants are included with higher values in the placebo group, without taking into account that symptoms usually decline over time (e.g. due to natural course of the disorder, regression to the mean, etc.). This was illustrated exemplarily with data from the Cross National Collaborative Panic Study, which is included in this review (Lavori 1995). Furthermore, the bias may be reinforced by censorship of participant data at protocol violation in the first weeks (e.g. Pecknold 1994; Sheehan 1993), which was a standard procedure accepted by the regulatory authorities at that time (Lavori 1992).

Two of the included studies tested the success of blinding in additional analysis (Margraf 1991; Munjack 1989b). The trials showed that physicians, Munjack 1989b, or participants and physicians, Margraf 1991, were able to guess the assignment with high accuracy. The other studies did not report on the integrity of the blinding, but we believe that it is reasonable to question the blinding of benzodiazepine and placebo comparisons in general.

We included five outcomes in the GRADE assessment: response rate, total number of dropouts, remission, panic symptoms, and number of dropouts due to adverse effects (see Summary of findings table 1). We assessed the quality of the evidence from 'very low' to 'low' for these outcomes. We downgraded the evidence for these outcomes one point from high to moderate quality due to study limitations (unclear allocation concealment, possibly broken blinded assessment, and high dropout rates (> 20%)) and one point from moderate to low quality due to publication bias. For the outcome panic symptoms, we downgraded one further point from low to very low quality due to wide confidence intervals. We did not downgrade for inconsistency, because the direction of the effect for each outcome appeared to be consistent across

studies. The heterogeneity therefore shows merely that there are differences regarding the effect size (low, medium, large), but does not reduce the confidence in the general conclusion (Guyatt 2011a). Furthermore, we did not downgrade because of indirectness, as we do not have evidence that there will be substantial differences if, for example, people with psychiatric comorbidities were included (Guyatt 2011b).

Potential biases in the review process

The funnel plots are indicative of the presence of a publication bias, and we identified only one unpublished trial for inclusion in our review. Most of the included studies were published more than 15 years ago, and the availability of information on the licensing procedures of these drugs is very limited. Considering that for some individual benzodiazepines only one study was included (see Analysis 1.12), we think that is rather likely that there are some other unpublished trials. Furthermore, we cannot rule out a sponsorship bias, which could lead to an overestimation of the effects of interventions.

Agreements and disagreements with other studies or reviews

Our results are consistent with the results of two previous reviews comparing benzodiazepines to placebo (Clum 1993; Wilkinson 1991). Both reviews showed superiority of benzodiazepines to placebo in the treatment of panic disorder in adults. Other reviews of individual benzodiazepines, like alprazolam and diazepam (Boyer 1995; Mattick 1990), also reported superiority of these drugs over placebo.

AUTHORS' CONCLUSIONS

Implications for practice

Although our analyses show a superiority of benzodiazepines over placebo in the short-term treatment of panic disorders, we believe that this advantage should not be used to support the prescription of benzodiazepines as first-line treatment in individuals with panic disorder. We found the quality of the evidence to be low, and according to our 'Risk of bias' assessment (see above), an overestimation of the efficacy of benzodiazepines seems likely.

Furthermore, our analysis was restricted to short-term trials, which do not reflect the risks of dependency and withdrawal symptoms associated with benzodiazepines. Only five of 24 studies reported the implementation of a discontinuation phase. Recent studies have shown that approximately 60% of people with panic disorder were found to be dependent on benzodiazepines (Fujii 2015; Schallenger 2016). Intake of benzodiazepines for more than three to four weeks was already associated with producing withdrawal symptoms or symptomatic rebound if the drug was ceased abruptly (Brett 2015; Schweizer 1998). As a consequence, treatment guidelines suggest that benzodiazepines should be avoided as first-line treatment or should generally only be used for limited time periods (Baldwin 2014; NICE 2011). However, it is unclear if the effect of short-term benzodiazepine treatment is sustained after treatment. Only two of the included studies reported discontinuation effects, and both studies concluded that most participants showed a worsening of panic symptoms after their benzodiazepine treatment, although their condition was still improved compared to baseline (Moroz 1999; Rosenbaum 1997).

Our review only included comparisons of benzodiazepines and placebo, but the latter is not available as a treatment option in clinical practice. We therefore believe that decisions in clinical practice should rely mainly on direct comparisons of active treatments available to clinicians, and also consider other treatments, such as antidepressants and psychotherapy. Both are recommended by guidelines as equivalent first-line treatment (NICE 2011). In a recent review between antidepressants and benzodiazepines, benzodiazepines did not perform better than antidepressants in terms of efficacy on panic symptoms, but some benefits for benzodiazepines were found in terms of acceptability and adverse effects during short-term treatment (Bighelli 2016). Another review did not show any differences between psychological therapies and benzodiazepines in terms of short-term efficacy or participants dropping out of the studies, although the evidence was judged to be of very low quality (Imai 2016). Both reviews indicate that psychological and pharmacological alternatives to benzodiazepine treatment are available. Finally, the choice of treatment should be guided by the patient's preference and should balance long-term benefits and harms from treatment.

Implications for research

The overall low quality of the evidence supports the need for high-quality studies. In particular, the methodological shortcomings in blinding, unequal dropout rates, and intention-to-treat analyses could be addressed in future studies. However, it is questionable if higher-quality studies will have an impact on the conclusions regarding the short-term efficacy or the long-term data on dependency and withdrawal, which are key issues in the clinical

decision on treatment with benzodiazepines. Evidence on the comparisons to other treatment options may thus be clinically more relevant. In order to form a basis for treatment decision making, the results of this systematic review will contribute to a Cochrane network meta-analysis of drug treatments for people with panic disorder that is in progress, and aims to rank available drug treatments for efficacy and tolerability. However, it will be necessary to evaluate if the serious flaws in the trials have an impact on this network meta-analysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Baker 2003

Methods	Study design: Randomised controlled trial
Participants	Diagnosis: DSM-IV panic disorder
	Method of diagnosis: Structured Clinical Interview for DSM-IV (modified version)
	Age: Clonazepam: mean = 47.3 (SE = 2.76); Placebo: mean = 44.4 (SE = 1.87)

Benzodiazepines versus placebo for panic disorder in adults (Review)

Baker 2003 (Continued)

Sex: Clonazepam: F = 30%; Placebo: F = 56%

Location: Canada (Toronto Western Hospital)

Comorbidities: not stated

Rescue medication: none

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Clonazepam</u> (n = 10)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: not stated</p> <p>(2) <u>Placebo</u> (n = 17)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: not stated</p>
Outcomes	<p>Time points for assessment: baseline, end of trial</p> <p>Primary outcomes:</p> <p>(1) Anxiety: HAMA, weekly</p> <p>(2) Daily diaries</p> <p>(3) General psychiatric symptomatology: SCL-90-R</p> <p>(4) Somatosensory Amplification Scale</p> <p>(5) Illness Intrusiveness Scale</p> <p>(6) Depression: HAMD</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: supported by a grant from the Heart and Stroke Foundation of Ontario</p> <p>Declarations of interest among the primary researchers: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding. Quote: "27 patients (...) were randomised in a double-blinded fashion to 4 weeks of treatment with clonazepam or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information

Baker 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates are not reported.
Selective reporting (reporting bias)	High risk	The efficacy data of rating scales are not reported. There are data on sleep measures only.
Other bias	Unclear risk	No evidence of other bias was found.

Beauclair 1994

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III Panic disorder or agoraphobia with panic attacks</p> <p>Method of diagnosis: semistructured interview</p> <p>Age: range: 21 to 49 years (median: 34)</p> <p>Sex: M = 12; F = 17</p> <p>Location: Canada; setting: outpatients</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Clonazepam (n = 13)</u></p> <p>Duration: 4 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 to 5 mg (the actual maximum daily dose was 3.5 mg)</p> <p>(2) <u>Placebo (n = 16)</u></p> <p>Duration: 4 weeks</p> <p>Treatment protocol: flexible</p>
Outcomes	<p>Time points for assessment: days 0, 7, 14, 21, 28</p> <p>Primary outcomes:</p> <p>(1) Anxiety: modified version of HAMA</p> <p>(2) Overall improvement: CGI of severity of panic disorder; at study entry and termination, Global Assessment Scale</p> <p>(3) Type/frequency/intensity/length: panic attacks: Panic Attack Index; 10-point scale</p> <p>(4) Depression: at study entry and termination, Hamilton Rating Scale for Depression (21-item HAM-D)</p> <p>(5) Impairment: Social Readjustment Rating Scale</p> <p>Secondary outcome:</p> <p>(1) Adverse events: at each visit, general inquiry</p>
Notes	Date of study: June 1987 to June 1988

Benzodiazepines versus placebo for panic disorder in adults (Review)

Beauclair 1994 (Continued)

Funding source: not stated

Declarations of interest among the primary researchers: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to 4 weeks of treatment". No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomly allocated to 4 weeks of treatment under double-blind conditions". "Medications were administered in tablets of identical appearance under double-blind conditions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Concentration of clonazepam in plasma were measured under double-blind conditions with placebo controls"
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in the number participants completing 4 weeks of treatment. (Clonazepam = 12/13 (92.3%), Placebo = 8/16 (50%).) Quote: "The proportion of patients treated with placebo who terminated the study prematurely (50%) was significantly higher than that in the clonazepam-treated group (15.4%)". "Two types of analysis were carried out on the data: an ITT on the 29 patients who entered the trial and an efficacy analysis on the subgroup of 20 patients who completed the full 4 weeks of treatment"
Selective reporting (reporting bias)	Low risk	The clinical measures declared in the methods are reported in the results.
Other bias	Unclear risk	Quote: "The authors thank Hoffman - La Roche for assistance in carrying out this study"

Carter 1995

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R Panic disorder with agoraphobia</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III-R, Upjohn version (SCID-UP-R); medical questionnaire; physical examination; laboratory test</p> <p>Age: not stated</p> <p>Sex: not stated</p> <p>Location: USA (10 study sites)</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	Participants were randomly assigned to either:

Carter 1995 (Continued)

(1) Adinazolam SR 30 mg (n = 79)

Duration: 4 weeks

Treatment protocol: fixed dose: 30 mg

(2) Adinazolam SR 60 mg (n = 81)

Duration: 4 weeks

Treatment protocol: fixed dose: 60 mg

(3) Adinazolam SR 90 mg (n = 72)

Duration: 4 weeks

Treatment protocol: fixed dose: 90 mg

(4) Placebo (n = 83)

Duration: 4 weeks

Outcomes	<p>Time points for assessment: baseline, weeks 1, 2, 4</p> <p>Primary outcomes:</p> <p>(1) Number of panic attacks: Panic Anxiety Attack Scale</p> <p>(2) Global improvement: CGI-I, CGI-S</p> <p>(3) Agoraphobia: SCL-90-R</p> <p>(4) Overall phobic avoidance: Patient-rated Phobia Scale (a modification of the Fear Questionnaire)</p> <p>Secondary outcome:</p> <p>(1) Adverse events: 35-item medical events checklist; non-pre-printed events recorded by investigators on the checklist form; pre-printed medical event reporting form</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: supported by grants from the Upjohn Company</p> <p>Declarations of interest among the primary researchers: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients (...) were randomly assigned to receive one of three doses of adinazolam or placebo". No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study is double-blind. Quote: "Medication was dispensed in blister packs with morning and evening doses cells, with contained a fixed number of identical tablets (containing either 15 mg of adinazolam or placebo)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information

Carter 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only modified ITT (1 postbaseline assessment) data available, number of randomised participants is unclear.
Selective reporting (reporting bias)	High risk	Side effects data published only selectively (discontinuation symptoms).
Other bias	Unclear risk	Supported by grants from the Upjohn Company

CNCPS 2° phase 1992

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder (partially with agoraphobia)</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III, Upjohn (SCID-UP)</p> <p>Age: Mean = 34</p> <p>Sex: F = 62%</p> <p>Location: At 14 centres (Belgium, Brazil, Canada, Colombia, France, Germany/Austria, Italy, Mexico, Spain, Sweden/Denmark, UK, USA)</p> <p>Comorbidities: Protocol: major depression (if secondary); Results: simple phobia, social phobia, major depression, dysthymia</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 386)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; mean = 5.7 mg/day (5.7 tablets)</p> <p>(2) <u>Imipramine (n = 391)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; mean = 155 mg/day (6.2 tablets)</p> <p>(3) <u>Placebo (n = 391)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible; 6.8 tablets/day</p>
Outcomes	<p>Time points for assessment: baseline, week 1, 4, 8</p> <p>Primary outcomes:</p> <p>(1) Overall clinical efficacy and improvement: physician's global improvement scale; a patient's global improvement scale (10-point scales)</p> <p>(2) Panic anxiety: participant's weekly diary, Panic Attack Scale</p> <p>(3) Phobias: modified Overall Phobia Scale (a 10-point scale); SCL-90</p> <p>(4) Anticipatory anxiety: percentage of time spent in anticipation of a panic episode</p>

CNCPS 2° phase 1992 (Continued)

(5) Anxiety: 14-item HAMA

(6) Social functioning: 5-point scale; 3 ratings specifying work-related disability, impairment of social life and leisure activities, impairment of life and home responsibilities

(7) Depression: 21-item HAMD

(8) Patient's self report: SCL-90 (total score)

Secondary outcome:

(1) Adverse events: adverse drug report, modified SAFTEE

Notes	<p>Date of study: 1984-87 (data collection), 1984-88 (data analysis and manuscript preparation)</p> <p>Funding source: This study has been sponsored and supported by the Upjohn Company, Kalamazoo, Michigan.</p> <p>Declarations of interest among the primary researchers: not stated</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At each centre patients were blindly and randomly assigned to alprazolam, imipramine or placebo treatment based on a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical capsules", "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further details
Incomplete outcome data (attrition bias) All outcomes	High risk	There were significant differences in the completion rate among the 3 treatment groups. Completers: alprazolam = 83%; imipramine = 70%; placebo = 56%. The reasons for participants' non-completion of the 8-week protocol differed statistically among the treatment groups.
Selective reporting (reporting bias)	High risk	Not all the outcome measures are reported, and several data (e.g. SD, N) are missing.
Other bias	Unclear risk	This study has been sponsored and supported by the Upjohn Company, Kalamazoo, Michigan.

Davidson 1994

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with agoraphobia</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III-R, Upjohn version (SCID-UP-R)</p>

Davidson 1994 (Continued)

Age: Adinazolam: mean = 36.1 (SD = 10.8); Placebo: mean = 35.5 (SD = 8.9)

Sex: Adinazolam: M = 34%, F = 66%; Placebo: M = 33%, F = 67%

Location: USA (at 4 centres: University of California, Duke University Medical Center, University of Missouri-Columbia, University of Wisconsin)

Comorbidities: controlled physical illness

Rescue medication: none

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Adinazolam SR (n = 99)</u></p> <p>Duration: 4 weeks</p> <p>Treatment protocol: flexible dosage; mean = 84.1 (SD = 28.6); range = 3.5 to 7.5 capsules</p> <p>(2) <u>Placebo (n = 103)</u></p> <p>Duration: 4 weeks</p> <p>Treatment protocol: flexible; mean = 92.3 (SD = 27.3 mg equivalents); range = 4 to 8 tablets</p>
Outcomes	<p>Time points for assessment: baseline, weeks 1, 2, 4</p> <p>Primary outcomes:</p> <p>(1) Overall improvement: CGI</p> <p>(2) Frequency/duration/intensity of panic attacks: Sheehan Panic and Anxiety Attack Scale</p> <p>(3) Agoraphobia: Phobia Severity Scale; SCL-90, phobic cluster</p> <p>Secondary outcomes:</p> <p>(1) Anxiety: HAMA; Sheehan Clinician Rated Anxiety Scale</p> <p>(2) Impairment: Sheehan Disability Scale</p> <p>(3) The main phobia of the Phobia Severity Scale</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: not stated</p> <p>Declarations of interest among the primary researchers: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a parallel, double-blind, flexible dose, 4 week efficacy and safety study with patients randomised to receive either adinazolam or matching placebo tablets". "Randomised assignment to treatment groups determined that equal numbers of patients received both treatment possibilities". No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment

Davidson 1994 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This was a parallel, double-blind, flexible dose, 4 week efficacy and safety study". "Medication was packed in individual bottles". No information on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were dropouts in each group (Drug 1 = 12 out of 99, Placebo = 15 out of 103), but there was no imbalance between the 2 groups. Quote: "No statistical difference was found in the dropouts rates between the two treatment groups"
Selective reporting (reporting bias)	High risk	Side effects only reported if group difference was statistically significant, SDs only reported as P value.
Other bias	Unclear risk	Bristol-Myers Squibb Pharmaceutical Research Institute was involved in this study. Analysis at baseline for centres, treatment and centre by treatment effects in baseline severity scores according to centre for situational panic attack frequency, unexpected panic attack duration, main phobia severity, and overall phobia severity

Garvey 1989

Methods	Study design: Randomised controlled trial
Participants	Diagnosis: DSM-III panic disorder with agoraphobia Method of diagnosis: not stated Age: mean = 40.0 (SD = 12) Sex: 61% women Location: USA; setting unclear Comorbidities: individuals with major depressive disorder, alcoholism during the previous 6 months, current or past mania or psychotic disorder, major medical problems were excluded. Rescue medication: not stated
Interventions	Participants were randomly assigned to either: (1) alprazolam arm Duration: 3 weeks Treatment protocol: dosage gradually increased to a maximum of 6 mg (2) diazepam arm Duration: 3 weeks Treatment protocol: dosage gradually increased to a maximum of 60 mg (3) placebo arm

Garvey 1989 (Continued)

Duration: 3 weeks

Total number of randomised participants = 30; number of participants per arm not provided

Outcomes	<p>The study is about urinary MHPG levels in relation to panic disorder treatment.</p> <p>Time points for assessment: before the beginning of treatment and after 3 weeks of treatment</p> <p>Outcomes:</p> <p>(1) MHPG urinary levels</p> <p>(2) HAMA</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: not stated</p> <p>Declarations of interest among the primary researchers: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "thirty consecutive patients meeting study criteria were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind treatment". No further details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind treatment". No further details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Unclear risk	Study on urinary MHPG levels; HAMA mentioned in methods section, but no results reported.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

GSK 1994

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III-R</p> <p>Age: Paroxetine: mean = 39.1 (SD = 11.1); Alprazolam: mean = 39.5 (SD = 12.5); Placebo: mean = 39.0 (SD = 11.8)</p>

GSK 1994 (Continued)

Sex: Paroxetine: M = 28; Alprazolam: M = 29; Placebo: M = 23

Location: 16 centres in the USA

Comorbidities: major depression (if secondary)

Rescue medication: none

Interventions

Participants were randomly assigned to either:

(1) Paroxetine (n = 77)

Duration: 10 weeks

Treatment protocol: flexible dosage; range: 10 to 60 mg/day

(2) Alprazolam (n = 77)

Duration: 10 weeks

Treatment protocol: flexible dosage; range: 1 to 6 mg/day

(3) Placebo (n = 72)

Duration: 10 weeks

Treatment protocol: flexible

Outcomes

Time points for assessment: not stated

Primary outcomes:

(1) Percentage of participants having zero full panic attacks during the last 2 weeks of treatment phase

(2) Mean change from baseline in the number of full panic attacks during the last 2 weeks of treatment phase

(3) Percentage of participants with a $\geq 50\%$ reduction from baseline in the number of full panic attacks during the last 2 weeks of treatment phase

(4) Overall improvement: CGI severity of Illness score

Secondary outcomes:

(1) Mean number of full and limited symptoms (all) panic attacks, and full situational and full unexpected panic attacks, per 2-week period

(2) Mean intensity of all and full panic attacks per 2-week period

(3) Per cent of time engaged in, and intensity of, anticipatory anxiety per 2 weeks

(4) Agoraphobia: Marks Sheehan Phobia Scale, Fear and Avoidance Scores

(5) Overall improvement: CGI Global improvement score

(6) Anxiety: HAMA

(7) Depression: MADRS

(8) Disability: Sheehan Disability Scale, Social Adjustment Self-Report Scale

Notes

Date of study: November 1992 to April 1994

Funding source: GlaxoSmithKline

Declarations of interest among the primary researchers: not stated

GSK 1994 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data: Drug 1 = 29 out of 77, Drug 2 = 17 out of 77, Placebo = 22 out of 72. LOCF data available.
Selective reporting (reporting bias)	Unclear risk	Only short study synopsis available.
Other bias	Unclear risk	No evidence of other bias was found.

Klosko 1990

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder with agoraphobia</p> <p>Method of diagnosis: Anxiety Disorder Interview Schedule-Revised</p> <p>Age: mean = 37 (SD = 11.04)</p> <p>Sex: M = 26% F = 74%</p> <p>Location: not stated (USA)</p> <p>Comorbidities: major depression (if secondary)</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 17)</u></p> <p>Duration: 15 weeks</p> <p>Treatment protocol: flexible dosage; mean = 4.60 (SD = 1.82)</p> <p>(2) <u>Panic control treatment (PCT) (behaviour therapy treatment group) (n = 18)</u></p> <p>Duration: 15 weeks</p> <p>Treatment protocol: 15 individual sessions of an integrated CBT in weekly meetings</p>

Klosko 1990 (Continued)

(3) Waiting list (n = 16)
Duration: 15 weeks

Treatment protocol: no treatment

(4) Placebo arm (n = 18)
Duration: 15 weeks

Treatment protocol: flexible dosage; mean = 5.08 (SD = 2.65)

Outcomes	Time points for assessment: clinical assessment before and after treatment; self monitoring measures throughout treatment Primary outcomes: (1) Anxiety episodes and panic attacks: diary (2) Anxiety: HAMA (3) Depression: HAMD (4) Global clinical severity ratings
Notes	Date of study: not stated Funding source: This research was supported in part by a grant from the National Institute of Mental Health (MH-36800) and the Upjohn Company. Declarations of interest among the primary researchers: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medication was supplied by the Upjohn Company in matching 1-mg tablets, packaged in matching bottles containing sufficient medication for 1 week, and was administered double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the ADIS-r administrators were blind to group assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Out of 69 initial subjects, 57 subjects completed the study and 12 subjects dropped out. A higher rate of drop out was observed in the placebo group compared with the other three groups. A chi-square analysis on these dropout frequencies was significant. Separate chi-squares on each pair of groups showed significant differences in between the placebo and alprazolam groups, the placebo and PCT groups and the placebo and waiting-list groups. Those who dropped from the study were compared with study completers on major pre-treatment variables. Since all the placebo subjects dropped from the study before completion of 3 weeks of treatment, endpoint analysis were not conducted. (...) Since the placebo group had a disproportionate number of dropouts, it is reasonable to argue that analysis of end state functioning that

Klosko 1990 (Continued)

includes only study completers represents a distortion of results. Given the reasons and the rapidity with which most subjects dropped from the study, it is likely that, at time of study withdrawal, dropouts maintained their pretreatment low end state functioning status."

Selective reporting (reporting bias)	High risk	Numerous outcomes, e.g. side effects, are not reported.
Other bias	Unclear risk	This research was supported in part by a grant from the National Institute of Mental Health (MH-36800) and the Upjohn Company.

Lydiard 1992

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III, Upjohn version</p> <p>Age: Placebo: mean = 36.3 (SD = 8.1); Alprazolam 2 mg: mean = 39.1 (SD = 9.5); Alprazolam 6 mg: mean = 36.2 (SD = 9.1)</p> <p>Sex: unclear</p> <p>Location: USA</p> <p>Comorbidities: major depression only if depressive symptoms were secondary to their panic symptoms; panic symptoms dominated the clinical picture; the symptoms of the panic disorder preceded the affective disorder chronologically</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam 2 mg (n = 30)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: fixed = 2 mg</p> <p>(2) <u>Alprazolam 6 mg (n = 31)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: fixed = 6 mg</p> <p>(2) <u>Placebo arm (n = 33)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: fixed</p>
Outcomes	<p>Time points for assessment: baseline, week 1, 2, 3, 4, 6</p> <p>Primary outcomes:</p> <p>(1) Frequency of panic attacks: participant's diary</p> <p>(2) Overall severity of phobia: 11-point scale derived from Marks and Mathews</p> <p>(3) Phobia: 11-point scale</p>

Lydiard 1992 (Continued)

- (4) Avoidance: 4-point scale
- (5) Anxiety: HAMA
- (6) Disability: 5-point Work and Social Disability Scale
- (7) Global improvement: 11-point scale

Secondary outcome:

- (1) Adverse events

Notes
Date of study: not stated

Funding source: not stated

Declarations of interest among the primary researchers: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was a double-blind study. Quote: "Identically appearing capsules containing alprazolam 1 mg or placebo were packaged for each study week"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	Unequal dropout rates. Quote: "Differential drop-out rates were noted across treatment groups, with 45% of placebo treated patients, 76.7% alprazolam 2 mg and 48.4% of the alprazolam 6 mg completing the study"
Selective reporting (reporting bias)	High risk	Numerical data of the clinical outcome measures described in the methods are not reported in the results. Only graphs for few outcome measures are presented. There are different reasons for missing data across groups.
Other bias	Unclear risk	No evidence of other bias was found.

Moroz 1999
Methods
Study design: Randomised controlled trial

Participants
Diagnosis: DSM-III-R panic disorder with or without agoraphobia

Method of diagnosis: Structured Clinical Interview for DSM-III-R and a psychiatric interview

Age: Clonazepam: mean = 36.7 (SD = 11.3); Placebo: mean = 36.8 (SD = 11.4)

Sex: Clonazepam: F = 141, M = 81; Placebo: F = 140, M = 76

Moroz 1999 (Continued)

Location: not stated (USA); setting: outpatients

Comorbidities: psychiatric (major depression, social phobia, obsessive-compulsive disorder, generalised anxiety disorder) were excluded.

Rescue medication: none

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Clonazepam</u> (n = 230)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; mean = 2.3 mg/day; range = 0.5 to 4 mg (daily dose)</p> <p>(2) <u>Placebo</u> (n = 225)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; mean = 3.0 mg/day</p>
Outcomes	<p>Time points for assessment: assessment week 1, 2, and 6. For CGI-S, PGI-C, WSDS and monitoring of adverse events: weeks 0, 1, 2, 3, 6. HAMA, HAM-D: at screening visit and week 6</p> <p>Primary outcomes:</p> <p>(1) Change from baseline in the number of panic attacks: diary</p> <p>(2) Severity of panic disorder: CGI-S</p> <p>(3) Change from baseline: CGI-C</p> <p>(4) PGI-C</p> <p>(5) Estimate of mean duration of anticipatory anxiety: % of time a participant spent experiencing anticipatory anxiety during the preceding week</p> <p>(6) Severity of fear associated with the main phobia: 11-point scale</p> <p>(7) Change in the avoidance (related to the main phobia): 5-point scale</p> <p>(8) Social and Work Impairment: WSDS</p> <p>(9) Anxiety: HAMA</p> <p>Secondary outcome:</p> <p>(1) Adverse events: monitoring of the adverse events</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: sponsored by Hoffmann-La Roche Inc., Nutley, NJ</p> <p>Declarations of interest among the primary researchers: not stated</p>
Risk of bias	
Bias	<p>Authors' judgement</p> <p>Support for judgement</p>
Random sequence generation (selection bias)	<p>Unclear risk</p> <p>No information on random sequence generation</p>
Allocation concealment (selection bias)	<p>Unclear risk</p> <p>No information on allocation concealment</p>

Moroz 1999 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "The study medications were clonazepam and identical-looking placebo tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in missing outcome data between the groups (Drug 1 = 44 out of 230, Placebo = 65 out of 225), with different reasons for missing data across groups. Furthermore, the total number of dropouts in each group is not fully transparent.
Selective reporting (reporting bias)	High risk	The outcomes of interest in the review are reported incompletely (no mean, SD) so that they cannot be entered into a meta-analysis.
Other bias	Unclear risk	Quote: "The demographic and baseline disease characteristics of the clonazepam and placebo ITT groups were similar" Sponsored by Hoffmann-La Roche Inc., Nutley, NJ

Munjack 1989a

Methods	Study design: Randomised controlled trial
Participants	Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks Method of diagnosis: not stated Age: mean = 31 (range = 18 to 62) Sex: M = 17; F = 38 Location: California, USA (psychiatric outpatients clinic) Comorbidities: not stated Rescue medication: none
Interventions	Participants were randomly assigned to either: (1) <u>Alprazolam (n = 20)</u> Duration: 5 weeks Treatment protocol: flexible dosage; range = 1.5 to 6 mg, mean = 3.62 (7.24 capsules, SD = 4.09) (2) <u>Propanolol (n = 23)</u> Duration: 5 weeks Treatment protocol: flexible dosage; mean = 184.60 (9.23 capsules, SD = 4.26) (3) <u>Placebo (n = 21)</u> Duration: 5 weeks Treatment protocol: flexible; mean = 9.90 capsules, SD = 3.74

Munjack 1989a (Continued)

Outcomes

Time points for assessment: weekly

Primary outcomes:

(1) Panic: Panic and Anxiety Attack Scales (Sheehan)

(2) Avoidance: Phobia Scale (Marks-Sheehan)

(3) Anxiety: HAMA

(4) Depression: HAMD

Secondary outcome:

(1) Adverse events: Side Effects Checklist

Notes

Date of study: not stated

Funding source: not stated

Declarations of interest among the primary researchers: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were randomly and blindly assigned to one of 3 treatment groups. All of the visually identical capsules contained either (...) were administered three times a day". Additional analysis of the success of blinding showed that physicians were able to distinguish between alprazolam and placebo regardless of the blinding procedure (Munjack 1989b).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; outcome assessments were conducted by physicians and independent "assessors"; results are reported separately, no further information available
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in missing outcome data between the groups (Drug 1 = 0, Placebo = 5). Quote: "A chi-square analysis indicated a significant difference in the dropout rates among the 3 treatment groups and specifically between alprazolam and placebo". Observed case analysis only
Selective reporting (reporting bias)	High risk	Not all the efficacy outcome measures described in the methods are reported in the results section (Sheehan). No baseline data are presented. No data on side effects
Other bias	Unclear risk	No evidence of other bias was found.

Noyes 1996

Methods

Study design: Randomised controlled trial

Participants

Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks

Noyes 1996 (Continued)

Method of diagnosis: Structured Clinical Interview for DSM-III, Upjohn version

Age: mean = 36.6 (SD = 10.5)

Sex: M = 84, F = 157

Location: University of Iowa (Iowa City, Iowa), University of Melbourne (Heidelberg, Australia)

Comorbidities: depression (if secondary)

Rescue medication: none

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Diazepam</u> (n = 81)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; 4.3 capsules/day</p> <p>(1) <u>Alprazolam</u> (n = 78)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; 4.9 capsules/day</p> <p>(2) <u>Placebo</u> (n = 79)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; 7.4 capsules/day</p>
Outcomes	<p>Time points for assessment: not stated</p> <p>Primary outcomes:</p> <p>(1) Frequency of panic attacks: panic diaries, scale</p> <p>(2) Anxiety: Sheehan's self rated anxiety scale, HAMA</p> <p>(3) Global improvement: 11-point global scale</p> <p>(4) Global phobia: 11-point global scale</p> <p>(5) Depression: POMS, HAMD</p> <p>(6) Global disability: WSDS</p> <p>Secondary outcome:</p> <p>(1) Adverse events: SAFTEE</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: supported by a grant from the Upjohn Company</p> <p>Declarations of interest among the primary researchers: not stated</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk No information on random sequence generation

Noyes 1996 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "this parallel-groups study was double-blind and placebo-controlled"; no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in dropouts in the groups. Quote: "The percentage of dropouts was 19.5% of subjects taking diazepam, 16.3% of those taking alprazolam, and 42.5% of subjects taking placebo ($p < 0.5$)". Analyses were made with both ITT participants and completer participants.
Selective reporting (reporting bias)	High risk	No data on the depression measures reported in the methods (HAMD, POMS) and on the 3 areas of functioning rated on 11-point linear scale
Other bias	Unclear risk	Supported by a grant from the Upjohn Company

Pecknold 1994

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder and extensive phobic avoidance (agoraphobia with panic attacks) or limited phobic avoidance</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III-R</p> <p>Age: for alprazolam CT, mean = 36.4 (SD = 10.5) (range 19 to 64); for alprazolam XR, mean = 33.8 (SD = 10.3) (range 24 to 65); for placebo, mean = 35.5 (SD = 10.0) (range 22 to 64)</p> <p>Sex: for alprazolam CT, 59% female; for alprazolam XR, 63% female; for placebo, 58% female</p> <p>Location: USA (2 sites: Rhode Island and Los Angeles) and Canada (1 site: Montreal)</p> <p>Comorbidities: major depression (if depressive symptoms were secondary to panic symptoms or if panic dominated the clinical picture and panic disorder preceded the development of the affective symptoms)</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam CT</u> (n = 69*)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 2 to 7(?) mg; mean = 3.95 (SD = 1.86)</p> <p>(2) <u>Alprazolam XR</u> (n = 70*)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 2 to 7(?) mg; mean = 4.35 (SD = 2.30)</p> <p>(2) <u>Placebo</u> (n = 70*)</p>

Pecknold 1994 (Continued)

Duration: 6 weeks

Treatment protocol: flexible dosage; range = 2 to 7(?) mg; mean = 5.46 (SD = 2.26)

*The number of participants in the different arms is inconsistently reported. We used the number of participants of the LOCF analyses.

Outcomes	Time points for assessment: at baseline and weekly thereafter for 6 weeks Primary outcomes: (1) Overall improvement (CGI): 7-point global scale (2) Number/duration/intensity of spontaneous and situational panic attacks: participants' diaries (3) Fear/avoidance: Marks-Mathews Phobia Scale (4) Overall phobia: not stated (5) Anxiety: HAMA (at baseline and week 3 and 5); Sheehan Patient Rated Anxiety Scale (6) Disability: WSDS (7) Depression: HAMD (at baseline and at the end of weeks 3 and 6) Secondary outcome: (1) Adverse effects: (SAFTEE-UP)	
Notes	Date of study: not stated Funding source: The study was supported by the Upjohn Company. Declarations of interest among the primary researchers: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No clear information on blinding. Quote: "This study was design as a double-blind (...). Medication was dispensed weekly to patients in two bottles"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear information on blinding. Quote: "This study was design as a double-blind (...). Medication was dispensed weekly to patients in two bottles"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only ITT population reported. There are inconsistencies in the reported N. Data censored for participant with at least 3 weeks of treatment. There is an imbalance in dropouts among the groups (Drug 1 = 7, Drug 2 = 12, Placebo = 20). Quote: "During the first 3 weeks of the study, 4.2% of the CT alprazolam, 14.3% of the XR alprazolam and 14.7% of the placebo recipients dropped out of the study after beginning medication from the total ITT group of 209 patients". "However, there was a significantly higher dropout rate, probably because of effectiveness, in the placebo group compared with the CT or XR groups"

Pecknold 1994 (Continued)

Selective reporting (reporting bias)	High risk	Quote: "When completer analysis showed no statistical significance, endpoint results were reported". Some scales are only reported not to have shown significant differences. 1 outcome measure (WSDS) is not reported in the results.
Other bias	Unclear risk	The study was supported by the Upjohn Company.

Rosenbaum 1997

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: SCID-Ro (a version of the Structured Clinical Interview for DSM-III-R) and a psychiatry interview</p> <p>Age: mean = 37.3, range = 18 to 76</p> <p>Sex: F = 56%</p> <p>Location: USA (12 sites); outpatient setting</p> <p>Comorbidities: none</p> <p>Rescue medication: none (protocol). generalised anxiety disorder, social phobia, major depression, obsessive-compulsive disorder (results section)</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Clonazepam 0.5 mg (n = 68)</u></p> <p>Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed dose = 0.5 mg</p> <p>(2) <u>Clonazepam 1.0 mg (n = 68)</u></p> <p>Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed dose = 1.0 mg</p> <p>(3) <u>Clonazepam 2.0 mg (n = 69)</u></p> <p>Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed dose = 2.0 mg</p> <p>(4) <u>Clonazepam 3.0 mg (n = 67)</u></p> <p>Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed dose = 3.0 mg</p> <p>(5) <u>Clonazepam 4.0 mg (n = 72)</u></p> <p>Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed dose = 4.0 mg</p> <p>(6) <u>Placebo arm (n = 69)</u></p> <p>Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p>

Rosenbaum 1997 (Continued)

Treatment protocol: fixed

Outcomes	Time points for assessment: at each visit (CGI-S, mean duration of anticipatory anxiety); at each post-baseline visit (CGI-C); at baseline, week 9, week 16 (severity of fear associated with the main phobia) Primary outcomes: (1) Number of panic attacks: participant's diary, interview (2) Overall improvement: CGI-S (3) Mean duration of anticipatory anxiety (4) Frequency of avoidance associated with the main phobia (agoraphobia): 5-point scale (5) Severity of fear associated with the main phobia: 11-point scale Secondary outcomes: (1) CGI-C; Patient's Global Impression of Change (CGI-P) (2) Overall impairment in work and social activities: 5-point scale (3) Adverse events	
Notes	Date of study: October 1992 to June 1995 Funding source: This clinical trial was supported by Hoffmann-La Roche. Declarations of interest among the primary researchers: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization to treatment groups was done by means of computer-generated codes for each centre, using the fixed-block method with a block size of six"
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "All study medications were taken in divided doses, half in the morning and half at bedtime, and were identical in appearance and packaging (blister cards)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only data for modified ITT reported.
Selective reporting (reporting bias)	High risk	Not all the data are reported completely, so some could not be entered into a meta-analysis.
Other bias	Unclear risk	This clinical trial was supported by Hoffmann-La Roche.

Savoldi 1990

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder with agoraphobia</p> <p>Method of diagnosis: not stated</p> <p>Age: mean = 37.7 (SD = 7.97)</p> <p>Sex: M = 12; F = 18</p> <p>Location: not stated</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Etizolam (n = 15)</u></p> <p>Duration: 4 weeks</p> <p>Treatment protocol: fixed dosage = 0.50 mg</p> <p>(2) <u>Placebo arm (n = 15)</u></p> <p>Duration: 4 weeks</p> <p>Treatment protocol: fixed</p>
Outcomes	<p>Time points for assessment: baseline, week 2, 4</p> <p>Primary outcomes:</p> <p>(1) Anxiety: HAMA, Covi Anxiety Scale</p> <p>(2) Agoraphobia: HAMA, item 2</p> <p>(3) Frequency of panic attacks: not stated</p> <p>(4) Depression: HAMD</p> <p>Secondary outcome:</p> <p>(1) Tolerability: 4-point scale, semi-structured interview</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: not stated</p> <p>Declarations of interest among the primary researchers: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated at random to receive twice daily doses of either etizolam or placebo". No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment

Savoldi 1990 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "32 patients were enrolled in a double-blind study. (...) The psychometric evaluations were carried out by two independent examiners, not the trial clinician". It is not clear who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "32 patients were enrolled in a double-blind study. (...) The psychometric evaluations were carried out by two independent examiners, not the trial clinician". It is not clear who was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in dropouts (Drug 1 = 1 out of 15, Placebo = 6 out of 15). The dropouts were not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	The frequency of panic attacks was not reported.
Other bias	Unclear risk	No evidence of other bias was found.

Schweizer 1992

Methods	Study design: Randomised controlled trial (cross-over design)
Participants	<p>Diagnosis: DSM-III-R panic disorder, either uncomplicated, with limited phobic avoidance, or with agoraphobia</p> <p>Method of diagnosis: not stated</p> <p>Age: mean = 35</p> <p>Sex: 3 males, 2 females</p> <p>Location: not stated</p> <p>Comorbidities: social phobia (n = 1)</p> <p>Rescue medication: none (besides midazolam when necessary)</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Midazolam</u> (n = 3 + 2)</p> <p>Duration: 3 + 3 weeks</p> <p>Treatment protocol: flexible dosage; range = 0.25 to 1 mg; mean number of doses (week 3) = 6.1 (0.44 mg/day)</p> <p>(2) <u>Placebo</u> (n = 2 + 3)</p> <p>Duration: 3 + 3 weeks</p> <p>Treatment protocol: flexible</p>
Outcomes	<p>Time points for assessment: baseline, week 1, 2, 3, 4, 5, 6</p> <p>Primary outcomes:</p> <p>(1) Number of panic attacks: participants' diaries</p> <p>(2) Global phobia: 11-point Global Phobia Scale</p>

Schweizer 1992 (Continued)

(3) Anxiety: HAMA; Sheehan Patient Rated Anxiety Scale

(4) Overall improvement: 7-point CGI-I

Notes	<p>Date of study: not stated</p> <p>Funding source: not stated</p> <p>Declarations of interest among the primary researchers: not stated</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study had a double-blind design. (...) Investigators were careful not to indicate anything about the order of timing of the crossover"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study had a double-blind design. (...) Investigators were careful not to indicate anything about the order of timing of the crossover"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual participant data available.
Selective reporting (reporting bias)	Unclear risk	No side effects reported.
Other bias	Unclear risk	Very small pilot cross-over trial

Schweizer 1993a

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R agoraphobia with panic attacks or panic disorder with limited phobic avoidance</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III, Upjohn version</p> <p>Age: mean = 35 (SD = 8.4)</p> <p>Sex: F = 116; M = 78</p> <p>Location: USA</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Alprazolam SR (n = 109)</p>

Benzodiazepines versus placebo for panic disorder in adults (Review)

Schweizer 1993a (Continued)

Duration: 6 weeks

Treatment protocol: flexible dosage; range = 1 to 10 mg; mean = 4.7 (SD = 2.5)

(2) Placebo (n = 108)

Duration: 6 weeks

Treatment protocol: flexible dosage

Outcomes	Time points for assessment: baseline, week 1 through 6 Primary outcomes: (1) Frequency of panic attacks: participant diary (2) Overall phobia: 11-point Global Phobia Scale (3) Global illness: 7-point CGI-S (4) Anxiety: 14-item HAMA; 40-item Sheehan Patient Rated Anxiety Scale (5) Depression: 21-item HAMD Secondary outcome: (1) Adverse events: 46-item symptom checklist	
Notes	Date of study: not stated Funding source: supported by a grant from the Upjohn Corporation Declarations of interest among the primary researchers: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomly assigned on a double-blind basis to 6 weeks of treatment with either sustained release alprazolam or placebo". "The study medication was provided in matching tablets (...)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear information on blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in the total number of dropouts between groups (Drug 1 = 17 out of 102, Placebo = 34 out of 92).
Selective reporting (reporting bias)	Low risk	All the efficacy outcome measures described in the methods are reported in the results section (they reported change scores).

Schweizer 1993a (Continued)

Other bias	Unclear risk	Supported by a grant from the Upjohn Corporation. Data analysis was performed by the Upjohn Corporation and by the Psychopharmacology Research Unit.
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Schweizer 1993b

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III</p> <p>Age: mean = 33, SD = 7, range 19 to 57</p> <p>Sex: Female = 75%</p> <p>Location: Pennsylvania</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 37)</u></p> <p>Duration: 8 weeks (maintenance treatment: 24 weeks)</p> <p>Treatment protocol: flexible dosage; range = 1 to 10 mg, mean = 5.4 (SD = 2.1) (endpoint)</p> <p>1) <u>Imipramine (n = 34)</u></p> <p>Duration: 8 weeks (maintenance treatment: 24 weeks)</p> <p>Treatment protocol: flexible dosage; range = 25 to 250 mg, mean = 152 (SD = 65) (endpoint)</p> <p>(2) <u>Placebo arm (n = 35)</u></p> <p>Duration: 8 weeks (maintenance treatment: 24 weeks)</p> <p>Treatment protocol: flexible dosage; number of pills = 7.0 (SD = 2.5) (endpoint)</p>
Outcomes	<p>Time points for assessment: at weekly intervals during the initial 6 weeks of treatment, and then after 2 weeks at week 8 (participants were then examined monthly for 6 months until the completion of the 32 weeks of study treatment)</p> <p>Primary outcomes:</p> <p>(1) Panic attacks frequency and severity: weekly diary, 36-item Clinician Rated Anxiety Scale, 2-item Hopkins Symptom Checklist</p> <p>(2) Generalised anxiety: 14-item HAMA, 7-item anxiety factor derived from the 80-item Clinician Rated Anxiety Scale</p> <p>(3) Phobias: severity of fear on an 11-point scale, degree of avoidance on a 5-point scale, overall severity of phobias on a 10-point scale</p> <p>(4) Disability: 5-point WSDS</p> <p>(5) Global improvement: 10-point bipolar improvement scale</p> <p>Secondary outcome:</p>

Schweizer 1993b (Continued)

(1) Safety: 41-item structured questionnaire, vital signs, laboratory evaluations

Notes	Date of study: not stated	
	Funding source: This study was supported by a research grant from the Upjohn Company, Kalamazoo, Michigan, and by Public Health Service grant MH-08957.	
	Declarations of interest among the primary researchers: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "Patients were dispensed identical capsules containing either 1 mg of alprazolam, 25 mg of imipramine (...)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in the total number of dropouts between the groups (Drug 1 = 4 out of 37, Placebo = 20 out of 35).
Selective reporting (reporting bias)	Low risk	All the efficacy outcome measures described in the methods are reported in the results.
Other bias	Unclear risk	This study was supported by a research grant from the Upjohn Company, Kalamazoo, Michigan, and by Public Health Service grant MH-08957.

Sheehan 1993

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with extensive phobic avoidance, panic disorder with limited phobic avoidance</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III (SCID-UP)</p> <p>Age: Alprazolam: mean = 36.4 (SD = 8.8); Buspirone: mean = 36.6 (SD = 9.4); Placebo: mean = 37.2 (SD = 10.9)</p> <p>Sex: Alprazolam: F = 76%, Buspirone: F = 67; Placebo: F = 77</p> <p>Location: USA</p> <p>Comorbidities: major depressive disorder (if secondary to panic disorder)</p> <p>Rescue medication: none</p>

Sheehan 1993 (Continued)

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 34)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 1.5 to 10 mg, mean = 5.2 (SD = 2.6)</p> <p>(1) <u>Buspirone (n = 34)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 15 to 100 mg, mean = 61 (SD = 26.5)</p> <p>(2) <u>Placebo (n = 33)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 3 to 20 capsules, mean = 16.5 capsules (SD = 5)</p>	
Outcomes	<p>Time points for assessment: baseline, weekly for 8 visits</p> <p>Primary outcomes:</p> <p>(1) Panic symptoms: Panic and Anticipatory Anxiety Scale, participant's diary</p> <p>(2) Anxiety: Sheehan Clinician Rated Anxiety Scale, Sheehan Patient Rated Anxiety Scale, HAMA</p> <p>(3) Depression: 31-item Beck Depression Inventory, HAMD, MADRS</p> <p>(4) Agoraphobia: Phobia Scale</p> <p>(5) Overall impairment: Disability Scale, SCL-90-R</p> <p>(6) Overall improvement: Clinician Rated Global Improvement (CGI-21)</p> <p>Secondary outcome:</p> <p>(1) Adverse events: 42-item symptoms and side effects inventory</p>	
Notes	<p>Date of study: not stated</p> <p>Funding source: This study was supported in part by grant 4447 from the Upjohn Company.</p> <p>Declarations of interest among the primary researchers: not stated</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a total of 101 patients entered the trial and were randomly assigned to the 3 treatment groups.". No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a double-blind design was used. Medication was prepared in identical-appearing capsules containing 0.5 mg of alprazolam, 5 mg of buspirone or placebo."
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind; no further information

Sheehan 1993 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Data censored for participant with at least 3 weeks of treatment, analyses mainly reported from observed case analysis.
Selective reporting (reporting bias)	High risk	Not all of the study's prespecified primary outcome measures have been reported (e.g. SCL-90, MADRS).
Other bias	Unclear risk	This study was supported in part by grant 4447 from the Upjohn Company. The results are based entirely on the authors' statistical analysis and management of the data and not on any analysis by the sponsors. The article was written exclusively by the authors without any assistance or input from any pharmaceutical company.

Sheikh 1999

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III-R - Patient version (SCID-P)</p> <p>Age: mean = 61.24 (SD = 5.27), range = 55 to 73</p> <p>Sex: M = 2; F = 32</p> <p>Location: USA</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 8)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 to 6 mg, mean = 2.87 (SD = 1.66)</p> <p>(2) <u>Imipramine (n = 10)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 10 to 200 mg, mean = 77.5 (SD = 59.4)</p> <p>(3) <u>Placebo arm (n = 7)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible</p>
Outcomes	<p>Time points for assessment: baseline, at each subsequent medication visit</p> <p>Primary outcomes:</p> <p>(1) Number/intensity of panic attacks: participant's diary</p> <p>(2) Anxiety: HAMA</p>

Sheikh 1999 (Continued)

(3) Depression: HAMD

(4) Overall improvement: CGI; PGI

Notes	<p>Date of study: 2-year period (1988-90)</p> <p>Funding source: This research was supported in part by the Medical Research Service of the VAPAHCS, by grant MH-49226 from the National Institutes of Health, US Department of Health and Human Services, and the Upjohn Company.</p> <p>Declarations of interest among the primary researchers: not stated</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Those subjects selected for inclusion were randomised to one of three medication treatment conditions". No information on sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medication for this double-blinded protocol were provided by the Upjohn Company in the form of identical looking capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 7 dropouts (6 in the placebo group, 0 in the alprazolam group, 1 in the imipramine group). There is an imbalance between the groups. Quote: "The small sample size prevents statistical analyses of the data". Placebo group analysed as LOCF, others as observed case.
Selective reporting (reporting bias)	Unclear risk	The results of the rating scales are all reported. No data on side effects, but they are not mentioned in the methods.
Other bias	Unclear risk	This research was supported in part by the Medical Research Service of the VAPAHCS, by grant MH-49226 from the National Institutes of Health, US Department of Health and Human Services, and the Upjohn Company.

Taylor 1990

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: panic disorder with phobic avoidance</p> <p>Method of diagnosis: Structured Clinical Interview for Diagnoses-Upjohn version (SCID-UP)</p> <p>Age: Alprazolam: mean = 35.0; Imipramine: mean = 34.1; Placebo: mean = 34.9</p> <p>Sex: Alprazolam: Male = 19%, Imipramine: 30%, Placebo: 31%</p> <p>Location: USA</p> <p>Comorbidities: none</p>

Taylor 1990 (Continued)

Rescue medication: none

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 26)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 to 8 mg, mean = 3.7</p> <p>(2) <u>Imipramine (n = 27)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 to 9 mg, mean = 4.9</p> <p>(3) <u>Placebo (n = 26)</u></p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible; number of pills: 2 to 10, mean = 6.8</p>
Outcomes	<p>Time points for assessment: baseline, weeks 1, 4, 8</p> <p>Primary outcomes:</p> <p>(1) Frequency/intensity of panic attacks: panic diary</p> <p>(2) Anxiety: HAMA</p> <p>(3) Depression: Beck Depression Inventory</p> <p>(4) Overall psychiatric symptomatology: SCL-90</p> <p>(5) Global improvement: 7-point scale</p> <p>(6) Work and social disability: 5-point scale</p> <p>(7) Avoidance: Marks/Mathews Fear Questionnaire</p> <p>Secondary outcome:</p> <p>(1) Adverse effects: SAFTEE-UP</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: This research was supported in part by National Institute of Mental Health grant 40118 and by a gift from the Upjohn Company.</p> <p>Declarations of interest among the primary researchers: not stated</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias)	High risk	"Double blind", "identical capsules". Additional analysis of the success of blinding showed that despite the blinding procedure, participants and physicians were able to distinguish between alprazolam and placebo.

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Taylor 1990 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	“Double blind”; no further information available
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis only, unequal dropout rate (Alprazolam: 8%, Placebo: 23%)
Selective reporting (reporting bias)	High risk	Almost all of the efficacy outcome measures described in the methods are reported in the results, but data are incomplete (standard deviations are not always presented). Furthermore, SAFTEE-UP event form is not reported.
Other bias	Unclear risk	This research was supported in part by National Institute of Mental Health grant 40118 and by a gift from the Upjohn Company.

Tesar 1991

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder with phobic avoidance</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-III-Upjohn version (SCID-UP)</p> <p>Age: Alprazolam: mean = 32.8 (SD = 8.9); Clonazepam: mean = 30.5 (SD = 6.5); Placebo: mean = 30.7 (SD = 9.0)</p> <p>Sex: Alprazolam: M = 42%; Clonazepam: M = 42%; Placebo: M = 27</p> <p>Location: USA (Clinical Psychopharmacology Unit at Massachusetts General Hospital)</p> <p>Comorbidities: major depression (if secondary to panic disorder)</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Alprazolam (n = 24)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 to 10 mg, mean = 5.39 (SD = 2.89)</p> <p>(2) <u>Clonazepam (n = 26)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 0.5 to 5 mg, mean = 2.5 (SD = 0.94)</p> <p>(3) <u>Placebo arm (n = 22)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible</p>
Outcomes	<p>Time points for assessment: baseline, week 3 and 6</p> <p>Primary outcomes:</p> <p>(1) Number/intensity/duration of panic attacks: participant's diary</p>

Tesar 1991 (Continued)

- (2) Severity of illness: CGI and PGI
- (3) Phobias: scale derived from 1 developed by Marks and Mathews; overall phobia rating
- (4) Overall disability: 5-point WSDS
- (5) Depression: 21-item Beck Depression Inventory

Secondary outcome:

- (1) Adverse events: SAFTEE

Notes

Date of study: not stated

Funding source: supported in part by a grant from the Upjohn Corporation, Kalamazoo, Michigan

Declarations of interest among the primary researchers: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "72 subjects (...) were randomised to a treatment group. The study utilised a double-blind, placebo controlled trial with random assignment and flexible dosing of study medication". No information on sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study utilised a double-blind, placebo-controlled trial (...)" "The study drugs were administered in identical capsules."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	There is an imbalance in dropouts between the groups (Drug 1 = 4 out of 24, Drug 2 = 2 out of 26, Placebo = 14 out of 22). Quote: "Follow-up chi-squared analysis indicated a significantly greater proportion of patients dropping out of the placebo group than the active treatment groups. The high dropout rate in the placebo group required a more complex evaluation of treatment outcome". For this reason both completer and endpoint analyses are provided.
Selective reporting (reporting bias)	Low risk	All the measures declared in the methods are reported in the results.
Other bias	Unclear risk	Supported in part by a grant from the Upjohn Corporation, Kalamazoo, Michigan

Uhlenhuth 1989
Methods

Study design: Randomised controlled trial

Participants

Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks

Method of diagnosis: Structured Clinical Interview for DSM-III-Upjohn version (SCID-UP, 1983 version)

Uhlenhuth 1989 (Continued)

Age: mean = 31.54, SD = 7.12

Sex: 58% female

Location: USA; setting: outpatients

Comorbidities: Individuals with another primary psychiatric disorder or a physical disorder judged likely to interfere with the study were excluded.

Rescue medication: not allowed

Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Alprazolam 2 mg arm (n = 20)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage 2 mg</p> <p>(2) Alprazolam 6 mg arm (n = 21)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage 6 mg</p> <p>(3) Imipramine arm (n = 20)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage 225 mg</p> <p>(4) Placebo arm (n = 20)</p> <p>Duration: 8 weeks</p>
Outcomes	<p>Time points for assessment: weeks 1, 2, 3, 4, 6, 8</p> <p>Outcomes:</p> <p>(1) Number of panic attacks (major, spontaneous, minor, situational)</p> <p>(2) Marks & Mathews Phobia Scale</p> <p>(3) Disability</p> <p>(4) HAMA</p> <p>(5) HAMD</p> <p>(6) SAFTEE-UP for adverse effects</p>
Notes	<p>Date of study: not stated</p> <p>Funding source: sponsored by Upjohn Company</p> <p>Declarations of interest among the primary researchers: not stated</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	<p>Unclear risk</p> <p>Quote: "random", no further information about the random sequence generation is provided</p>

Uhlenhuth 1989 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "All patients received two identical appearing capsules four times daily"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "two sets of outcome analysis were employed; one included all 81 patients who entered treatment, and the other included only the 63 patients who completed at least 4 weeks of treatment. Both sets of analysis presented here were based on the final (last available) clinical score for each patient (endpoint analysis). Patterns of dropout by treatment were analysed by survival analysis using the actuarial life table method."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Unclear risk	Sponsored by Upjohn Company; the role of the funder in planning, conducting and writing the study is not discussed.

Valenca 2000

Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-IV panic disorder with agoraphobia</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-IV</p> <p>Age: Clonazepam group: mean = 37.5 (SD = 6.6); Placebo group: mean = 36.8 (SD = 7.2)</p> <p>Sex: M = 10; F = 14</p> <p>Location: University of Rio de Janeiro (at the Laboratory of Panic and Respiration)</p> <p>Comorbidities: none</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) <u>Clonazepam (n = 14)</u></p> <p>Duration: 6 weeks</p> <p>Treatment protocol: fixed dosage: 2 mg/day</p> <p>(2) <u>Placebo arm (n = 10)</u></p> <p>Duration: 6 weeks</p>
Outcomes	<p>Time points for assessment: not stated</p> <p>Primary outcomes:</p>

Valenca 2000 (Continued)

- (1) Number of panic attacks: participant's diary
- (2) Global improvement of panic disorder: CGI
- (3) Anxiety: HAMA
- (4) Panic-associated symptom scale (PASS) (panic attacks, anticipatory anxiety, phobias)

Notes
Date of study: not stated

Funding source: not stated

Declarations of interest among the primary researchers: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All 24 subjects were randomly assigned to either treatment with clonazepam or placebo." No further details
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding is only mentioned in the study title; no further information.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding is only mentioned in the study title; no further information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Observed case data only, missing 1 person per group
Selective reporting (reporting bias)	High risk	The study protocol is not available. An efficacy outcome (PGI) reported in the results was not prespecified in the methods section. This outcome is reported incompletely (no baseline data).
Other bias	Unclear risk	Supported by the Brazilian Council for Scientific and Technological Development (CNPq)

CBT: cognitive-behavioural therapy

CGI: Clinical Global Impression

CGI-C: Clinical Global Impression of Change

CGI-I: Clinical Global Impression - Improvement

CGI-S: Clinical Global Impression - Severity

CT: compressed tablet

DSM: Diagnostic and Statistical Manual of Mental Disorders

F: female

HAMA: Hamilton Anxiety Rating Scale

HAMD: Hamilton Depression Rating Scale

ITT: intention-to-treat

LOCF: last observation carried forward

M: male

MADRS: Montgomery-Asberg Depression Rating Scale

MHPG: 3-methoxy-4-hydroxyphenylglycol

PGI-C: Patient's Global Impression of Change

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POMS: Profile of Mood States
SAFTEE: Systematic Assessment of Treatment-Emergent Events
SCID: Structured Clinical Interview
SCL-90-R: Symptom Checklist-90-Revised
SD: standard deviation
SE: standard error
SR: sustained release
WSDS: Work and Social Disability Scale
XR: extended release

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ananth 1979	Wrong comparator (no placebo group)
Ballenger 1988	Wrong diagnosis (the main diagnosis is agoraphobia, and less than 30% of participants suffer from panic disorder)
Balon 1991	No data (According to authors clinical data are lost)
Balon 1993	No data (no relevant clinical results)
Barbosa 1980	Wrong diagnosis (anxiety disorder)
Bernardi 1988	Wrong comparator (comorbidity of anxiety and depression)
Bueno 1988	Wrong diagnosis (anxiety disorder)
Chen 1997	Wrong comparator (no placebo group)
Chen 1998	Wrong comparator (buspirone, diazepam)
Chen 2003	Wrong comparator (mianserin, alprazolam)
Chouinard 1982	Wrong diagnosis (psychoneurotic patients)
Chouinard 1983	Wrong diagnosis (generalised anxiety and panic disorder)
Cohn 1984	Wrong diagnosis (anxiety disorder)
Cooper 1990	Wrong diagnosis (anxiety disorder)
Cooper 1991	Wrong diagnosis (anxiety disorder)
Csanalosi 1977	Wrong diagnosis (anxiety disorder)
Cunha 1988	Wrong diagnosis (anxiety disorder)
Dager 1992	No data (the short-term outcome data are not available (author did not provide data))
Dasberg 1974	Wrong diagnosis (anxiety disorder)
Davis 1981	Wrong study design (no RCT)
De Candia 2009	Wrong diagnosis (mild to moderate anxiety disorder)

Study	Reason for exclusion
de Jonghe 1989	Wrong diagnosis (generalised anxiety disorder and panic disorder)
De Rosa 1980	Wrong diagnosis (anxiety disorder)
Diukova 1993	Wrong diagnosis ('autonomic crisis')
Downing 1978	Wrong diagnosis (anxiety disorder)
Downing 1979	Wrong diagnosis (anxiety disorder)
Downing 1983	Wrong diagnosis (anxiety disorder)
Dunner 1986	Wrong diagnosis (generalised anxiety disorder, and only a minority of participants have agoraphobia with panic attacks or panic disorder)
Fava 1989	To avoid double inclusion of participants (according to the author, the sample was derived from a larger study; but it is unclear which study)
Filip 1981	Wrong diagnosis (anxiety disorder)
Franulic 1989	No data (no relevant clinical results)
Greiss 1980	Wrong diagnosis (anxiety disorder)
Hare 1974	Wrong comparator (no placebo group)
Hofmeijer-Sevink 2017	Wrong intervention (D-Cycloserine Enhancement)
Hu 2002	Wrong comparator (psychotherapy and drug)
Huppert 2004	Wrong comparator (CBT, medication)
Kahn 1986	Wrong diagnosis (anxiety disorder)
Kaplan 2000	Wrong study design (comparison with healthy people)
Keller 1993	Wrong diagnosis (primary depression)
Kerry 1983	Wrong diagnosis (anxiety disorder)
Klein 1988	Wrong study design (no RCT)
Klerman 1990	Wrong study design (no RCT)
Knijnik 1990	Wrong diagnosis (anxiety disorder)
Laakmann 1980	Wrong diagnosis (anxiety disorder)
Lapierre 1975	Wrong diagnosis (anxiety disorder)
Lorch 1995	Wrong intervention (no monotherapy)
Marks 1993	Wrong intervention (no monotherapy)
Mavissakalian 1982	Wrong comparator (antidepressants)

Study	Reason for exclusion
McCurdy 1978	Wrong diagnosis (anxiety disorder and depressive symptomatology)
McEvilly 1981	Wrong diagnosis (anxiety disorder)
Mellman 1986	Wrong study design (withdrawal study)
Miretzky 1992	Wrong comparator
Mueller 1986	Wrong diagnosis (anxiety disorder)
Muncy 1991	Wrong comparator
Nair 1982	Wrong diagnosis (anxiety disorder)
Nanivadekar 1973	Wrong diagnosis (anxiety disorder)
Ogunremi 1973	Wrong diagnosis (healthy participants)
Padron 1974	Wrong comparator (no placebo group)
Pasini 1972	Wrong diagnosis (anxiety disorder)
Piedade 1987	Wrong diagnosis (anxiety disorder)
Pollack 1998	Wrong comparator (antidepressants)
Pollack 2002	Wrong intervention (no benzodiazepines)
Pols 1996	Wrong study design (induced panic attacks)
Porta 1974	Wrong diagnosis (anxiety disorder)
Predescu 1969	Wrong study design (not an RCT)
Raffaele 2002	Wrong comparator
Rapaport 2000	Wrong intervention (concomitant psychological therapy (combination with CBT))
Rifkin 1991	Wrong study design (no RCT)
Rizley 1986	Wrong comparator (no placebo group)
Rynn 2003	Wrong comparator (imipramine, buspirone, placebo)
Saiz-Ruiz 1992	Wrong comparator (antidepressants)
Sciegghi 1986	Wrong diagnosis (neurotic anxiety)
Sladka 1979	Wrong diagnosis (anxiety disorder)
Sonne 1986	Wrong comparator (alprazolam, bromazepam, no placebo group)
Taylor 1982	Wrong intervention (Concomitant psychological therapy)
Telch 1985	Wrong comparator (antidepressants)

Study	Reason for exclusion
Terra 1971	Wrong diagnosis (anxiety disorder)
Tesar 1990	Wrong study design (no RCT)
Tyrer 1984	Wrong diagnosis (generalised anxiety disorder)
Van Balkom 1996	Wrong comparator
Van Boeijen 2007	Wrong comparator
Versiani 1983	Wrong diagnosis (anxiety disorder)
Wiesner 1993	Wrong intervention (benzodiazepine agonist)
Woods 1988	Wrong intervention (benzodiazepine antagonist)
Zmorski 1985	Wrong diagnosis (anxiety disorder)

CBT: cognitive-behavioural therapy

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Anon 1994](#)

Methods	Placebo-controlled study
Participants	People with panic disorder
Interventions	Imipramine, diazepam, baclofen, and propranolol
Outcomes	
Notes	Publication is in Russian. We were unable to retrieve a full text.

[Bernik 1983](#)

Methods	Double-blind study
Participants	People with anxiety
Interventions	Alprazolam, oxazepam, and placebo
Outcomes	
Notes	Publication is in Portuguese. We were unable to retrieve a full text.

[Ciraulo 1990](#)

Methods	14-week, randomised, parallel, double-blind, fixed-dosage, placebo-controlled study
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Ciraulo 1990 (Continued)

Participants	People with agoraphobia with panic attacks, or panic disorder with limited phobic avoidance, based on DSM-III criteria
Interventions	Alprazolam (1 to 10 mg/day), Placebo (max 10 tablets/day)
Outcomes	Metabolite plasma levels: blood sample Anxiety: CRAS, PRAS Overall assessment: Physician Global Rating Adverse events: SAFTEE-UP
Notes	This study evaluated the relationship of parent compound and metabolites. It was unclear if relevant clinical data were generated.

Coryell 1989

Methods	8-week, randomised, double-blind trial
Participants	People with panic disorder according to DSM-III-R
Interventions	Diazepam, alprazolam, placebo (dosage unclear)
Outcomes	Depression: HAMD Anxiety: HAMA Overall improvement: 10-point scale
Notes	This study was designed to assess the influence of dexamethasone plasma levels on treatment, and the clinical data are not published. It was unclear if data relevant to our review were analysed.

Fisekovic 2005

Methods	12-week, placebo-controlled study
Participants	People with diagnosed panic disorder with or without agoraphobia according to ICD-10
Interventions	Sertraline (50 mg/d), alprazolam (1 to 1.5 mg/d)
Outcomes	Panic attacks, agoraphobia, anticipatory anxiety
Notes	The abstract mentions a placebo-controlled group, but no information on placebo is reported in the main text.

Gladsjo 1997

Methods	8-week, randomised study
Participants	People with panic disorder according to DSM-IV

Gladsjo 1997 (Continued)

Interventions	Alprazolam XR (2 mg), placebo
Outcomes	Neuropsychological performance: neuropsychological test performance
Notes	Conference abstract, no further information available

Ipca Laboratories

Methods	Randomised, active- and placebo-controlled study, 3 months
Participants	People with panic disorder diagnosed by DSM-IV criteria
Interventions	Clonazepam CR (0.5 and 1 mg), alprazolam XR (0.5 and 1 mg), placebo
Outcomes	Change from baseline (decrease) in the number of panic attacks, CGI-S score for panic disorder and CGI-I score for panic disorder, phobic avoidance, and anticipatory anxiety
Notes	The trial register lists an abstract from 2012 that would be relevant to this review, but the record was updated and changed in 2014. The registry entry now represents a study without a placebo-controlled group. All contacts to the individuals listed in the registry failed, and the company that registered the trial did not respond.

Picano 1971

Methods	Clinical trial
Participants	
Interventions	Lorazepam
Outcomes	
Notes	Conference abstract, no further information available

Tesar 1988

Methods	Randomised, parallel, double-blind, flexible-dose study
Participants	People with panic disorder or agoraphobia with panic attacks
Interventions	Clonazepam (0.5 mg), alprazolam (1.0 mg), placebo
Outcomes	Frequency and intensity of panic attacks, duration and intensity of anticipatory anxiety, extent of phobic avoidance, CGI, PGI-I, degree of generalised anxiety, WSDS scores and depression ratings
Notes	Conference abstract, no further information available

Valenca 2003

Methods	6-week, randomised, parallel, fixed-dose study
Participants	People with panic disorder with agoraphobia according to DSM-IV
Interventions	Clonazepam (2 mg/day), placebo
Outcomes	Frequency of panic attacks, anxiety (HAMA), CGI, PGI
Notes	Details on the blinding are not reported; it was unclear if the study was double-blinded.

CGI-I: Clinical Global Impression - Improvement

CGI-S: Clinical Global Impression - Severity

CR: controlled release

CRAS: Clinician rated anxiety scale

DSM: Diagnostic and Statistical Manual of Mental Disorders

HAMA: Hamilton Anxiety Rating Scale

HAMD: Hamilton Depression Rating Scale

ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems

PGI-I: Patient Global Impression of Improvement

PRAS: Patient rated anxiety scale

SAFTEE-UP: Systematic Assessment for Treatment Emergent Events

SR: sustained release

WSDS: Work and Social Disability Scale

XR: extended release

DATA AND ANALYSES

Comparison 1. Benzodiazepines versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment response	16	2476	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.39, 1.96]
2 Total number of dropouts	21	3558	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.39, 0.64]
3 Treatment remission	15	2907	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.38, 1.88]
4 Panic symptom scales and global judgement on a continuous scale	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Endpoint data	7	1489	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.22, -0.61]
4.2 Change score data	4	719	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.87, -0.13]
5 Frequency of panic attacks	16	2129	Mean Difference (IV, Random, 95% CI)	-2.12 [-3.07, -1.17]
6 Agoraphobia	13	2371	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.50, -0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Endpoint data	8	1654	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.59, -0.17]
6.2 Change score data	5	717	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.55, -0.08]
7 General anxiety (HAMA)	17	2549	Mean Difference (IV, Random, 95% CI)	-5.24 [-6.59, -3.90]
8 Depression	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Endpoint data	8	968	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.08, -0.32]
8.2 Change score data	4	441	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.48, 0.04]
9 Social functioning	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Endpoint data	5	1207	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.65, -0.42]
9.2 Change score data	3	246	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.88, 0.24]
10 Number of dropouts due to adverse effects	14	3263	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.16, 2.15]
11 Number of participants experiencing at least 1 adverse effect	4	658	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.02, 1.37]
12 Subgroup analysis: drugs - response	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Adinazolam	2	517	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.89, 2.25]
12.2 Alprazolam	7	895	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.29, 2.32]
12.3 Clonazepam	5	948	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.29, 2.22]
12.4 Diazepam	1	160	Risk Ratio (M-H, Random, 95% CI)	2.17 [1.46, 3.23]
12.5 Etizolam	1	30	Risk Ratio (M-H, Random, 95% CI)	2.4 [1.12, 5.13]
12.6 Midazolam	1	5	Risk Ratio (M-H, Random, 95% CI)	3.75 [0.27, 52.64]
13 Subgroup analysis: drugs - dropouts	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Adinazolam	2	517	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.57, 1.52]
13.2 Alprazolam	14	1992	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.35, 0.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3 Clonazepam	5	960	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.31, 1.14]
13.4 Diazepam	1	160	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.28, 0.76]
13.5 Etizolam	1	30	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.22]
14 Sensitivity analysis: exclusion high risk of bias - response	3	215	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.67, 4.84]
15 Sensitivity analysis: exclusion high risk of bias - dropouts	2	210	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.27, 1.03]
16 Sensitivity analysis: exclusion > 20% dropouts - response	6	640	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.17, 2.71]
17 Sensitivity analysis: exclusion > 20% dropouts - dropouts	4	608	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.39]
18 Sensitivity analysis: exclusion comorbidities - response	11	1778	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.38, 1.94]
19 Sensitivity analysis: exclusion comorbidities - dropouts	13	1917	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.77]

Analysis 1.1. Comparison 1 Benzodiazepines versus placebo, Outcome 1 Treatment response.

Analysis 1.2. Comparison 1 Benzodiazepines versus placebo, Outcome 2 Total number of dropouts.

Analysis 1.3. Comparison 1 Benzodiazepines versus placebo, Outcome 3 Treatment remission.

Analysis 1.4. Comparison 1 Benzodiazepines versus placebo, Outcome 4 Panic symptom scales and global judgement on a continuous scale.

Analysis 1.5. Comparison 1 Benzodiazepines versus placebo, Outcome 5 Frequency of panic attacks.

Analysis 1.6. Comparison 1 Benzodiazepines versus placebo, Outcome 6 Agoraphobia.

Analysis 1.7. Comparison 1 Benzodiazepines versus placebo, Outcome 7 General anxiety (HAMA).

Analysis 1.8. Comparison 1 Benzodiazepines versus placebo, Outcome 8 Depression.

Analysis 1.9. Comparison 1 Benzodiazepines versus placebo, Outcome 9 Social functioning. **Analysis 1.10. Comparison 1 Benzodiazepines versus placebo, Outcome 10 Number of dropouts due to adverse effects.**

Analysis 1.11. Comparison 1 Benzodiazepines versus placebo, Outcome 11 Number of participants experiencing at least 1 adverse effect.

Analysis 1.12. Comparison 1 Benzodiazepines versus placebo, Outcome 12 Subgroup analysis: drugs - response.

Analysis 1.13. Comparison 1 Benzodiazepines versus placebo, Outcome 13 Subgroup analysis: drugs - dropouts.

**Analysis 1.14. Comparison 1 Benzodiazepines versus placebo,
Outcome 14 Sensitivity analysis: exclusion high risk of bias - response.**

**Analysis 1.15. Comparison 1 Benzodiazepines versus placebo,
Outcome 15 Sensitivity analysis: exclusion high risk of bias - dropouts.**

**Analysis 1.16. Comparison 1 Benzodiazepines versus placebo,
Outcome 16 Sensitivity analysis: exclusion > 20% dropouts - response.**

Analysis 1.17. Comparison 1 Benzodiazepines versus placebo, Outcome 17 Sensitivity analysis: exclusion > 20% dropouts - dropouts.

Analysis 1.18. Comparison 1 Benzodiazepines versus placebo, Outcome 18 Sensitivity analysis: exclusion comorbidities - response.

**Analysis 1.19. Comparison 1 Benzodiazepines versus placebo,
Outcome 19 Sensitivity analysis: exclusion comorbidities - dropouts.**

APPENDICES

Appendix 1. CCMDCTR: core MEDLINE search strategy

Core Ovid MEDLINE search used to inform the Cochrane Common Mental Disorders Specialised Register (CCMD-CTR).
A weekly search alert based on Condition + RCT filter only.

1. [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/

2. [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).ti,kf.

3. [RCT filter]:

(controlled clinical trial.pt. or randomized 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 substitut* 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 randomized 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.)

4. (1 and 2 and 3)

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

Similar weekly search alerts are also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

A quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL) is conducted c/o the Cochrane Register of Studies Online (CRSO).

Appendix 2. Update search strategy (2014/15)

Cross-search of the Cochrane Common Mental Disorders Specialised Register (CCMD-CTR) (studies and references registers) (26 March 2014 and 11 September 2015), including reports of relevant RCTs from MEDLINE, EMBASE, PsycINFO, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

The update search was conducted across three panic reviews simultaneously: (*BZDs vs PLO*; *ADs vs PLO*; *ADs vs BZDs*)

#1 Panic

#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*)

#3 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Bupropion 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)

#4 (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 Lofepamine* 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*)

#5 (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizipine 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)

#6 (#2 or #3 or #4 or #5)

#7 (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"))

#8 (#1 and (#6 or #7))

#9 ("anxiety disorder*" and not (agoraphobi* or panic or (social and (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or "post trauma*" or posttrauma*)):ti,ab,kw,ky,emt,mh,mc

#10 (#9 and (#6 or #7))

Appendix 3. Update search strategies (2017/18)

In May 2017 the Group's Specialised Register (CCMDCTR) was out-of-date due to staff changes. At this time searches were conducted on the following core biomedical databases (from 1 Jan 2014 to 3 May 2017). This search was repeated on 29 May 2018.

Ovid XSearch MEDLINE, Embase, PsycINFO

PsycINFO 1806 to April Week 4 2017, Embase 1974 to 2017 Week 18, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to 29 May 2018

[Condition]

(panic* or agoraphobi* or ADNOS).ti,ab,kf,kw,id.

(panic* or panik* or paniq*).ot.

3. PANIC DISORDER/

4. PANIC/

5. PANIC ATTACK/

6. AGORAPHOBIA/

7 or/1-6

[Intervention]

8. exp BENZODIAZEPINES/

9. exp BENZODIAZEPINE DERIVATIVE/

10. (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 Metaclozepam 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-Drug* or Z Drug*).af.

11. or/8-10

[RCT filter]

12. trial.ti.

13. (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf,kw,id.

14. (RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,kf,kw,id.

15. ((single or double or triple) adj2 (blind* or mask* or dummy)).ti,ab,kf,kw,id.

16. placebo.hw,ti,ab,kf,kw,id.

17. (control* adj2 (trial or group?)).ab.

18. RANDOMIZED CONTROLLED TRIAL.sh,pt.

19. CONTROLLED CLINICAL TRIAL/ and placebo.af.

20. DOUBLE BLIND PROCEDURE/

21. DOUBLE BLIND METHOD/

22. (clinical trial or empirical study).md.

23. or/12-22

[Combine sets]

24. (7 and 11 and 23)

25. ((animal or nonhuman) not (human and (animal or nonhuman))).hw.

26. (24 not 25)

[Date limits]

27. (2014* or 2015* or 2016* or 2017* or 2018*).yr.

28. (2014* or 2015* or 2016* or 2017* or 2018*).dd.

29. ((2014* or 2015* or 2016* or 2017* or 2018*).dc,ed. and (medline* or pubmed* or in-data-review or in-process or publisher).st.)

30. (2014* or 2015* or 2016* or 2017* or 2018*).an. and (PsycINFO database record).ab.

31. or/27-30

32. (26 and 31)

33. remove duplicates from 32

Ovid Field Tags

ab: abstract

af: all fields

hw: subject heading word

id: key concept (PsycINFO)

kf: keyword heading word (author assigned word) (MEDLINE)

kw: keyword heading word (author assigned word) (Embase)

md: methodology (PsycINFO)

ot: original title

ti: title

Benzodiazepines versus placebo for panic disorder in adults (Review)

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rn:Name of substance (MEDLINE, Embase)

Date Limit Tags

an: accession number (PsycINFO)

dd: date delivered (Embase)

dc: date created (MEDLINE)

ed: entry date (MEDLINE)

st: status (MEDLINE)

yr: year of publication

CENTRAL (c/o Cochrane Register of Studies Online (CRSO))

#1(((panic* or agoraphobi*) and (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 Metaciazepam 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-Drug* or Z Drug*))) :TI,AB,KY AND 31/01/2014 TO 31/05/2017:DL n = 33

Cochrane Specialised Register (CCMDCTR)

((panic* or agoraphobi*) and (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 Metaciazepam 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-Drug* or Z Drug*))

Limited to date of record entry = 01/01/2014 to 30/06/2016 n = 79

International Trial Registers

ClinicalTrials.gov: Interventional Studies | PANIC OR AGORAPHOBIA | Adult | Studies received from 01/01/2014 to 05/03/2017 n = 25 (manually screened for BZD studies, n = 1)

WHO International Clinical Trials Registry Portal (ICTRP): Condition = PANIC OR AGORAPHOBIA Studies received from 01/01/2014 to 05/03/2017 n = 104 studies (manually screened for BZD studies, n = 2)

No additional trial protocols were retrieved from the international trial registries 29-May-2018.

CONTRIBUTIONS OF AUTHORS

GG devised the idea for the review. GG, CB, and AC worked on the first draft of the protocol. MK, SJD, and FG provided suggestions. FG, JB, and MK collected the data; JB, FG, and MK conducted the analyses; MC, IB, AC, TAF, FG, and GG provided suggestions and input; JB, FG, and MK drafted and critically revised the manuscript; all authors reviewed and approved the final version of the review.

DECLARATIONS OF INTEREST

JB: none.

FG: none.

GG: none.

CB: none.

AC: none.

MC: none.

Benzodiazepines versus placebo for panic disorder in adults (Review)

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IB: none.

SJD: none.

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MK: none.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the course of this review the DSM-5 was published. We extended the inclusion criteria for studies using DSM-5 diagnostic criteria. However, we were unable to identify any such study in this review.

We added a subgroup analysis for the individual medications to explore potential differences within the group of benzodiazepines. In response to an external reviewer request, we added meta-regression analyses to explore the possible influence of trial duration on the primary outcomes.

In the protocol we had planned to calculate agreement in the selection of studies using Cohen's Kappa (K). However, the few discordances were resolved reaching a consensus through discussion between review authors, so we decided not to include a formal measure of agreement.

NOTES

This review is one of a number of separate reviews examining the efficacy and tolerability of pharmacological and non-pharmacological treatments for panic disorders ([Bighelli 2016](#); [Bighelli 2018](#)). These individual reviews will then be combined in a multiple-treatment meta-analysis using multiple-treatments model methodology (protocol to be published in the Cochrane Database of Systematic Reviews). Please note that the majority of the text in the methods sections for these reviews is identical since the full reviews will be following the same methodology.

INDEX TERMS

Medical Subject Headings (MeSH)

Agoraphobia [complications] [drug therapy]; Benzodiazepines [*therapeutic use]; Buspirone [therapeutic use]; Imipramine [therapeutic use]; Numbers Needed To Treat; Panic Disorder [complications] [*drug therapy]; Paroxetine [therapeutic use]; Patient Dropouts [statistics & numerical data]; Placebos [therapeutic use]; Propranolol [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction

MeSH check words

Adult; Aged; Humans; Middle Aged; Young Adult