

This is a repository copy of *Pharmacological treatments in panic disorder in adults:a network meta-analysis*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/206239/>

Version: Accepted Version

Article:

Guaiana, Giuseppe, Meader, Nicholas orcid.org/0000-0001-9332-6605, Barbui, Corrado et al. (12 more authors) (2023) Pharmacological treatments in panic disorder in adults:a network meta-analysis. Cochrane Database of Systematic Reviews. CD012729. ISSN 1469-493X

<https://doi.org/10.1002/14651858.CD012729.pub3>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Manuscript Number:	COCHRANEEMD-2022-00463R2
Full Title:	Pharmacological treatments in panic disorder in adults: a network meta-analysis
Article Type:	Review: Intervention
Section/Category:	Central Editorial Service
Corresponding Author:	Giuseppe Guaiana, M.D., Ph.D. Western University Schulich School of Medicine & Dentistry St Thomas, CANADA
Order of Authors:	Giuseppe Guaiana, M.D., Ph.D.
	Nicholas Meader
	Corrado Barbui
	Simon JC Davies
	Toshi Furukawa
	Hisei Imai
	Sofia Dias
	Deborah M Caldwell
	Markus Koesters
	Aran Tajika
	Irene Bighelli
	Alessandro Pompoli
	Andrea Cipriani
	Sarah Dawson
	Lindsay Robertson

RevMan: review – intervention; 954813111214410260 (version 2.6)

Status: UNPUBLISHED DRAFT

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

Table of contents

[Abstract](#)

[Plain language summary](#)

[Summary of findings](#)

[Background](#)

[Description of the condition](#)

[Description of the intervention](#)

[How the intervention might work](#)

[Why it is important to do this review](#)

[Objectives](#)

[Methods](#)

[Criteria for considering studies for this review](#)

[Search methods for identification of studies](#)

[Data collection and analysis](#)

[Results](#)

[Description of studies](#)

[Risk of bias in included studies](#)

[Effects of interventions](#)

[Discussion](#)

[Summary of main results](#)

[Overall completeness and applicability of evidence](#)

[Quality of the evidence](#)

[Potential biases in the review process](#)

[Agreements and disagreements with other studies or reviews](#)

[Authors' conclusions](#)

[Acknowledgements](#)

[History](#)

[Contributions of authors](#)

[Declarations of interest](#)

[Sources of support](#)

[Internal sources](#)

[External sources](#)

[Differences between protocol and review](#)

[Characteristics of studies](#)

[Characteristics of included studies \[ordered by study ID\]](#)

[Characteristics of excluded studies \[ordered by study ID\]](#)

[Appendices](#)

[Appendix 1. Cochrane Specialized Register](#)

[Appendix 2. Other database searches](#)

[Appendix 3. Node-splitting for response: direct, indirect and network estimates](#)

[Appendix 4. Node splitting for dropout: direct, indirect and network estimates](#)

[Appendix 5. WinBUGS and OpenBUGS code](#)

[References](#)

[References to studies included in this review](#)

[References to studies excluded from this review](#)

[Additional references](#)

[References to other published versions of this review](#)

[Additional tables](#)

Editors: Cochrane Common Mental Disorders Group

Contact Person: Giuseppe Guaiana (giuseppe.guaiana@gmail.com)

Department of Psychiatry

Western University

Saint Thomas Elgin General Hospital

189 Elm Street

St Thomas

ON
N5R 5C4
Canada

Giuseppe Guaiana [1] Nicholas Meader [2] [3] Corrado Barbui [4] [5] Simon JC Davies [6] Toshi A Furukawa [7]
Hissei Imai [7] Sofia Dias [2] Deborah M Caldwell [8] Markus Koesters [9] Aran Tajika [10] Irene Bighelli [11]
Alessandro Pompoli [12] Andrea Cipriani [13] [14] [15] Sarah Dawson [8] Lindsay Robertson [16]

[1] Department of Psychiatry, Western University, St
Thomas, Canada

[2] Centre for Reviews and Dissemination, University of
York, York, UK

[3] Cochrane Common Mental Disorders, University of
York, York, UK

[4] Department of Neurosciences, Biomedicine and
Movement Sciences, Section of Psychiatry, University
of Verona, Verona, Italy

[5] Cochrane Global Mental Health, University of
Verona, Verona, Italy

[6] Geriatric Psychiatry Division, CAMH, University of
Toronto, Toronto, Canada

[7] Department of Health Promotion and Human
Behavior, Kyoto University Graduate School of
Medicine/School of Public Health, Kyoto, Japan

[8] Population Health Sciences, Bristol Medical School,
University of Bristol, Bristol, UK

[9] Center for Evidence-Based Healthcare, University
Hospital Carl Gustav Carus and Carl Gustav Carus
Faculty of Medicine, Technische Universität Dresden,
Chemnitz, Germany

[10] Department of Psychiatry, Kyoto University
Hospital, Kyoto, Japan

[11] Klinik und Poliklinik für Psychiatrie und
Psychotherapie, Technische Universität München
Klinikum rechts der Isar, München, Germany

[12] Private practice, no academic affiliations,
Malcesine, Italy

[13] Department of Psychiatry, University of Oxford,
Oxford, UK

[14] Warneford Hospital, Oxford Health NHS
Foundation Trust, Oxford, UK

[15] Oxford Precision Psychiatry Lab, Oxford Health
Biomedical Research Centre, Oxford, UK

[16] Newcastle upon Tyne, UK

Citation

Guaiana G, Meader N, Barbui C, Davies SJC, Furukawa TA, Imai H, Dias S, Caldwell DM, Koesters M, Tajika A, Bighelli I, Pompoli A, Cipriani A, Dawson S, Robertson L. Pharmacological treatments in panic disorder in adults: a network meta-analysis. *Cochrane Database of Systematic Reviews* TBD, Issue TBD. Art. No.: CD012729. DOI: [10.1002/14651858.CD012729.pub3](https://doi.org/10.1002/14651858.CD012729.pub3).

Dates

Revision published: Issue TBD, TBD (TBD)

Version published (citation changed): Issue TBD, TBD (TBD)

Review first published: Issue TBD, TBD

Protocol first published: Issue 7, 2017

.....

Abstract

Background

A panic attack is a discrete period of fear or anxiety that has a rapid onset and reaches a peak within 10 minutes. The main symptoms involve bodily systems, such as racing heart, chest pain, sweating, shaking, dizziness, flushing, churning stomach, faintness and breathlessness. Other recognised panic attack symptoms involve fearful cognitions, such as the fear of collapse, going mad or dying, and derealisation (sensation that the world is unreal). Panic disorder is common in the general population with a prevalence of 1% to 4%. The treatment of panic disorder includes psychological and pharmacological interventions, including antidepressants and benzodiazepines.

Objectives

To compare, via network meta-analysis, individual drugs (antidepressants and benzodiazepines) or placebo in terms of efficacy and acceptability in the acute treatment of panic disorder, with or without agoraphobia.

To rank individual active drugs for panic disorder (antidepressants, benzodiazepines and placebo) according to their effectiveness and acceptability.

To rank drug classes for panic disorder (SSRIs, SNRIs, TCAs, MAOIs and BDZs and placebo) according to their effectiveness and acceptability.

To explore heterogeneity and inconsistency between direct and indirect evidence in the network meta-analysis.

Search methods

We searched the Cochrane Common Mental Disorders Specialised Register, the Cochrane Library (Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR)), together with Ovid Embase, MEDLINE and PsycINFO till May 26, 2022.

Selection criteria

Randomised trials of people aged 18 year or older of either sex and any ethnicity with clinically diagnosed panic disorder with or without agoraphobia were included. Trials that compared the effectiveness of antidepressants and benzodiazepines with each other or with a placebo were included.

Data collection and analysis

Two reviewers independently screened titles/abstracts and full texts, extracted data, and assessed risk of bias. We analysed dichotomous data and continuous data as Risk Ratios (RRs), Mean Differences (MD), or Standardised Mean Difference (SMD): response to treatment (i.e. substantial improvement from baseline as defined by the original investigators: dichotomous outcome), total number of dropouts due to any reason (as a proxy measure of treatment acceptability: dichotomous outcome), Remission (i.e. satisfactory end-state as defined by global judgement of the original investigators: dichotomous outcome), panic symptom scales and global judgement (continuous outcome), frequency of panic attacks (as recorded, for example, by a panic diary; continuous outcome), agoraphobia (dichotomous outcome). Certainty of evidence was assessed using threshold analyses.

Main results

Overall, 70 trials were included in this review. The sample sizes ranged between 5 and 445 participants in each arm. Total sample size per study ranges from 10 to 1168. Thirty-five studies included sample sizes over 100. There was evidence from forty-eight RCTs (N=10,118) that most medications were more effective in the response outcome than placebo. In particular, diazepam, alprazolam, clonazepam, paroxetine, venlafaxine, clomipramine, fluoxetine and adinazolam showed the strongest effect, with diazepam, alprazolam and clonazepam ranking as the most effective. Heterogeneity has been found for most comparisons, but our threshold analyses suggest this is unlikely to impact the NMA findings. Results from sixty-four RCTs (N= 12,310) suggest that most medications were either associated with reduced or similar risk of drop-outs as placebo. Alprazolam and diazepam were associated with a lower drop out rate compared to placebo and were ranked as the most tolerated of all the medications examined. Thirty-two RCTs (N=8569) were included in the remission outcome. Most medications were more effective than placebo, namely desipramine, fluoxetine, clonazepam, diazepam, fluvoxamine, imipramine, venlafaxine, paroxetine and their effect were clinically meaningful. Amongst those medications, desipramine and alprazolam were ranked the highest. Thirty-five RCTs have been included (N=8826) for the continuous outcome (reduction in panic scales scores). Brofaromine, clonazepam and reboxetine had the strongest reductions in panic symptoms compared to placebo, but results were based on either one trial or very small trials. Forty-one RCTs have been included (N=7853) and were analysed in the frequency of panic attack outcome. Only clonazepam and alprazolam showed a strong reduction in the frequency

of panic attacks compared to placebo as were ranked as highest. Twenty-six RCTs (N=7044) provided data for agoraphobia. The strongest reductions in agoraphobia symptoms were found for citalopram, reboxetine, escitalopram, clomipramine and diazepam, compared to placebo.

For pooled interventions, the two outcomes examined were the primary outcomes (response and drop out). The classes of medication examined were: SSRIs, SNRIs, TCAs, MAOIs and BDZs. For the response outcome, all classes of medications examined (SSRIs, SNRIs, TCAs, MAOIs, BDZs) were more effective than placebo. TCAs as a class ranked as the most effective, followed by BDZs and MAOIs. SSRIs as a class ranked fifth on average while SNRIs were ranked as the lowest. When classes of medications were compared with each others for the response outcome, no difference was found between classes. Comparisons between MAOIs and TCAs and between BDZs and TCAs also suggested no differences between these medications, but the results were imprecise. For the drop out outcome, BDZs was the only class associated with a lower drop out compared to placebo, and they were ranked as first in terms of tolerability. The other classes did not show any difference in drop-outs compared to placebo. In terms of ranking, TCAs are on average second to BDZs, followed by SNRIs, then by SSRIs and lastly by MAOIs. BDZs were associated with a lower drop out rates compared to SSRIs, SNRIs and TCAs.

The quality of the studies comparing antidepressants with placebo was moderate, while the quality of the studies comparing BDZs with placebo and antidepressants was low.

Authors' conclusions

SSRIs, SNRIs (venlafaxine), TCAs, MAOIs, and BDZs may be effective and with little differences between classes in terms of efficacy. However, it's important to note that the reliability of these findings may be limited due to the overall low quality of the studies, with all trials rated unclear or high across multiple domains. Within classes, some differences emerged; for example amongst SSRIs paroxetine and fluoxetine seems to have stronger evidence of efficacy than sertraline. Benzodiazepines appear to have a small but significant advantage in terms of tolerability (incidence of dropouts) over other classes.

Plain language summary

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

Why is this review important?

People with panic disorder are profoundly impacted by this condition often experiencing challenges engaging with work, education and social or family life. We want to evaluate which medication treatments, if any, are the most effective and safe. In particular, we aim to assess if the NMA findings are of sufficient validity to identify the best medication treatments for panic disorder, in order to improve patient care. These analyses will also generate suggestions for future research to reduce key uncertainties in the evidence base.

Who will be interested in this research?

The research in this Cochrane Review will interest:

- people who decide policy, and influence decisions about the prescription of medications for panic disorder;
- people who prescribe these medicines to people with panic disorder;
- people with panic disorder;
- those who support and care for them

What did we want to find out?

We wanted to find out how well antidepressants, BDZs and azapirones work to improve panic disorder symptoms in adults (i.e. people aged 18 years or older).

We wanted to know how these medications affect:

- symptoms of panic disorder;
- dropout as a measure of side effects of medication
- recovery: no longer meeting diagnostic criteria for panic disorder;
- response or remission: scores on a scale indicating an important reduction in panic or no longer experiencing panic;
- reduction in frequency of panic attacks;
- reduction in agoraphobia.

What did we do?

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 antidepressants, benzodiazepines, azapirones 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 70 studies in our review for a total of 12,703 participants. The last date of our search is 26 May 2022.

What does the evidence from the review tell us?

- We found that most medications may have been more effective in the of response outcome than placebo. In particular, diazepam, alprazolam, clonazepam, paroxetine, venlafaxine, clomipramine, fluoxetine and adinazolam showed the strongest effect. Also, most medications were either associated with reduced or similar risk of drop-outs as placebo. Alprazolam and diazepam were associated with a lower drop out rate compared to placebo and were ranked as the most tolerated of all the medications examined.
- Most medications may have been more effective in remitting the symptoms of panic disorder and their effect were clinically meaningful. As for the reduction in panic scales scores, brofaromine, clonazepam and reboxetine seems to have the strongest reductions in panic symptoms compared to placebo, but results were based on either one trial or very small trials. For the frequency of panic attack outcome, only clonazepam and alprazolam showed a strong reduction in the frequency of panic attacks compared to placebo. The strongest reductions in agoraphobia symptoms were found for citalopram, reboxetine, escitalopram, clomipramine and diazepam, compared to placebo.
- If we consider the classes of medications together (SSRIs, SNRIs, TCAs, MAOIs and BDZs), all classes of medications examined were more effective than placebo. TCAs as a class ranked as the most effective, followed by BDZs and MAOIs. SSRIs as a class ranked fifth on average while SNRIs were ranked as the lowest.
- If classes of medications are compared with each others for the response outcome, no difference is found between classes. For the drop out outcome, BDZs was the only class associated with a lower drop out compared to placebo, and they were ranked as first in terms of tolerability. The other classes did not show any difference in drop-outs compared to placebo.
- It is important to notice that, while the quality of the studies comparing antidepressants with placebo was acceptable, the quality of the studies comparing BDZs with placebo and antidepressants was low. This may limit the applicability of our results.
- Our review has limitations as it is based on short term studies and the potential for abuse associated with BDZ medications.

What should happen next?

- Almost all the studies examined in this NMA were of short duration. For the BDZs, there has been a considerable debate on whether they can be used in the long-term given their propensity to abuse, possible risk for tolerance. More research on the long-term effect (i.e longer than 8 weeks, maybe up to 1 year) is needed.
- It will be important to systematically assess the efficacy of medications compared to talking therapies, perhaps in a NMA. Data from depression seems to show that psychotherapies can lead to a more sustained effect. The same may apply to anxiety disorders in general and panic disorder in particular and needs to be investigated.

Summary of findings

Summary of findings 1

Summary of findings: response at end of treatment

Population: people with panic disorder diagnosis Settings: Inpatient, outpatient and primary care Intervention: antidepressants (such as sertraline) or benzodiazepines (such as diazepam) Comparison: placebo, alternative antidepressant or benzodiazepine				
Anticipated Absolute Effects (95% CrI)*				
48 RCTs, 10,118 participants	Assumed comparator risk per 1000	Corresponding intervention risk per 1000 (95% CrI)	Relative effect (NMA): RR (95% CrI)	Threshold analysis
Diazepam vs Placebo	617	401 (173 to 592)	0.65 (0.28 to 0.96)	No concerns
Alprazolam vs Placebo	617	419 (241 to 568)	0.68 (0.39 to 0.92)	No concerns
Clonazepam vs Placebo	617	438 (253 to 592)	0.71 (0.41 to 0.96)	No concerns
Escitalopram vs Placebo	617	481 (259 to 635)	0.78 (0.42 to 1.03)	No concerns
Fluoxetine vs Placebo	617		0.78	No concerns

		481 (259 to 617)	(0.42 to 1.00)	
Adinazolam vs Placebo	617	506 (308 to 617)	0.82 (0.50 to 1.00)	No concerns
Imipramine vs Placebo	617	506 (247 to 672)	0.82 (0.40 to 1.09)	No concerns
Paroxetine vs Placebo	617	524 (395 to 598)	0.85 (0.64 to 0.97)	No concerns
Venlafaxine vs Placebo	617	518 (370 to 598)	0.84 (0.60 to 0.97)	No concerns
Clomipramine vs Placebo	617	524 (352 to 611)	0.85 (0.57 to 0.99)	No concerns
Fluvoxamine vs Placebo	617	531 (327 to 648)	0.86 (0.53 to 1.05)	No concerns
Citalopram vs Placebo	617	537 (352 to 629)	0.87 (0.57 to 1.02)	No concerns
Sertraline vs Placebo	617	549 (413 to 629)	0.89 (0.67 to 1.02)	No concerns
Desipramine vs Placebo	617	580 (265 to 845)	0.94 (0.43 to 1.37)	No concerns
Buspirone vs Placebo	617	703 (296 to 1271)	1.14 (0.48 to 2.06)	No concerns
Ritanserin vs Placebo	617	734 (6 to 1666)	1.19 (0.01 to 2.70)	No concerns
Etizolam vs Placebo	617	358 (19 to 882)	0.58 (0.03 to 1.43)	Findings sensitive to imprecision ¹
Reboxetine vs Placebo	617	475 (148 to 734)	0.77 (0.24 to 1.19)	Findings sensitive to imprecision ¹
Moclobemide vs Fluoxetine	185	213 (52 to 771)	1.15 (0.28 to 4.17)	No concerns
Citalopram vs Fluoxetine	185	281 (159 to 1097)	1.52 (0.86 to 5.93)	No concerns
Desipramine vs Fluoxetine	185	216 (83 to 783)	1.17 (0.45 to 4.23)	No concerns
Paroxetine vs Sertaline	556	506 (322 to 645)	0.91 (0.58 to 1.16)	No concerns
Paroxetine vs Venlafaxine	330	333 (277 to 416)	1.01 (0.84 to 1.26)	No concerns
Imipramine vs Fluvoxamine	379	326 (163 to 462)	0.86 (0.43 to 1.22)	No concerns
Ritanserin vs Fluvoxamine	379	595 (243 to 1762)	1.57 (0.64 to 4.65)	No concerns
Paroxetine vs Clomipramine	314	323 (232 to 506)	1.03 (0.74 to 1.61)	No concerns
Moclobemide vs Clomipramine	314	298 (60 to 612)	0.95 (0.19 to 1.95)	No concerns
Citalopram vs Clomipramine	314	374 (279 to 647)	1.19 (0.89 to 2.06)	No concerns
Alprazolam vs Imipramine	550	424 (215 to 671)	0.77 (0.39 to 1.22)	No concerns
Alprazolam vs Paroxetine	351	291 (176 to 393)	0.83 (0.50 to 1.12)	No concerns
Escitalopram vs Citalopram	484	499 (257 to 886)	1.03 (0.53 to 1.83)	No concerns
Diazepam vs Alprazolam	294	315 (153 to 585)	1.07 (0.52 to 1.99)	No concerns
Buspirone vs Alprazolam	294	547 (326 to 1558)	1.86 (1.11 to 5.30)	No concerns

1. 95% CrI crosses invariant range

*The **corresponding risk** (and its 95% credible interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CrI). In comparisons with placebo, estimates of assumed risk were based on the mean risk of non-response in

the placebo group. In head-to-head comparisons, estimates of assumed risk were based on the median risk of non-response in the comparator group as there were fewer trials.

CrI=credible interval, RR=risk ratio, RCT=randomised controlled trial

Summary of findings 2

Summary of findings: drop out at end of treatment

Population: people with panic disorder diagnosis				
Settings: Inpatient, outpatient and primary care				
Intervention: antidepressants (such as sertraline) or benzodiazepines (such as diazepam)				
Comparison: placebo, alternative antidepressant or benzodiazepine				
Anticipated Absolute Effects (95% CrI)*				
64 RCTs; 12,310 participants	Assumed comparator risk per 1000	Corresponding intervention risk per 1000 (95% CrI)	Relative effect: RR (95% CrI)	Threshold analysis
Fluvoxamine vs placebo	340	398 (289 to 564)	1.17 (0.85 to 1.66)	No concerns
Paroxetine vs placebo	340	364 (313 to 364)	1.07 (0.92 to 1.07)	No concerns
Imipramine vs placebo	340	289 (214 to 381)	0.85 (0.63 to 1.12)	No concerns
Venlafaxine vs placebo	340	337 (272 to 411)	0.99 (0.80 to 1.21)	No concerns
Clomipramine vs placebo	340	330 (252 to 422)	0.97 (0.74 to 1.24)	No concerns
Sertraline vs placebo	340	343 (275 to 445)	1.01 (0.81 to 1.31)	No concerns
Escitalopram vs placebo	340	231.2 (129 to 367)	0.68 (0.38 to 1.08)	No concerns
Citalopram vs placebo	340	299.2 (211 to 408)	0.88 (0.62 to 1.20)	No concerns
Desipramine vs placebo	340	214.2 (48 to 578)	0.63 (0.14 to 1.70)	Incoherence ¹
Fluoxetine vs placebo	340	384.2 (204 to 646)	1.13 (0.60 to 1.90)	Incoherence ²
Reboxetine vs placebo	340	136 (44 to 398)	0.40 (0.13 to 1.17)	No concerns
Clonazepam vs placebo	340	319.6 (251 to 384)	0.94 (0.74 to 1.13)	No concerns
Adinazolam vs placebo	340	404.6 (296 to 575)	1.19 (0.87 to 1.69)	No concerns
Alprazolam vs placebo	340	156.4 (112 to 224)	0.46 (0.33 to 0.66)	No concerns
Etizolam vs placebo	340	125.8 (3 to 847)	0.37 (0.01 to 2.49)	Imprecision ³
Buspirone vs placebo	340	622.2 (398 to 1136)	1.83 (1.17 to 3.34)	No concerns
Diazepam vs placebo	340	170 (78 to 309)	0.50 (0.23 to 0.91)	No concerns
Imipramine vs Fluoxetine	50	38 (20 to 72)	0.75 (0.40 to 1.44)	No concerns
Citalopram vs Fluoxetine	50	39 (21 to 77)	0.78 (0.42 to 1.53)	No concerns
Desipramine vs Fluoxetine	50	28 (7 to 80)	0.56 (0.13 to 1.59)	No concerns
Mirtazapine vs Fluoxetine	50	35 (5 to 107)	0.70 (0.09 to 2.13)	No concerns
Brofaromine vs Fluvoxamine	194	204 (103 to 371)	1.05 (0.53 to 1.91)	No concerns
Imipramine vs Fluvoxamine	194	142 (93 to 202)	0.73 (0.48 to 1.04)	No concerns
Paroxetine vs Sertraline	265	281 (220 to 356)	1.06 (0.83 to 1.34)	No concerns
Brofaromine vs Clomipramine	255	324 (179 to 561)	1.27 (0.70 to 2.20)	No concerns
Adinazolam vs Clomipramine	255	316 (232 to 446)	1.24 (0.91 to 1.75)	No concerns
Moclobemide vs Clomipramine	255	286 (151 to 497)	1.12 (0.59 to 1.95)	No concerns
	255	224 (156 to 316)		No concerns

Imipramine vs Clomipramine			0.88 (0.61 to 1.24)	
Citalopram vs Clomipramine	255	235 (158 to 329)	0.92 (0.62 to 1.29)	No concerns
Paroxetine vs Clomipramine	255	283 (217 to 378)	1.11 (0.85 to 1.48)	No concerns
Buspirone vs Imipramine	302	649 (395 to 1295)	2.15 (1.31 to 4.29)	No concerns
Alprazolam vs Imipramine	302	166 (118 to 226)	0.55 (0.39 to 0.75)	No concerns
Diazepam vs Alprazolam	167	177 (87 to 328)	1.06 (0.52 to 1.97)	No concerns
Buspirone vs Alprazolam	167	660 (338 to 1411)	3.96 (2.03 to 8.47)	No concerns
Alprazolam vs Clonazepam	77	40 (25 to 61)	0.52 (0.33 to 0.79)	No concerns
Paroxetine vs Venlafaxine	257	278 (224 to 355)	1.08 (0.87 to 1.38)	No concerns
Escitalopram vs Citalopram	231	180 (104 to 285)	0.78 (0.45 to 1.23)	No concerns

¹Direct estimates but not indirect estimates crossed equivalence range ²Indirect estimates but not direct estimates crossed equivalence range ³95% CrI crossed equivalence

*The **corresponding risk** (and its 95% CrI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CrI). In comparisons with placebo, estimates of assumed risk were based on the mean risk of drop out in the placebo group. In head-to-head comparisons, estimates of assumed risk were based on the median risk of drop out in the comparator group as there were fewer trials

CrI=credible interval, RR=risk ratio, RCT=randomised controlled trial

Background

Description of the condition

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

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

Panic disorder is common in the general population; it occurs in 1% to 4% of people (lifetime prevalence) (Eaton 1994; Bijl 1998; Kessler 2012). In primary care settings, panic has been reported to have a prevalence of around 10% (King 2008). This is because common mental disorders are more often dealt with in primary care (King 2008). Women and previously married people have consistently elevated odds of panic (Kessler 2006). There seems to be some weak association between unemployment and retirement and the likelihood of suffering from panic disorder (Kessler 2006). Its cause is not fully understood and probably there are several reasons why panic occurs. Biological theories incorporate the faulty triggering of an inbuilt anxiety response, possibly a suffocation alarm. Evidence for this comes from biological challenge tests (lactate and carbon dioxide trigger panic in those with the disorder) and from animal experiments and neuroimaging studies in humans that show activation of fear circuits in the brain, such as that involving a part of the brain called periaqueductal grey matter (Gorman 2000).

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

Panic disorder, with or without agoraphobia, co-occurs very frequently with other psychiatric disorders, such as drug dependence, major depression, bipolar I disorder, social phobia, specific phobia, and generalised anxiety

disorder (Grant 2006). It is estimated that generalised anxiety disorder co-occurs in 68% of people with panic disorder, whilst 24% to 88% of people with panic disorder have major depression (Starcevic 2009).

Description of the intervention

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

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

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

How the intervention might work

Antidepressant drugs augment the function of the monoamines serotonin and noradrenaline. Serotonergic antidepressants (SSRIs) promote the transmission of the neurotransmitter serotonin across brain synapses. They most notably do it in the part of the brain called dorsal raphe nucleus (Briley 1993). They prevent reuptake of serotonin into nerve terminals by inhibiting serotonin transporters, thus allowing more serotonin to be available for neurotransmission. In panic disorder, imaging studies have revealed reduced expression of the 5HT_{1A} serotonin receptor (Nash 2008), which has an inhibitory function, so the increased serotonin throughput may in part serve to overcome this deficit of inhibition. Noradrenergic antidepressants can similarly increase transmission of the catecholamine noradrenaline. Some antidepressants, such as the serotonin-norepinephrine reuptake inhibitor (SNRI) drugs (e.g. venlafaxine, duloxetine) and TCAs, can enhance both serotonin and noradrenaline transmission by inhibiting both transporters.

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

Why it is important to do this review

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

Pharmacological treatments are widely used in clinical practice to treat panic disorder. To our knowledge, the last meta-analysis specifically focused on benzodiazepines for panic disorder was published in 1991 (Wilkinson 1991); and the last two meta-analyses focusing on antidepressants for this condition were published more than 10 years ago and 7 years ago (Bakker 2002 and Andrisano 2013 respectively). Standard pair-wise meta-analyses of psychopharmacological interventions in panic disorder have been published within Cochrane (Imai 2014; Bighelli 2016; Bighelli 2018; Breilmann 2019). Other reviews have been published on combined psychotherapy and pharmacotherapy in panic disorder (Furukawa 2007; Watanabe 2009). However, given the

complexity of the condition it is very important to carry out a comprehensive and comparative evaluation of the main pharmacological treatment options within the framework of a network meta-analysis (NMA). NMAs produce estimates of the relative effects between any pair of interventions in the network, and usually yields more precise estimates than a single direct or indirect estimate (Higgins 2019).

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

Objectives

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

Methods

Criteria for considering studies for this review

Types of studies

We included double-blind randomised controlled trials (RCTs) compared to one another, one of the included drugs (see [Types of interventions](#)) or placebo, in the acute treatment of panic disorder. We excluded trials in which drugs are used as an augmentation strategy to any other psychotropic drugs. For trials that had a cross-over design, we only considered results from the first randomisation period. Cluster-randomised trials were included only if intracluster correlation coefficients were reported. If reported as double-blind, we included the study. Any risk of bias associated with implementing this procedure informed our risk of bias assessment.

We excluded:

- Relapse prevention trials;
- Studies in patients with a diagnosis of panic disorder where the effects of treatments were measured after panic attacks have been induced (for example with CO₂ inhalations or lactate infusions);
- Studies administering psychosocial therapies targeted at panic disorder concurrently;
- Studies comparing psychosocial interventions; and
- Quasi-randomised trials.

Types of participants

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

Participant characteristics

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

Diagnosis

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

Comorbidities

When the study eligibility focused on agoraphobia rather than panic disorder, and was operationally diagnosed according to the above-named criteria, and when we could safely assume that at least some of the patients experience panic disorder as defined by the above criteria, we included the study. Considering that over 95% of patients with agoraphobia seen clinically suffer from panic disorder as well (Goisman 1995), we planned to

investigate the effect of their inclusion in a subgroup analysis. However, this subgroup analysis was not possible as all studies included people with agoraphobia.

We excluded trials in which all participants had a concurrent primary diagnosis of any psychiatric disorder other than panic disorder or agoraphobia when the focus was not the treatment of panic disorder. We excluded trials in which participants had a serious concomitant medical illness.

Setting

Inpatient, outpatient and primary care.

Subset data

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

Types of interventions

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

Antidepressants

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

Benzodiazepines (BDZs)

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

Placebo

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

Types of outcome measures

We included studies that met the above inclusion criteria regardless of whether they reported on the following primary and secondary outcomes, which were pre-defined at the protocol stage (Guaiana 2020). We chose continuous and dichotomous data as they provide complementary data.

Primary outcomes

1. Response to treatment (i.e. substantial improvement from baseline as defined by the original investigators). We used the following definitions of response: "much or very much improved" according to the Clinical Global Impression Change Scale; more than 40% reduction in the Panic Disorder Severity Scale score; or more than 50% reduction in the Fear Questionnaire Agoraphobia Subscale. When multiple measures were used, we gave preference to the most global measure.
2. Total number of dropouts due to any reason (as a proxy measure of treatment acceptability).

Secondary outcomes

3. Remission (i.e. satisfactory end-state as defined by global judgement of the original investigators). Examples of this outcome included “panic free” and “no or minimal symptoms” according to the Clinical Global Impression Severity Scale. When multiple measures were used, we gave preference to the most global measure.
4. Panic symptom rating scales and global clinical judgement on a continuous scale. Examples included Panic Disorder Severity Scale total score (0 to 28), Clinical Global Impression Severity Scale (1 to 7), and Clinical Global Impression Change Scale (1 to 7).
5. Frequency of panic attacks per unit of time (ex. days, weeks, months..., as recorded, for example, by a panic diary).
6. Agoraphobia symptom (as measured, for example, by the Fear Questionnaire, Mobility Inventory, or behavioural avoidance test).

When more than one scale was available in the paper, preference was given in the following order:

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

Once the scale was chosen, if both self- and observer-rated assessments were available, we gave preference to the latter. The actual measure entered into the meta-analysis is indicated at the top of the listings in [Characteristics of included studies](#).

Timing of outcome assessment

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

Hierarchy of outcome measures

When several possible outcome measures were reported for the same outcome, we used the primary outcome according to the original study.

Search methods for identification of studies

Trials which included at least two of the interventions were eligible for inclusion in the review. We searched for all possible comparisons formed by the interventions of interest, as defined above.

Electronic searches

We searched the following databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource (all years to 17 May 2022).

- Cochrane Common Mental Disorders Specialised Register (CCMDCTR) (all available years) ([Appendix 1](#))
- Cochrane Central Register of Controlled Trials (CENTRAL; May 2022) in the Cochrane Library;
- Ovid MEDLINE databases (2014 to 17 May 2022) ([Appendix 2](#));
- Ovid Embase (2014 to May Week 2 2022);
- Ovid PsycINFO (2014 to May Week 2 2022).

The trial registers ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry Platform (apps.who.int/trialsearch) were searched via CCMDCTR and CENTRAL on the Cochrane Library.

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

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

Searching other resources

Two review authors checked independently the reference lists of all included studies, non-Cochrane systematic reviews and major textbooks of affective disorders (written in English), for published reports and citations of

unpublished research. We also conducted a citation search via the Web of Science (included studies only) to identify additional works; and we contacted experts in the field.

Data collection and analysis

Selection of studies

At least two review authors independently screened titles and abstracts for inclusion all studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications and two review authors independently screened them and identified studies for inclusion, and identified and recorded reasons for exclusion of these ineligible studies.

The two review authors resolved any disagreement through discussion or, when required, through consultation with a third member of the review team. We identified and excluded duplicate records and collated multiple reports related to the same study so that each study rather than each report is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

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

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

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

We compiled a table of important trial and patient characteristics and visually inspected the similarity of factors we considered likely to modify treatment effect.

We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We resolved disagreements through consensus or by involving a third person. One review author transfer data into the Review Manager 5 (Review Manager 2014), WinBUGS or OpenBUGS software. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

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

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

For each trial, we assessed the following domains:

- Sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessors;
- Incomplete outcome data;
- Selective reporting.

We judged each domain as being at a low, high or unclear risk of bias. We also extracted relevant text which underpinned our judgement and presented this in the 'Risk of bias' tables.

We decided to include sponsorship bias because of the high number of sponsored studies. Scientific literature on depression (Cristea 2017), shows some level of sponsorship bias, which may be applicable to anxiety.

Measures of treatment effect

Dichotomous data

For binary outcomes we estimated the risk ratio (RR) and its 95% confidence interval (CI) using a random-effects model. It has been shown that a random-effects model has good generalisability ([Furukawa 2002](#)); and that RR is more intuitive than odds ratio (OR) ([Boissel 1999](#)). Furthermore, ORs tend to be interpreted as RR by clinicians ([Deeks 2000](#)). This may lead to an overestimation of the impression of the effect ([Higgins 2019](#)).

Continuous data

(1) Summary statistics

Different studies used varied panic rating scales; therefore we used standardised mean differences (SMD) to pool across continuous data. We interpreted the magnitude of SMDs using standard rules of thumb ([Cohen 1992](#)). If all included studies used the same instrument, we used mean difference (MD).

(2) Endpoint versus change data

Trials report results a combination of endpoint means and change from baseline means of assessment rating scales. We preferred to use 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 extracted the change from baseline data in separate analyses. If we used MD, we pooled results from change from baseline and endpoint data in the same analysis.

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

Relative treatment rankings

We estimated the mean rank (and their 95% Crls) for all treatments.

Unit of analysis issues

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 appropriately analysed these data taking into account intraclass correlation coefficients to adjust for cluster effects. Where trialists had not adjusted for the effects of clustering, we attempted to do this by obtaining an intraclass correlation coefficient and then following the guidance given in chapter 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019](#)).

Cross-over trials

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

Studies with multiple treatment groups

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

Dose-ranging studies

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

Dealing with missing data

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

(1) Dichotomous outcomes

We calculated response, or remission on treatment, using an intention-to-treat analysis (ITT). We followed the principle 'once randomised always analysed'. Where participants left the study before the intended endpoint, we assumed that they would have experienced the negative outcome. 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 analysed

the validity of the above approach by sensitivity analysis. If necessary, authors of studies were contacted to obtain data or clarification (or both).

(2) Continuous outcomes

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

(3) Skewed or qualitative data

Where available we presented skewed and qualitative data descriptively.

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

(4) Missing statistics

When only P or SE values 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

We assumed a homogeneous between-study variability across studies (Lu 2004). We based the statistical assessment of heterogeneity in the entire network on the magnitude of the heterogeneity standard deviation parameter, τ^2 , estimated from the model and the 95% prediction interval for the relative treatment effects.

Inconsistency can be considered an additional layer of heterogeneity which can occur in networks of evidence. It can occur when there is a discrepancy between a direct and indirect estimate of treatment effect. We conducted node-splitting analyses to identify in greater detail inconsistencies in the network (van Valkenhoef 2016). We conducted these analyses on the two primary outcomes: response to treatment and total dropouts for any reason.

Assessment of reporting biases

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

Assessment of transitivity across treatment comparisons

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

- (1) We assessed whether the included interventions were similar when they were evaluated in RCTs with different designs; for example, whether antidepressants were administered in the same way in studies comparing antidepressants to placebo and in those comparing antidepressants to benzodiazepines.
- (2) We compared the distribution of the potential effect modifiers across the different pair-wise comparisons.

Data synthesis

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

We initially considered, three possible models:

1. A class (lumped) model (i.e. antidepressants (ADs) and benzodiazepines (BDZs) were compared with each other and with placebo).

2. An individual treatment model (i.e. all ADs and BDZs listed in the 'Types of Intervention' section were compared with each other and with placebo).
3. A hierarchical model (class-effects) where we included both class and treatments.

We concluded it was feasible to conduct individual-effects and class-effects models, we initially compared goodness of fit statistics of these models. We measured goodness of fit of the model to the data by the posterior mean of the residual deviance. This is defined as the difference between the deviance for the fitted model and the deviance for the saturated model, where deviance measures the fit of the model to the data points using the likelihood function. Convergence was assessed using two chains and based on the Brooks-Gelman-Rubin diagnostic tool in WinBUGS.

Where neither individual-effects nor class-effects models fitted the data adequately we explored potential sources of heterogeneity, inconsistency, and risk of bias.

Subgroup analysis and investigation of heterogeneity

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

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

Sensitivity analysis

The following sensitivity analyses were planned a priori. We examined if the results changed and checked for the robustness of the observed findings by:

1. Excluding trials with imputed response rate;
2. Excluding studies using ad hoc outcome scale versus studies using a validated scale such as the Panic Disorder Severity Scale (PDSS) Panic Disorder Severity Scale, Clinical Global Impression Severity Scale, and Clinical Global Impression Change Scale (for response and remission outcomes only);
3. Conducting bias-adjustment models for the two primary outcomes (Dias 2013b). The following models were fitted.

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

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

b) Bias arising from missing data: as we've noted above, trial analyses of missing data may have resulted in bias. Therefore, we aimed to estimate the magnitude of "informative missing parameters" and assess the impact of adjusting for these effects in the network meta-analyses. We proposed to conduct sensitivity analyses for the two primary outcomes. However, data were not reported in sufficient detail to enable us to conduct these sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables for the primary outcomes: response and total number of dropouts.

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

However, only frequentist NMA estimates are compatible with CINeMA software. The complexity of our analyses required modelling to be conducted in a Bayesian framework. Therefore, we were unable to use the CINeMA approach in our review. There are also potential limitations with the Puhan 2014 approach noted in a recent paper (Phillippo 2019). Since confidence ratings are based on individual pairwise comparisons, rather than the

network as a whole, applying this method could have potentially generated logically incoherent judgements in some contexts.

We therefore used threshold analyses to explore the impact of potential biases and evaluate the confidence in our NMA estimates (Phillippo 2018; Phillippo 2019). We conducted threshold analyses at the contrast level (Phillippo 2019). We judged a clinically important effect to consist of OR = 0.67 or OR = 1.50 compared with placebo for both primary outcomes. Some concerns with imprecision were indicated by a 95% CrI exceeding 0.67 or 1.50 depending on effect direction. Major concerns with imprecision were indicated by a 95% CrI exceeding both 0.67 and 1.50. We estimated invariant intervals where any changes (at the contrast level) within this threshold would not impact our conclusions on the precision of our NMA estimates.

To assess the impact of risk of bias we conducted meta-regression analyses to examine whether each of the domains of the risk of bias tool were associated with outcome.

To assess the impact of heterogeneity we compared whether findings based on 95% CrIs led to different conclusions than analyses based on 95% Prediction Intervals (PIs) which capture heterogeneity not taken into account by CrIs. That is we examined when the 95% CrI was within the invariant interval and the 95% PI extended beyond the invariant interval.

In terms of incoherence, where inconsistency between direct and indirect evidence was identified in our analyses we assessed the extent to which the conclusions were likely to be robust to these data issues.

Similarly, if indirectness was identified we assessed the likely impact on our conclusions based on the estimated invariant intervals. However, indirectness was not identified for any analyses.

We formally checked the presence of publication bias with visual inspection of funnel plots on the head-to-head published Cochrane review (Bighelli 2018).

Results

Description of studies

Results of the search

The search and selection of the studies have been done in the previous Cochrane head-to-head comparisons reviews on antidepressants and benzodiazepines in panic disorder (Bighelli 2016), on antidepressants versus placebo in panic disorder (Bighelli 2018), on benzodiazepines versus placebo in panic disorder (Breilmann 2019). This NMA includes all the studies selected in those reviews. Two new searches were done on 1 February 2021 and on 26 May 2022. No new studies in addition to the ones already included in the previous Cochrane head-to-head comparison have been found after the two new searches.

The number of records identified by the searches was 3,677 and 3,199 remained after de-duplication. We excluded 3,013 references after assessment of titles and abstracts. We retrieved 186 full-text articles for full inspection. Of these, 116 studies were excluded. Finally, 70 trials including 12,703 participants, were included in the review. See Figure 1 for a PRISMA flow diagram (Moher 2009) depicting the study selection process.

Included studies

Seventy trials were included in this review (see Characteristics of included studies and Figure 1).

Sample sizes

The sample sizes ranged between 5 and 445 participants in each arm. Total sample size per study ranges from 10 to 1168. Thirty-five studies included sample sizes over 100.

Setting

A total of 29 trials enrolled only outpatients, three trials enrolled only inpatients, and both inpatients and outpatients were enrolled in three trials. For the remaining 35 trials the setting was unclear. Thirty-three trials were conducted in the USA, four in the Netherlands, two in Italy, four in Canada, three in Brazil, two in China, two in UK, four in Japan, one in Finland; 13 trials were multinational, and two did not provide information about the country.

Participants

The proportion of women ranged from 40% to 90%. Mean age of participants ranged from 32 to 46 years.

Interventions

Fifty-two trials included two arms, while the remaining studies had three arms. Eight trials included a comparison between antidepressants and benzodiazepines, 15 between individual antidepressants, and two trials between individual benzodiazepines. 55 trials had a placebo arm.

Duration of the intervention

Intervention duration ranged from 4 to 24 weeks.

Outcomes

Fifty trials reported data on response rates, while the number of dropout for any reason was reported in 64 trials. Thirty-six trials reported on remission rates, 37 trials reported data on panic symptoms, 40 on frequency of panic attacks, 25 on agoraphobia outcomes.

Excluded studies

There were 116 excluded studies. The most common reason for exclusion was that participants did not meet our inclusion criteria for panic disorder (51 studies). The next most common reason for exclusion was not meeting our study design criteria (31 studies), then comparator not meeting our inclusion criteria (13 studies). Intervention inclusion criteria were not met in 15 studies, one study was conducted in a population which did not meet our inclusion criteria, and finally five studies did not provide sufficient data to be included in our review (see [Characteristics of excluded studies](#) and [Figure 1](#)).

Risk of bias in included studies

For details of the 'Risk of bias' judgements for each study, see 'Characteristics of included studies'. Graphical representations of the overall risk of bias in included studies are presented in [Figure 2](#) and [Figure 3](#).

Allocation

Allocation concealment and random sequence generation were rarely reported in sufficient detail. For random sequence generation, only four studies were rated at low risk of bias, all other studies were rated at unclear risk of bias. For allocation concealment, only five studies were rated at low risk of bias, all other studies were rated at an unclear risk of bias.

Blinding

Twenty-six studies were judged at low risk of bias for blinding of participants and personnel, two studies were judged to be at high risk of bias, all the other studies had unclear risk of bias.

Fourteen studies were judged at low risk of bias for blinding of outcome assessment, one study at high risk of bias, all the other studies were judged to be at unclear risk of bias.

Incomplete outcome data

Seventeen studies were judged to be at low risk for incomplete outcome data, twenty-four studies were judged to be at high risk of bias and all the other studies were judged to be at unclear risk of bias.

Selective reporting

Twenty-seven studies were judged to be at low risk of bias, twenty four studies were judged to be at high risk of bias, all the other studies were judged to be at unclear risk of bias.

Other potential sources of bias

Eight studies were judged to be at low risk of bias, thirty-five studies were judged to be at high risk of bias, all the other studies were at unclear risk of bias. The most common reason for studies to be at high risk was potential or actual sponsorship bias.

Effects of interventions

A. Primary outcomes

Response

Model selection

[Figure 4](#) presents a network plot for each individual treatment compared with placebo and other interventions. Nodes and width of the edges were weighted by sample size. Forty-eight RCTs and 10,118 participants were included in the main NMA. Results from [Figure 4](#) are commented below.

[Table 1](#) summarises the model selection process. We began by fitting the two models proposed in our protocol: an individual-effects model of antidepressants and benzodiazepines and a class-effects model that included individual medications but also allowed clustering between treatments from the class. Neither model fitted the data well therefore we assessed goodness of fit for individual-effects models with a covariate for publication date, adjustment for baseline risk, and bias adjustment for small studies models.

The model that included a covariate for publication date did not substantially improve goodness of fit. However, models adjusting for baseline risk or small study effects fitted the data better than either the individual effects or class-effects models. However, the bias adjustment model had a lower between-study standard deviation (SD=0.28, 95% CrI 0.05 to 0.50) than the baseline risk model (SD=0.54, 95% CrI 0.35 to 0.78). The bias adjustment model (mean=108.6) also had a lower total residual deviance than the baseline risk model (mean=112.4), we therefore selected this model for our main results.

We ran models for an initial 50,000 iterations and confirmed that the model had reached convergence. We discarded the initial 50,000 iterations and ran the model for 100,000 further iterations.

Assessment of transitivity: node-splitting analyses and inspection of residual deviances

Consistent with the protocol, to aid model-selection we first explored the potential for inconsistency (transitivity) between direct and indirect evidence using node-splitting analyses.

There was evidence of inconsistency for the brofaromine–fluvoxamine–placebo loop (brofaromine vs placebo, $p=0.001$; fluvoxamine vs placebo, $p=0.008$; brofaromine vs fluvoxamine, $p=0.001$). For further details, please see [Appendix 3](#). This is consistent with the residual deviances in the standard NMA model which also suggested these trials were outliers. In addition, threshold analyses found that NMA findings were sensitive to imprecision in the comparison between brofaromine and fluvoxamine (see [Figure 5](#)).

Given these issues with the brofaromine-fluvoxamine-placebo evidence loop we excluded these studies ([Van Vliet 1993](#); [Van Vliet 1996](#)) from the main analysis. In addition, we also identified problematic residual deviances for another study ([Schweizer 1992](#)) with only five participants and 100% events in one arm, and therefore also excluded this study from the main analyses.

Of course, it is never possible to affirm the transitivity assumption with certainty. However, the above measures have helped to explore transitivity and to minimise the potential for violation of this assumption.

Meta-regression analyses

The main purpose of the meta-regression analyses were to identify potential prognostic factors associated with treatment effect which may contribute to risk of intransitivity. We planned to assess the impact of three covariates in meta-regression analyses (presence of agoraphobia, publication date and placebo response rate). It was not possible to assess the impact of agoraphobia as all studies included participants with this condition (see [Table 2](#)). In addition, we planned to adjust for small-study effects in a sensitivity analysis, but due to poor fit for the models proposed in the protocol this model became our main analyses.

There may be a strong association between the variance in individual studies and response, but the credible intervals were wide ($\beta=-1.20$, 95% CrI -2.59 to 0.46). The bias estimate also suggested there is likely some variation in effect due to small study bias (Kappa 1.41, 95% CrI 0.15 to 2.98). However, there was a lot of variability in estimating this parameter.

There was a strong association between effect estimates and placebo response rates with a tight CrI ($\beta=-0.79$, 95% CrI -1.02 to -0.40). However, the heterogeneity estimate was a little higher than for the no covariate model (SD=0.57, 95% CrI 0.39 to 0.81).

Publication date was not associated with effect estimates ($\beta=-0.03$, 95% CrI -0.06 to 0.04) and had a limited impact on heterogeneity (no covariate model= SD 0.50, 95% CrI 0.28 to 0.79; covariate model=SD 0.45, 95% CrI 0.23 to 0.74)

Sensitivity analyses

We also identified several methodological factors that may contribute to intransitivity these were explored below.

1) Excluding trials with imputed response rate

Excluding four trials with imputed response rates did not impact on goodness of fit. For example, the individual effects model had a very high total residual deviance (mean= 117, from 98 data points) indicating a poor fit with the data. Excluding these studies also did not reduce heterogeneity (SD=0.57, 95% CrI 0.33 to 0.90).

2) Excluding studies using ad hoc outcome scale versus studies using a validated panic scale

Most trials did not use a validated panic scale, therefore 30 trials were excluded in the sensitivity analyses leaving only 21 included studies. Total residual deviance remained high (mean=53.46, from 48 data points) and heterogeneity slightly increased (SD=0.58, 95% CrI 0.12 to 1.25).

3) Bias adjustment model (missing data)

Bias adjustment models were not possible as insufficient data were reported in individual trials. Most studies either conducted last observation carried forward (LOCF) analyses or did not report method of incomplete outcome data management.

See [Summary of findings table 1](#) for more information.

Main results

Although we focus on the findings of the model adjusting for small-study effects, comparisons between medications and placebo for the model adjusting for baseline risk are also provided in [Table 3](#).

Most medications were more effective than placebo. The following medications were effective and 95% CrI did not cross the equivalence range:

- diazepam (RR 0.65, 95% CrI 0.28 to 0.96; mean rank=3, 95% CrI 1 to 15)
- alprazolam (RR 0.68, 95% CrI 0.39 to 0.92; mean rank=4, 95% CrI 1 to 11)
- clonazepam (RR 0.71, 95% CrI 0.41 to 0.94; mean rank=6, 95% CrI 2 to 13)
- paroxetine (RR 0.85, 95% CrI 0.64 to 0.97; mean rank=11, 95% CrI 6 to 16)
- venlafaxine (RR 0.84, 95% CrI 0.60 to 0.97; mean rank=11, 95% CrI 4 to 17)

The following medications were more effective than placebo but the 95% CrI crossed the equivalence range:

- escitalopram (RR 0.78, 95% CrI 0.39 to 1.03; mean rank=8, 95% CrI 1 to 18)

- fluoxetine (RR 0.78, 95% CrI 0.43 to 1.00; mean rank=8, 95% CrI 2 to 17)
- adinazolam (RR 0.82, 95% CrI 0.49 to 1.00; mean rank=9, 95% CrI 2 to 17)
- imipramine (RR 0.82, 95% CrI 0.40 to 1.09; mean rank=9, 95% CrI 2 to 18)
- clomipramine (RR 0.85, 95% CrI 0.57 to 0.99; mean rank=11, 95% CrI 4 to 17)
- fluvoxamine (RR 0.86, 95% CrI 0.53 to 1.05; mean rank=12, 95% CrI 3 to 18)
- citalopram (RR 0.87, 95% CrI 0.57 to 1.02; mean rank=12, 95% CrI 3 to 18)
- sertraline (RR 0.89, 95% CrI 0.66 to 1.02; mean rank=13, 95% CrI 6 to 18)

For three medications, 95% CrI crossed the equivalence range in both directions but not the invariant range:

- desipramine (RR 0.94, 95% CrI 0.43 to 1.37; mean rank=15, 95% CrI 2 to 20)
- buspirone (RR 1.14, 95% CrI 0.48 to 2.06; mean rank=19, 95% CrI 2 to 20)
- ritanserin (RR 1.19, 95% CrI 0.01 to 2.70; mean rank=20, 95% CrI 1 to 20)

For two medications, 95% CrI crossed both the equivalence range and invariant range:

- etizolam (RR 0.58, 95% CrI 0.03 to 1.43; mean rank=2, 95% CrI 1 to 20)
- reboxetine (RR 0.77, 95% CrI 0.24 to 1.19; mean rank=7, 95% CrI 1 to 19)

Threshold analysis

Risk of bias: meta-regression analyses did not find an association between effect estimates and domains (attrition bias and outcome reporting bias) judged to potentially be at risk of bias.

Imprecision: Imprecision of findings were of potential concern, 95% CrIs crossed our a priori determined equivalence range for most comparisons (e.g. escitalopram vs placebo, fluoxetine vs placebo, adinazolam vs placebo). There were particular concerns about imprecision for three comparisons (desipramine vs placebo, buspirone vs placebo, ritanserin vs placebo) since the 95% CrI crossed the equivalence range in both directions.

However, threshold analyses suggested the NMA findings were robust to imprecision for most comparisons. Although findings were sensitive to imprecision for the following comparisons (see [Figure 5](#)) this imprecision is unlikely to impact on effect estimates for other medications in the network as they were both based on one small RCT and not directly compared with other medications:

- etizolam vs placebo: OR 0.28 (95% CrI 0.01 to 5.69); RR 0.58 (95% CrI 0.03 to 1.43)
- reboxetine vs placebo: OR 0.46 (95% CrI 0.10 to 1.86); RR 0.77 (95% CrI 0.24 to 1.19)

Heterogeneity: For the following comparisons the prediction interval (PI), but not the credible interval, crossed our a priori equivalence range suggesting a potential concern with heterogeneity:

- fluoxetine vs placebo (OR 0.50, 95% PI 0.19 to 1.22)
- sertraline vs placebo (OR 0.60, 95% PI 0.24 to 1.51)
- venlafaxine vs placebo (OR 0.58, 95% PI 0.29 to 1.20)
- fluvoxamine vs placebo (OR 0.61, 95% PI 0.26 to 1.52)
- clomipramine vs placebo (OR 0.61, 95% PI 0.28 to 1.28)
- imipramine vs placebo (OR 0.53, 95% PI 0.17 to 1.65)
- paroxetine vs placebo (OR 0.59, 95% PI 0.31 to 1.22)
- adinazolam vs placebo (OR 0.54, 95% PI 0.23 to 1.26)
- sertraline vs paroxetine (OR 0.90, 95% PI 0.36 to 2.26)
- paroxetine vs alprazolam (OR 0.61, 95% PI 0.23 to 1.55)

However, the threshold analysis indicated heterogeneity was unlikely to impact on NMA findings. Prediction intervals remained within the invariant intervals for all three comparisons (see [Figure 5](#)).

Indirectness: We identified several factors that may impact on the directness of the evidence:

- In some studies, the placebo arm has more dropouts than the active treatment arm.
- Different methodology is used in newer studies compared to older studies
- Some studies have used validated measures while some others has used clinician judgement
- Some medications like for example etizolam are not widely used in practise

Incoherence (transitivity): Node-splitting analyses found evidence of incoherence for the brofaromine–fluvoxamine–placebo loop. However, since studies within this evidence loop were excluded from the main analyses there were no longer concerns about potential incoherence.

Small-study effects: We found evidence of small-study bias. The base-case models proposed in our protocol all fitted the data poorly. However, analyses adjusted for the magnitude of the variance of individual studies substantially improved model fit. This suggests findings from studies with larger sample sizes (and smaller variances) may have differed from smaller studies (and larger variances). However, it is unclear whether the NMA findings were impacted by any residual bias.

Drop out

Figure 6 presents a network plot for each individual treatment compared with placebo and other interventions. Nodes were weighted by the number of studies and width of the edges was weighted by the inverse of the variance. Sixty-four RCTs including 12,310 participants were included in the NMA. Results from Figure 6 are commented below.

We fitted two models-one that included individual antidepressants and benzodiazepines and a class-effects model that included medications but also allowed clustering between treatments from the class. Neither model fitted the data well, for example, total residual deviance was much higher than the number of data points (see Table 4). Therefore, we selected the model with adjustment for small study effects for the main results.

We ran models for an initial 50,000 iterations and confirmed that the model had reached convergence. We discarded the initial 50,000 iterations and ran the model for 100,000 further iterations.

Node-splitting analyses: assessment of transitivity

Consistent with the protocol, to aid model-selection we first explored the potential for inconsistency between direct and indirect evidence using node-splitting analyses. There were a number of inconsistencies identified between direct and indirect evidence: fluoxetine vs placebo ($p=0.03$), sertraline vs placebo ($p=0.04$), sertraline vs paroxetine ($p=0.04$), fluvoxamine vs imipramine ($p=0.03$), desipramine vs placebo ($p=0.03$), desipramine vs fluoxetine ($p=0.03$), clonazepam v alprazolam ($p=0.03$), sertraline vs paroxetine ($p=0.04$), fluvoxamine vs imipramine ($p=0.05$). In addition, the difference between clomipramine vs paroxetine ($p=0.06$) was borderline statistically significant. For further details please see Appendix 4.

Meta-regression analyses

The main purpose of the meta-regression analyses were to identify potential prognostic factors associated with treatment effect which may contribute to risk of intransitivity. We planned to assess the impact of three covariates in meta-regression analyses (presence of agoraphobia, publication date and placebo response rate) . It was not possible to assess the impact of agoraphobia as all studies included participants with this condition (see Table 2). In addition, we planned to adjust for small-study effects in a sensitivity analysis, but due to poor fit for the models proposed in the protocol this model became our main analyses.

Meta-regression analyses were only possible for the association between effect estimates and the size of variance in individual studies. There was a strong association between the variance for included trials and the effects ($\beta=-1.07$, 95% CrI -1.77 to -0.38; $\kappa=0.71$, 95% CrI 0.09 to 1.55). There was a more precise estimate of small studies bias for drop-outs with both lower and upper credible interval suggesting substantial bias. When comparing the smallest to largest study the exaggeration of effect is estimated to be 3.207 on logOR scale and 24.705 on OR scale. As above, this is potentially an over-estimate of the likely bias as reflected by relatively wide credible intervals. However, even at the lower credible interval there is strong suggestion of bias (exaggeration can vary between 3.61 and 184.69 on OR scale based on credible intervals).

It was not possible to conclude anything regarding the association between the other covariates and effect estimates. All the meta-regression models crashed for this outcome, the likely cause of these problems were a number of studies with zero events as well as other studies with very low number of events. Therefore, we fitted models with a continuity correction (adding 0.5 to all cells in the 2x2 table in studies with no events in either intervention or control). We also fitted models with varying priors for the heterogeneity parameter (a minimally informative prior with large variance compared with an informative prior for mental health studies), it was not possible to run either of these models. We then excluded studies from the analyses where there were zero events either in the intervention or control group. However, there still remained a number of studies with a small number of events and this model also failed to run.

See Summary of findings table 2 for more information.

Main results

Most medications were either associated with reduced or similar proportion of subjects who dropped out, compared to placebo (see Table 5).

There was a reduction in drop out rate compared with placebo for these medications, 95% CrIs did not cross the equivalence range or invariant range:

- alprazolam (RR 0.46, 95% CrI 0.33 to 0.65; mean rank=3, 95% CrI 1 to 6)
- diazepam (RR 0.50, 95% CrI 0.23 to 0.91; mean rank=3, 95% CrI 1 to 9)

There was no difference in drop out rate compared with placebo for these medications, 95% CrIs did not cross the equivalence range or invariant range:

- venlafaxine (RR 0.99, 95% CrI 0.80 to 1.21; mean rank=12, 95% CrI 6 to 18)

- sertraline (RR 1.00, 95% CrI 0.80 to 1.30; mean rank=13, 95% CrI 7 to 18)
- paroxetine (RR 1.07, 95% CrI 0.92 to 1.07; mean rank=15, 95% CrI 10 to 19)

For one medication, there was an increased drop out rate compared with placebo that did not cross the equivalence range:

- buspirone (RR 1.83, 95% CrI 1.14 to 3.34; mean rank=21, 95% CrI 18 to 21)

Several medications had a reduced drop out rate compared with placebo, 95% CrIs crossed the equivalence range but not the invariant range:

- reboxetine (RR 0.40, 95% CrI 0.13 to 1.17; mean rank=3, 95% CrI 1 to 15)
- escitalopram (RR 0.68, 95% CrI 0.38 to 1.08; mean rank=6, 95% CrI 2 to 15)
- imipramine (RR 0.85, 95% CrI 0.63 to 1.12; mean rank=8, 95% CrI 4 to 15)
- citalopram (RR 0.88, 95% CrI 0.62 to 1.20; mean rank=9, 95% CrI 5 to 17)

There was no difference in drop out rate compared with placebo for these medications, however 95% CrIs crossed the equivalence range but not invariant range:

- clonazepam (RR 0.92, 95% CrI 0.63 to 1.22; mean rank=10, 95% CrI 5 to 18)
- clomipramine (RR 0.96, 95% CrI 0.74 to 1.24; mean rank=11, 95% CrI 6 to 17)
- fluvoxamine (RR 1.16, 95% CrI 0.85 to 1.63; mean rank=17, 95% CrI 9 to 20)
- adinazolam (RR 1.19, 95% CrI 0.87 to 1.68; mean rank=17, 95% CrI 9 to 20)

For two medications compared with placebo, 95% CrIs were wide and crossed the equivalence range in both directions but not invariant range:

- desipramine (RR 0.63, 95% CrI 0.14 to 1.73; mean rank=5, 95% CrI 1 to 20)
- fluoxetine (RR 1.13, 95% CrI 0.62 to 1.94; mean rank=16, 95% CrI 5 to 20)

For one medication compared with placebo, 95% CrI crossed the equivalence range in both directions and also crossed the invariant range:

- etizolam (RR 0.39, 95% CrI 0.01 to 2.69; mean rank=2, 95% CrI 1 to 21)

Threshold analysis

Risk of bias: We were unable to assess the association between effect estimates and the impact of risk of bias. Therefore, it is unclear the extent to which our findings are sensitive to domains (attrition bias and outcome reporting bias) where a substantial proportions of studies were rated at a high or unclear risk of bias.

Imprecision: NMA findings were not sensitive to imprecision for any comparisons with the exception of etizolam vs placebo, a small trial of 30 participants. It is unlikely this imprecision substantially impacted on effect estimates for other medications in the network.

Heterogeneity: There was evidence of substantial heterogeneity. For the following comparisons 95% prediction intervals extended beyond the equivalence range in both directions, whilst 95% credible intervals were within the equivalence range, potentially indicating major concerns with heterogeneity:

- Sertraline versus placebo (OR 1.00, 95% PI 0.59 to 1.78)
- Venlafaxine versus placebo (OR 0.98, 95% PI 0.58 to 1.68)

However, the threshold analysis indicated this heterogeneity was unlikely to impact on NMA findings (Figure 7). 95% PIs remained within the invariant intervals for both comparisons.

For several medications, 95% PIs extended beyond the equivalence range in one direction in comparison with 95% CrIs:

- clomipramine versus placebo (OR 0.94, 95% PI 0.56 to 1.72)
- paroxetine versus placebo (OR 1.11, 95% PI 0.68 to 1.81)
- clonazepam versus placebo (OR 0.88, 95% PI 0.46 to 1.61)
- alprazolam versus placebo (OR 0.36, 95% PI 0.22 to 0.64)
- paroxetine versus Sertraline (OR 1.10, 95% PI 0.62 to 1.88)
- paroxetine versus Venlafaxine (OR 1.13, 95% PI 0.65 to 1.94)
- imipramine versus Clomipramine (OR 0.83, 95% PI 0.45 to 1.63)
- paroxetine versus Clomipramine (OR 1.18, 95% PI 0.64 to 2.03)
- citalopram versus Clomipramine (OR 0.88, 95% PI 0.45 to 1.67)
- escitalopram versus Citalopram (OR 0.70, 95% PI 0.32 to 1.53)

But the threshold analysis indicated this heterogeneity was unlikely to impact on NMA findings. 95% PIs remained within the invariant intervals for all these comparisons.

Incoherence (transitivity): Node splitting analyses identified incoherence between direct and indirect evidence for several comparisons. However, the NMA findings were sensitive to incoherence for two comparison:

- Desipramine versus placebo: direct estimates crossed the invariant threshold (log OR -2.30, 95% CrI -4.40 to -0.77) but not indirect (log OR 1.30, 95% CrI -1.60 to 4.90) or network (log OR -1.5, 95% CrI -2.90 to -0.23) estimates. This incoherence may reflect the instability of estimates in an evidence loop based on two small trials: desipramine versus placebo (N=56) and desipramine versus fluoxetine (N=22).
- Fluoxetine versus placebo: indirect estimates crossed the invariant threshold (log OR -1.60, 95% CrI -3.60 to 0.08) but not direct (log OR 0.48, 95% CrI -0.38 to 1.40) or network (log OR 0.04, 95% CrI -0.72 to 0.81) estimates. This incoherence may partly be explained by small study effects, since the fluoxetine versus placebo estimate was based on a larger trial (N=180) whereas head-to-head trials between fluoxetine and other medications were mainly based on small trials: vs imipramine (N=18), citalopram (N=42), desipramine (N=22), mirtazapine (N=30). Therefore, the bias-adjusted analyses may have reduced the impact of the incoherence in these estimates.

Reporting bias/small study effects: We found evidence of small-study bias therefore our main findings were based on a model adjusting for this potential bias. The base-case models proposed in our protocol all fitted the data poorly. However, analyses adjusted for the magnitude of the variance of individual studies led to acceptable model fit. This suggests findings from studies with larger sample sizes (and smaller variances) may have differed from smaller studies (and larger variances). However, it is unclear whether the NMA findings were impacted by any residual bias.

Remission

Figure 8 presents a network plot for each individual treatment compared with placebo and other interventions. Nodes were weighted by the number of studies and width of the edges was weighted by the inverse of the variance. Thirty-two RCTs including 8,569 participants were included in the NMA.

We began by fitting both individual effects and class effects models but neither fitted the data well (see Table 6). Given limited differences between the individual-level and class-level models, we focused on the individual-level model. High deviances (>2) were observed for five mostly small studies (Black 1993, Pohl 1989b, Nair 1996, Klosko 1990, GSK 1994/04). Removing these studies improved the fit of the model. In addition, the between study standard deviation was 0.22 (95% CrI 0.02 to 0.42). Since the removal of outliers led to acceptable fit we selected this model for further analyses.

Table 7 summarises the NMA findings on remission. Most medications were more effective than placebo:

- desipramine (RR 0.66, 95% CrI 0.29 to 0.97; mean rank=2, 95% CrI 1 to 13)
- alprazolam (RR 0.65, 95% CrI 0.44 to 0.84; mean rank=2, 95% CrI 1 to 5)
- fluoxetine (RR 0.77, 95% CrI 0.46 to 0.96; mean rank=5, 95% CrI 1 to 13)
- clonazepam (RR 0.76, 95% CrI 0.53 to 0.92; mean rank=5, 95% CrI 1 to 11)
- diazepam (RR 0.74, 95% CrI 0.43 to 0.96; mean rank=5, 95% CrI 1 to 13)
- fluvoxamine (RR 0.77, 95% CrI 0.50 to 0.95; mean rank=6, 95% CrI 1 to 12)
- imipramine (RR 0.79, 95% CrI 0.57 to 0.94; mean rank=7, 95% CrI 2 to 12)
- venlafaxine (RR 0.87, 95% CrI 0.70 to 0.96; mean rank=10, 95% CrI 5 to 13)
- paroxetine (RR 0.88, 95% CrI 0.71 to 0.97; mean rank=10, 95% CrI 6 to 13)

Two medications probably were more effective than placebo but 95% CrIs crossed our equivalence range:

- sertraline (RR 0.86, 95% CrI 0.68 to 1.01; mean rank=9, 95% CrI 3 to 15)
- escitalopram (RR 0.92, 95% CrI 0.65 to 1.09; mean rank=12, 95% CrI 3 to 16)

Three medications may be no different from placebo, but there was considerable uncertainty about these estimates as 95% CrIs crossed our equivalence range in both directions:

- citalopram (RR 0.97, 95% CrI 0.73 to 1.15; mean rank=13, 95% CrI 6 to 16)
- buspirone (RR 0.99, 95% CrI 0.65 to 1.24; mean rank=14, 95% CrI 3 to 16)
- clomipramine (RR 1.01, 95% CrI 0.83 to 1.16; mean rank=15, 95% CrI 9 to 16)

Sensitivity analysis

Most trials did not include a validated panic scale, therefore this sensitivity analyses excluding unvalidated scales included only 15 trials and 12 medications:

- clonazepam RR 0.20 (95% CrI 0.01 to 0.88)
- alprazolam RR 0.56 (95% CrI 0.24 to 0.89)

- imipramine RR 0.78 (95% CrI 0.45 to 1.04)
- fluoxetine RR 0.80 (95% CrI 0.46 to 1.04)
- sertraline RR 0.86 (95% CrI 0.75 to 1.09)
- paroxetine RR 0.86 (95% CrI 0.61 to 1.03)
- venlafaxine RR 0.87 (95% CrI 0.68 to 1.00)
- escitalopram RR 0.92 (95% CrI 0.58 to 1.14)
- fluvoxamine RR 0.93 (95% CrI 0.71 to 1.09)
- buspirone RR 0.94 (95% CrI 0.52 to 1.21)
- citalopram RR 0.98 (95% CrI 0.65 to 1.18)

Effect estimates for these remaining treatments did not differ substantially from the main analyses for most treatments. There were two exceptions, in the main analyses there were four trials of clonazepam and only one small trial (N=24) in the sensitivity analyses (Valenca 2000) which had a very high placebo non-response rate (90%) which may have led to an over-estimate of the effectiveness of clonazepam. In addition, fluvoxamine was less effective compared to placebo in the sensitivity analysis compared with the main analyses. One trial was excluded from the sensitivity analysis (Hoehn-Saric 1993), this was a relatively small trial (N=50) and had a very high placebo non-response rate (84%) which may have led to an over-estimate of effectiveness of fluvoxamine in the main analyses.

Panic scales

Figure 9 presents a network plot for each individual treatment compared with placebo and other interventions for change from baseline. Figure 10 presents a network plot for endpoint scores. Nodes and width of edges were weighted by sample size. Thirty-five RCTs including 8,826 participants were included in the NMAs.

Studies reported change from baseline and/or endpoint scores therefore we analysed these data separately. We fitted two models-one that included individual antidepressants and benzodiazepines and a class-effects model that included medications but also allowed clustering between treatments from the class. Both models fitted the data well therefore we selected the simpler individual-effects model for both change from baseline (between study standard deviation= 0.63, 95% CrI 0.33 to 1.30) and endpoint data (between study standard deviation= 0.46, 95% CrI 0.29 to 0.82) (see Table 8). Below we summarise the NMA endpoint data but for more details and change from baseline data see Table 9.

Compared with placebo there was a large reduction in panic symptoms for the following interventions, however they were all based on either one trial or a few small trials:

- brofaromine SMD -3.78 (95% CrI -5.02 to -2.55), mean rank 1 (95% CrI 1 to 2)
- clonazepam SMD -2.36 (95% CrI -3.27 to -1.45), mean rank= 2 (95% CrI 1 to 3)
- reboxetine SMD -1.03 (95% CrI -2.13 to 0.08), mean rank=3 (95% CrI 2 to 10)

Compared with placebo there were medium-to-large imprecise reductions in panic symptoms for these interventions:

- clomipramine SMD -0.68 (95% CrI -1.38 to 0.03), mean rank= 5 (95% CrI 3 to 9)
- alprazolam SMD -0.48 (95% CrI -1.19 to 0.24), mean rank= 6 (95% CrI 3 to 11)

Compared with placebo there were small reductions in panic symptoms for these interventions:

- imipramine SMD -0.28 (95% CrI -1.03 to 0.47), mean rank= 7 (95% CrI 3 to 12)
- fluvoxamine SMD -0.17 (95% CrI -0.79 to 0.45), mean rank=8 (95% CrI 5 to 11)
- paroxetine SMD -0.22 (95% CrI -0.69 to 0.25), mean rank=8 (95% CrI 5 to 11)
- adinazolam SMD -0.18 (95% CrI -1.00 to 0.63), mean rank= 8 (95% CrI 4 to 12)
- venlafaxine SMD 0.30 (95% CrI -0.39 to 0.99), mean rank=12 (95% CrI 7 to 12)

Frequency of panic attacks

Figure 11 presents a network plot for each individual treatment compared with placebo and other interventions. Nodes were weighted by the number of studies and width of the edges was weighted by the inverse of the variance. Forty-one RCTs including 7,853 participants were included in the NMA.

We fitted two models-one that included individual antidepressants and benzodiazepines and a class-effects model that included medications but also allowed clustering between treatments from the class. Both models fitted the data well, we therefore preferred the individual effects model as the more complex class effects model was not found to fit the data any better (see Table 10).

Examining the network plot there was one study of midazolam compared with placebo with only five participants. Given the very large effect size, and lack of connection to other nodes in the network, we excluded this study from the individual effects model. This led to a much better fit compared with the main individual effects model,

total residual deviance remained acceptable (mean=88.04, from 90 data points). We therefore selected this sensitivity analysis for the main results. Between study standard deviation was 2.72 (2.06 to 3.69).

Main results

Compared with placebo, only two medications were associated with reduction in frequency of panic attacks that did not include zero in the 95% credible intervals (see [Table 11](#)):

- desipramine: MD -4.60 (-10.55 to 1.33), mean rank=2 (95% CrI 1 to 14)
- clonazepam: MD -3.76 (-7.61 to -0.03), mean rank=3 (95% CrI 1 to 12)
- alprazolam: MD -2.58 (-4.79 to -0.43), mean rank=6 (95% CrI 2 to 12)

Compared with placebo, several medications were associated with a reduction of at least one panic attack, but with wide 95% credible intervals:

- reboxetine: MD -3.54 (-8.57 to 1.50), mean rank=4 (95% CrI 1 to 14)
- paroxetine: MD -1.97 (95% CrI -4.22 to 0.27), mean rank=7 (95% CrI 2 to 13)
- sertraline: MD -1.68 (95% CrI -4.81 to 1.42), mean rank=8 (95% CrI 2 to 15)
- venlafaxine: MD -1.28 (95% CrI -3.93 to 1.37), mean rank=9 (95% CrI 3 to 15)

Compared with placebo, several medications were associated with either no reduction or less than one panic attack, but with wide 95% credible intervals:

- clomipramine: MD -0.96 (95% CrI -4.06 to 2.15), mean rank=10 (95% CrI 3 to 15)
- fluoxetine: MD -0.71 (-6.30 to 4.89), mean rank=10 (95% CrI 1 to 16)
- imipramine: MD -0.71 (-6.43 to 5.03), mean rank=10 (95% CrI 1 to 16)
- adinazolam: MD -0.33 (-3.75 to 3.08), mean rank=11 (95% CrI 3 to 16)
- diazepam: MD -0.66 (-7.67 to 6.35), mean rank=11 (95% CrI 1 to 16)
- fluvoxamine: MD 0.06 (95% CrI -3.46 to 3.55), mean rank=12 (95% CrI 4 to 15)

Agoraphobia

[Figure 12](#) (change from baseline) and [Figure 13](#) (endpoint) presents a network plot for each individual treatment compared with placebo and other interventions. Nodes were weighted by the number of studies and width of the edges was weighted by the inverse of the variance. Twenty-six RCTs including 7,044 participants were included in the NMAs.

We removed two small studies ([Van Vliet 1993](#); [Van Vliet 1996](#)) with high deviances (>3) that were clear outliers and represented a risk to transitivity assumption.

Individual-effects and class-effects models both fitted the data well for both endpoint and change from baseline, we therefore selected the individual effects model for both datasets (see [Table 12](#) for further details). The results below are for endpoint data (for further details and change from baseline data see [Table 13](#)).

Main results

Compared with placebo, there were several medications associated with medium-to-large reductions in agoraphobia symptoms:

- citalopram SMD -0.87 (95% CrI -1.32 to -0.41), mean rank= 2 (95% CrI 1 to 7)
- reboxetine SMD -0.86 (95% CrI -1.62 to -0.11), mean rank= 2 (95% CrI 1 to 10)
- escitalopram SMD -0.78 (95% CrI -1.40 to -0.16), mean rank= 3 (95% CrI 1 to 10)
- clomipramine SMD -0.60 (95% CrI -1.18 to -0.01), mean rank= 5 (95% CrI 1 to 11)
- diazepam SMD -0.52 (95% CrI -1.14 to 0.08), mean rank= 6 (95% CrI 1 to 12)

Compared with placebo, there were several medications associated with a small-to-medium reduction in agoraphobia symptoms, but 95% CrIs were mainly imprecise:

- fluvoxamine SMD -0.50 (95% CrI -1.42 to 0.41), mean rank= 6 (95% CrI 1 to 13)
- alprazolam SMD -0.46 (95% CrI -0.75 to -0.20), mean rank= 6 (95% CrI 3 to 10)
- desipramine SMD -0.41 (95% CrI -1.22 to 0.39), mean rank= 7 (95% CrI 1 to 14)
- paroxetine SMD -0.30 (95% CrI -0.76 to 0.16), mean rank= 8 (95% CrI 3 to 13)
- imipramine SMD -0.22 (95% CrI -0.59 to 0.16), mean rank= 9 (95% CrI 5 to 13)

There were three medications, in comparison with placebo associated either with negligible change or small increase in agoraphobia symptoms. However, in each case 95% credible intervals for these estimates were very wide:

- buspirone SMD -0.03 (95% CrI -0.77 to 0.70), mean rank= 11 (95% CrI 3 to 14)

- adinazolam SMD 0.10 (95% CrI -0.57 to 0.76), mean rank= 13 (95% CrI 5 to 14)
- ritanserin SMD 0.22 (95% CrI -0.63 to 1.08), mean rank= 13 (95% CrI 5 to 14)

2. Pooled intervention classes

Data for individual interventions were insufficiently precise to compare across active interventions. Therefore, we also conducted analyses on pooled intervention classes (SSRIs, SNRIs, TCAs, MAOIs, benzodiazepines) comparing the effectiveness of these intervention classes with placebo and one another. We limited our analyses to the primary outcomes of response and dropout.

Response

Figure 14 illustrates the network of comparisons included in the NMA. The bias adjustment model best fitted the data, therefore we based our estimates on this model (see Table 14). Between-study standard deviation = 0.25 (95% CrI 0.04 to 0.44). All intervention classes were effective compared with placebo (see Table 15):

- SSRIs: RR 0.83 (95% CrI 0.63 to 0.96), mean rank=5 (95% CrI 2 to 6)
- SNRIs: RR 0.85 (95% CrI 0.63 to 0.97), mean rank=5 (95% CrI 1 to 6)
- TCAs: RR 0.82 (95% CrI 0.57 to 0.96), mean rank=4 (95% CrI 1 to 6)
- MAOIs: RR 0.79 (95% CrI 0.52 to 0.96), mean rank=3 (95% CrI 1 to 6)
- BDZs: RR 0.78 (95% CrI 0.52 to 0.95), mean rank=3 (95% CrI 1 to 6)

There was no difference between the following classes with all 95% CrIs remaining within the equivalence range:

- SNRIs vs SSRIs: RR 1.01 (95% CrI 0.86 to 1.21)
- TCAs vs SSRIs: RR 0.98 (95% CrI 0.81 to 1.13)

There was no difference between the following classes, although 95% CrIs crossed the equivalence range:

- TCAs vs SNRIs: RR 0.97 (95% CrI 0.75 to 1.16)
- MAOIs vs SSRIs: RR 0.95 (95% CrI 0.74 to 1.10)
- BDZs vs SSRIs: RR 0.94 (95% CrI 0.74 to 1.08)
- MAOIs vs SNRIs: RR 0.94 (95% CrI 0.69 to 1.14)
- BDZs vs SNRIs: RR 0.94 (95% CrI 0.69 to 1.11)
- MAOIs vs TCAs: RR 0.97 (95% CrI 0.75 to 1.19)
- BDZs vs TCAs: RR 0.96 (95% CrI 0.75 to 1.17)

There was also no difference, but 95% CrI crossed both sides of the equivalence range:

- BDZs vs MAOIs: RR 1.00 (95% CrI 0.77 to 1.27)

Dropout

Figure 15 illustrates the network of comparisons included in the NMA for drop out. The bias adjustment model best fitted the data, therefore we based our estimates on this model (see Table 16). Between standard deviation was 0.38 (95% CrI 0.22 to 0.58).

Benzodiazepines (BDZs) were the only treatment where dropout was less likely than placebo (see Table 17):

- BDZs: RR 0.63 (0.45 to 0.83), mean rank=1 (95% CrI 1 to 2)
- SSRIs: RR 1.01 (0.85 to 1.22), mean rank=5 (95% CrI 2 to 7)
- SNRIs: RR 0.97 (0.73 to 1.33), mean rank=4 (95% CrI 2 to 7)
- TCAs: RR 0.89 (0.67 to 1.14), mean rank=3 (95% CrI 2 to 6)
- MAOIs: RR 1.06 (0.58 to 1.80), mean rank=6 (95% CrI 1 to 7)

BDZs were associated with a reduced risk of dropout compared with the following treatment classes:

- SSRIs: RR 0.51 (0.35 to 0.73)
- SNRIs: RR 0.55 (0.32 to 0.92)
- TCAs: RR 0.63 (0.41 to 0.92)

There were differences in risk of drop out (although the 95% CrIs crossed the equivalence range) for the following treatment classes:

- BDZs vs MAOIs: RR 0.60 (0.32 to 1.07) - favours BDZs
- TCAs vs SSRIs: RR 0.88 (0.66 to 1.12) - favours TCAs

There was no difference in risk of drop out (although the 95% CrI cross the equivalence range) for the following treatment classes:

- SNRIs vs SSRIs: RR 0.96 (0.71 to 1.33)

It was unclear if there was a difference in risk of drop out for the following treatments (95% CrIs crossed the equivalence range in both directions:

- MAOIs vs SSRIs: RR 1.05 (0.58 to 1.76)
- TCAs vs SNRIs: RR 0.91 (0.61 to 1.31)
- MAOIs vs SNRIs: RR 1.10 (0.56 to 1.93)
- MAOIs vs TCAs: RR 1.20 (0.69 to 1.97)

Discussion

Summary of main results

1. Individual interventions analysis

There was evidence from forty-eight RCTs (N=10,118) that most medications may have been more effective in the of response outcome than placebo. In particular, diazepam, alprazolam, clonazepam, paroxetine, venlafaxine, clomipramine, fluoxetine and adinazolam showed the strongest effect, with **diazepam**, **alprazolam** and **clonazepam** ranking as the most effective. Escitalopram, imipramine, fluvoxamine, citalopram and sertraline are more effective than placebo, but the results are imprecise given the wider 95% CrI. Desipramine, buspirone, ritanserin, etizolam and reboxetine do not seem to be more effective than placebo but the 95% CrIs were very wide. Heterogeneity has been found for most comparisons, but our threshold analyses suggest this is unlikely to impact the NMA findings. Out of the included trials, only 21 used a validated panic scale. The sensitivity analysis conducted on the studies using a validated panic scale showed a slight increase in heterogeneity. In terms of ranking, diazepam, alprazolam and clonazepam ranked as most effective, followed by fluoxetine and adinazolam. Paroxetine, venlafaxine and clomipramine ranked the lowest.

Results from sixty-four RCTs (N= 12,310) suggest that most medications were either associated with reduced or similar risk of drop-outs as placebo. **Alprazolam** and **diazepam** were associated with a lower drop out rate compared to placebo and were ranked as the most tolerated of all the medications examined. No difference in drop out rate was found for venlafaxine, sertraline and paroxetine compared with placebo. Buspirone was associated with a higher rate of drop-outs and was ranked as least tolerated medication. While reboxetine, escitalopram, imipramine and citalopram showed a reduction in drop our rates compared to placebo, the effects are imprecise due to the wide 95% CrI. Similarly, clonazepam, clomipramine, fluvoxamine, adinazolam, desipramine, fluoxetine and etizolam did not show any difference in drop out rates compared to placebo, but the effects are imprecise due to the wide 95% CrI. The drop out outcome showed evidence of substantial heterogeneity. Also, incoherence was identified in the desipramine versus placebo and in the fluoxetine versus placebo comparisons, mostly due to effect of small studies.

Thirty-two RCTs (N=8,569) were included in the remission outcome. Most medications seemed to be more effective than placebo, namely desipramine, fluoxetine, clonazepam, diazepam, fluvoxamine, imipramine, venlafaxine, paroxetine and their effect were clinically meaningful. Amongst those medications, **desipramine** and **alprazolam** were ranked the highest; fluoxetine, clonazepam, diazepam, fluvoxamine and imipramine were ranked in the middle; venlafaxine and paroxetine were ranked lowest. Sertraline and escitalopram were more effective than placebo, but their effects are imprecise due to the wide 95% CrI. Citalopram, buspirone and clomipramine may not be more effective than placebo but the 95% CrIs were very wide indicating considerable uncertainty. Most studies did not include a validated panic scale. However, sensitivity analysis including studies using a validated panic scale, did not differ substantially from the main analysis, except for clonazepam, whose effect may have been overestimated by a high placebo non-response rate, and fluvoxamine, which was less effective than placebo, compared to the main analyses.

Thirty-five RCTs have been included (N=8,826) for the continuous outcome (reduction in panic scales scores). Brofaromine, clonazepam and reboxetine had the strongest reductions in panic symptoms compared to placebo, but results were based on either one trial or very small trials. Clomipramine, imipramine and alprazolam showed evidence of reduction in panic scale scores compared to placebo, but reductions showed a high level of imprecision. Venlafaxine, fluvoxamine, paroxetine and adinazolam showed small reduction in panic scale scores compared to placebo. **Brofaromine** ranked the highest, followed by clonazepam and reboxetine, while clomipramine, imipramine and alprazolam had an intermediate ranking. However, these results are either based on small trials or are imprecise. Venlafaxine, fluoxetine, paroxetine and adinazolam showed the lowest ranking as they reduced panic symptoms to a minor extent.

Forty-one RCTs have been included (N=7,853) were analysed in the frequency of panic attack outcome. Only **clonazepam** and **alprazolam** showed a strong reduction in the frequency of panic attacks compared to placebo as were ranked as highest. Fluoxetine, reboxetine, paroxetine, sertraline and venlafaxine tended to reduce panic attacks, but credible intervals were wide. Weak effects have been found for clomipramine, adinazolam,

imipramine, desipramine, diazepam and fluvoxamine. Ranking is difficult to interpret for most medications other than clonazepam and alprazolam due to imprecision.

Twenty-six RCTs (N=7044) provided data for agoraphobia. The strongest reductions in agoraphobia symptoms were found for citalopram, reboxetine, escitalopram, clomipramine and diazepam, compared to placebo. Smaller effects were observed for alprazolam, fluvoxamine, desipramine, paroxetine and imipramine compared to placebo, with imprecise results. Negligible or small effects were found for buspirone, adinazolam and ritanserin, compared to placebo and results were imprecise. **Citalopram** and **reboxetine** were ranked as the highest in terms of reduction in agoraphobia, while escitalopram, clomipramine and diazepam were ranked as less effective.

2. Pooled intervention classes

The two outcomes examined were the primary outcomes (response and drop out). The classes of medication examined were: SSRIs, SNRIs, TCAs, MAOIs and BDZs.

For the response outcome, all classes of medications examined (SSRIs, SNRIs, TCAs, MAOIs, BDZs) seem to be more effective than placebo. **TCAs** as a class ranked as the most effective, followed by BDZs and MAOIs. SSRIs as a class ranked fifth on average while SNRIs were ranked as the lowest. However, differences in rankings do not reflect substantial differences in effectiveness between these classes. If classes of medications are compared with each others for the response outcome, no difference is found between classes. Comparisons between MAOIs and TCAs and between BDZs and TCAs also suggested no differences between these medications, but the results were imprecise.

For the drop out outcome, **BDZs** was the only class associated with a lower drop out compared to placebo, and they were ranked as first in terms of tolerability. The other classes did not show any difference in drop-outs compared to placebo. In terms of ranking, TCAs are on average second to BDZs, followed by SNRIs, then by SSRIs and lastly by MAOIs. BDZs were associated with a lower drop out rates compared to SSRIs, SNRIs and TCAs. BDZs were also associated with a lower drop out rates compared to MAOIs, but the results were imprecise due to the wide 95% CrI. Similarly, TCAs were associated with a lower drop out rates than SSRIs, but results were also imprecise, due to wide 95% CrI. SSRIs were associated with the same risk in drop out as SNRIs, but results were imprecise due to the wide 95% CrI. It was not possible to determine whether MAOIs were associated with a higher or lower drop out compared to SSRIs, SNRIs and TCAs, due to the 95% CrI crossing the equivalence range in both directions. For the same reason, it was not also clear whether TCAs were associated with a higher or lower drop out compared to SNRIs.

Overall completeness and applicability of evidence

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. Also, 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 of the world. 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.

For the antidepressants versus placebo studies, the majority of RCTs provided data for the primary outcomes specified in the protocol, allowing us to include a considerable number of studies and participants in the analyses. It was therefore possible to generate useful information on the efficacy and acceptability of antidepressants in comparison with placebo. In terms of applicability, considering the high number of studies and participants, we can argue that this population may reflect in a satisfactory way the characteristics of people with panic disorder seen in 'real world' settings, despite the well-known limitations of all randomised studies that should always be acknowledged. One limitation to generalisability may also be connected with the exclusion of studies in which regular use of benzodiazepines was allowed, since this practice might be common in real-life settings.

For the BDZs versus placebo studies, the completeness and applicability may have been limited by various factors. 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. Moreover, we did not investigate other side effects of BDZs (cognitive impairment, risk of falls, tolerance, dependence, less optimal reaction time, risk of dangers when using instruments, etc), which may have limited the applicability of our findings. It is important to point out the implications and consequences of longer BDZ use. A recent population-based study (Davies 2022) reported significant excess of hospital attendance for falls, fractures, long-term care admission and death over a 1-year follow-up period in continuous BDZs users relative to intermittent users after a

180-day index period. Unlike the issue of short-term tolerability, these aspects of BDZ-related adverse outcomes in the long term cannot be addressed in the present review using data from randomised trials of a median of only 8 weeks' treatment. Nevertheless, in younger adults not at immediate risk of the adverse outcomes described above, especially those with no history of substance misuse, BDZs, with their good short-term tolerability and rapid onset of action, may well have a useful role in the initial or short-term management of panic disorder, when antidepressants may not be practicable after initial management of panic disorder. However, it is worth noting that the findings presented in this review may be limited by the low quality of the trials comparing BDZs to placebo and BDZs to antidepressants.

For the studies comparing antidepressants and benzodiazepines, the identified studies are not sufficient to comprehensively address the objectives. The majority of studies enrolled a very small number of participants and did not provide data for all the outcomes specified in the protocol. Only short-term data on acceptability and adverse effects of antidepressants and benzodiazepines were available. Clinically, this is a major limitation as long-term use of benzodiazepines is controversial due to concerns about adverse psychological and physical effects, physical dependence and withdrawal. Similar concerns have been raised for long-term exposure to antidepressants, in particular the SSRIs.

Quality of the evidence

Quality of studies varied depending on the comparisons, and was usually low or unclear.

For the studies comparing antidepressants with placebo, the overall methodological quality of the included studies was unclear. No study showed an overall low risk of bias. The majority of studies showed mixed features, with a large prevalence of unclear risk of bias in different domains; however, this may reflect a lack of exhaustive reporting rather than a clear evidence of bias. In general, confidence in the estimates of effect ranged from 'low' to 'moderate' for most of the outcomes assessed. Study findings were generally quite precise, with small confidence intervals and a high number of participants. Reasons to downgrade the quality of the evidence were primarily due to limitations in the included studies and inconsistency (heterogeneity between studies' results). In agreement with this judgement, we argue that, for the primary outcomes, treatment estimates may be considered quite robust, and further research is unlikely to change our confidence in the estimate of effect.

For the studies comparing benzodiazepines with placebo, the overall methodological quality of the included studies was poor. We rated all studies as having an unclear risk of bias in at least three domains. In addition, the majority of the studies had a high risk of bias in at least one domain, including a high risk of attrition bias and 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. The missing data 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.). Furthermore, the bias may be reinforced by censorship of participant data at protocol violation in the first weeks, which was a standard procedure accepted by the regulatory authorities in the past.

For the studies comparing antidepressants with benzodiazepines, the overall methodological quality of the included studies was poor. No study showed an overall low risk of bias. The majority of studies showed mixed features, with a large prevalence of an unclear risk of bias in different domains, which seems to reflect the lack of exhaustive reporting rather than a clear evidence of bias. In general, the confidence in the estimate of effect appeared to be from 'very low' to 'moderate' for most of the outcomes assessed. This judgement is primarily due to limitations in the included studies (high dropout rates), imprecision (wide confidence intervals) and inconsistency (heterogeneity between studies results). In accordance with that, any estimate of effect should be considered very uncertain, and further research is very likely to change the estimate of effect and thus the degree of confidence for its applicability in routine clinical practice.

Potential biases in the review process

Several potential biases have been identified in the review process.

The search and selection of the studies have been done in the previous Cochrane head-to-head comparisons on panic disorder ([Bighelli 2016](#); [Bighelli 2018](#); [Breilmann 2019](#)), as this NMA includes all the studies selected in those reviews and no new studies.

Several possible limitations of this review should be highlighted for all the studies. Some limitations are intrinsically related to the actual process of retrieving, collecting, selecting and extracting data. In order to reduce the potential bias of this complex process two review authors independently worked on each of these steps. It has been highlighted that two independent extractors are overall more reliable than extraction performed by a single author followed by verification by a second author. We applied the same process for the 'Risk of bias' assessment. Furthermore, disagreements were always discussed with a third author. Another relevant problem concerns the 'systematic' nature of the search. We chose to include only randomised studies as they provide the strongest level of evidence available. In this type of review there is some risk of publication bias, which means that negative studies may not have been published. Although the search was thorough, it is possible that we may

not have identified some unpublished studies, considering that there are no shared procedures to perform this kind of search. It is expected that the analysis of published literature only would lead to overestimation of the efficacy of a given intervention. Finally, it is important to bear in mind that some included studies were funded by the pharmaceutical industry, and this may again introduce an overestimation of the efficacy of interventions.

For the antidepressants versus placebo comparisons, we formally checked the presence of publication bias with visual inspection of funnel plots on the head-to-head published Cochrane review (Bighelli 2018). Regarding the primary outcome, 'Failure to respond', a visual inspection of the funnel plot suggested that some studies with a low number of participants favouring placebo against TCAs may be missing, and this may have led to an overestimation of the efficacy of TCAs compared to placebo. For the primary outcome, 'Total dropouts', a visual investigation of the funnel plot suggested that some small studies favouring placebo against SSRIs might be missing, and this might have led to an overestimation of the acceptability of SSRIs.

For the benzodiazepines versus placebo comparisons, we formally checked the presence of publication bias with visual inspection of funnel plots on the head-to-head published Cochrane review (Breilmann 2019). The funnel plots are indicative of the presence of a publication bias, and we identified only one unpublished trial for inclusion in the 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, we think that is rather likely that there are some other unpublished trials.

For the antidepressants versus placebo comparisons, the impact of unpublished literature on the results of this review is uncertain, however it is expected that the analysis of only published literature would lead to overestimation of the efficacy of a given intervention. We did not check this formally with a funnel plot analysis in the Cochrane head-to-head review (Bighelli 2016), as less than 10 studies contributed to any analyses, thus making the funnel plot methodology less informative.

Agreements and disagreements with other studies or reviews

This NMA review is based on the Cochrane head-to-head comparisons on panic disorder published in previous years (Bighelli 2016; Bighelli 2018; Breilmann 2019). The Cochrane head-to-head review on antidepressants versus placebo in panic (Bighelli 2018) showed that antidepressants as a group are more effective than placebo, although the evidence was of low quality. Antidepressants as a class were less tolerated than placebo. The Cochrane head-to-head review on BDZs versus placebo (Breilmann 2019) showed that BDZs as a group are more effective than placebo, although the evidence was of low quality. BDZs as a class was more tolerated than placebo. The Cochrane head-to-head review on antidepressants versus BDZs (Bighelli 2016) showed that antidepressants as a class were not more or less effective than BDZs. Remission rates showed a benefit for BDZs compared to antidepressants, but the effect was very small and close to no difference. In terms of tolerability, the review found evidence suggesting a benefit for benzodiazepines compared to antidepressants when looking at number of dropouts due to any cause. The methodology in this NMA allowed us to rank treatments which was the advantage compared to the Cochrane head-to-head comparisons. In line with the previous Cochrane head-to-head meta-analyses, antidepressants and BDZs seem effective compared to placebo. However, we found that some BDZs ranked higher, if compared to placebo, in terms of efficacy and tolerability, except for remission where desipramine ranked as high as alprazolam. For class comparisons, the head-to-head NMA comparing antidepressants and BDZs (Bighelli 2016) did not show any difference. Our NMA, instead, ranked TCAs antidepressants as the class with the strongest effect, compared to placebo. However, in line with the Bighelli 2016 review, our NMA found no difference between classes of medications for response outcomes. For tolerability outcomes, in line with the Bighelli 2016, BDZs were ranked as the most tolerated class of medications for panic disorder.

Two other NMAs have been published on panic disorder (Chawla 2022; Du 2021). To our knowledge these are the only other NMAs published on the topic.

Du 2021 is based on 42 trials comparing ADs and BDZs (a lower number compared to our NMA), all published, and also included single-blind trials, unlike our review. This review did not adjust for small study bias. Du and colleagues concluded that escitalopram and venlafaxine, as well as, BDZs are effective choices for panic disorder. Du and colleagues findings are similar to this review - although they compared BDZs as a class with other individual ADs. We also found that most ADs and BDZs were more effective than placebo, and also found no substantial differences between these medication classes.

Chawla 2022 is based on 87 trials, a higher number of trials compared to our NMA. This is likely explained by Chawla and colleagues broader inclusion criteria. Our review only included monotherapy of ADs and BDZs whereas Chawla and colleagues included monotherapy and combination therapy, and included further medication classes (azapirones, beta-blockers). A further difference was that our review only included double-blind trials, Chawla and colleagues also included single-blind trials. However, it should be noted that reporting of blinding was unclear in many studies so the impact of this inclusion criterion on results is unclear. Apart from the studies that Chawla had included but were ineligible for our review as per our eligibility criteria, there was one unpublished study that we had missed that they had included (Pfizer 2008). By contrast, some studies seemed to be eligible as per their study protocol but were not included in their review. Whereas our current review adjusted for small study bias, the review by Chawla and colleagues did not. Given the large number of small studies included in this NMA, and the potential risk of bias identified, this is an important advantage of our current review. Chawla and colleagues conclude that SSRIs provide high rates of remission, with sertraline and escitalopram

associated with a higher remission and low risk of adverse events. However, the authors pointed out that the studies had moderate to very low certainty levels of evidence, mostly as a result of within study bias, inconsistency, and imprecision of the findings reported. They did not recommend BDZs as first-line treatments due to potential risk of adverse events. They found that BDZs were more effective than SSRI and SNRIs, whereas our review did not find substantial differences between these medication classes. This difference in findings is probably accounted for by the bias adjustment used in our analyses, in our unadjusted analyses we found similar effects to Chawla and colleagues. We feel that the methodology used in our review such as limiting to double-blind studies and adjusting for small study effects make our findings more robust.

Authors' conclusions

Implications for practice

This Cochrane review seems to suggest that SSRIs, SNRIs (venlafaxine), TCAs, MAOIs, and BDZs may be effective and with little differences between classes in terms of efficacy. However, it's important to note that the reliability of these findings may be limited due to the overall low quality of the studies, with all trials rated unclear or high across multiple domains.

Within classes, some differences emerged for example amongst SSRIs paroxetine and fluoxetine seems to have stronger evidence of efficacy than sertraline. Benzodiazepines appear to have a small but significant advantage in terms of tolerability (assessed by the incidence of dropouts) over other classes over the time period of the studies (median 8 weeks).

Existing guidelines ([Katzman 2014](#); [Baldwin 2014](#); [Andrews 2018](#)) and other systematic reviews on panic disorder ([Chawla 2022](#); [Du 2021](#)) favour SSRIs and sometimes the SNRI venlafaxine as first-line treatment. In light of this, our findings bring up two issues for clinicians to consider:

1. Amongst SSRIs, are paroxetine and fluoxetine preferable to sertraline and citalopram/escitalopram on the basis of the finding of slightly better efficacy? However, paroxetine is known to be associated with difficult withdrawal and is a strong mechanistic CYP2D6 inhibitor while fluoxetine and its metabolite nor-fluoxetine inhibit a range of important CYP enzymes, increasing the likelihood of drug interactions. In contrast, sertraline is a substrate of multiple CYPs but a strong inhibitor of none and is not noted for problems on withdrawal, so these benefits might offset the slightly weaker evidence of efficacy.
2. BDZs performed well on efficacy and tolerability in the time frame examined here (4-24 weeks with a median of 8 weeks), but most guidelines advise that they are not used as first-line treatment. The British Association of Psychopharmacology guidelines ([Baldwin 2014](#)) state that BDZs "*will usually be reserved for the further treatment of patients who have not responded to at least three previous treatments*". Thus, while the findings for BDZs were positive in terms of efficacy and tolerability in the short term, the limitation that we could not examine the consequences of longer-term use despite there being well-characterised concerns, means that the evidence reported in this Cochrane review is insufficient to override the many current treatment guidelines that suggest that BDZs may be a less desirable choice overall than SSRIs and SNRIs. For antidepressants, the evidence seems to show that their use may be safe in the long-term ([Wilkinson 2016](#)). Moreover, guidelines encourage prescribers and patients to keep using antidepressants as prophylaxis for periods of at least 6 months to 2 years after response ([Andrews 2018](#); [Baldwin 2014](#); [Cleare 2015](#); [Katzman 2014](#)).

Finally, while some guidelines recommend other drugs such as buspirone, gabapentin, and mirtazapine, there is a lack of positive randomised evidence to support these drugs in panic disorder.

Another important point to bear in mind is the relationship between pharmacological treatments and psychotherapy in panic. The evidence for depression points in the direction of superiority of psychotherapy (alone or in combination with medications) in the long term ([Furukawa 2021](#)). It will be important not to discount the relevance of psychotherapy and its combination with pharmacotherapy in the treatment of panic disorder.

Implications for research

Threshold analyses found that the NMA results were relatively robust to the impact of potential biases. Future randomised studies may not add much to our overall findings comparing all medications to placebo and comparing medication classes. However, some uncertainties remain. Comparisons of individual medications are still very imprecise. It is worth mentioning that the networks themselves might not be fully mature, adding another layer of uncertainty to the conclusions drawn from the review. In addition, few studies measured quality of life and social functioning.

An important limitation of this NMA is the fact that there are limited studies in the past 15 years. Most clinical drug trials of panic disorder date back to the 1980s and 1990s and there are not many recent trials on panic. Research methodology may have become more refined over time. It will be highly desirable to carry out new trials on antidepressants and benzodiazepines in panic disorders, possibly comparing them to novel treatments. A search on [clinicaltrials.gov](#) done on March 2, 2023 showed that there are very few ongoing clinical studies on pharmacological treatment in panic disorder.

A further limitation is that almost all the studies examined in this NMA were of short duration. This may have had some implication for the long-term efficacy in clinical setting of the medication examined. For the BDZs, there has been a considerable debate on whether they can be used in the long-term given their propensity to abuse, possible risk for tolerance ([Horowitz 2021](#)) and the existence of withdrawal symptoms ([Allison 2003](#)). Some authors advocate against the long-term use of BDZs in any case ([Horowitz 2021](#)). Nonetheless, other authors have been more open to the idea of using BDZs in case other treatments, such as antidepressants, fail and when the likelihood of abuse is low ([Silberman 2021](#); [Hirschtritt 2021](#)). Experts belonging to the International Task Force on BDZs talk about a "bias" against BDZs ([Silberman 2021](#)). They say that the evidence that BDZs are likely to be abused in any case, that they create tolerance or are dangerous in overdose, does not match the beliefs many clinicians have against them ([Silberman 2021](#)). The use of antidepressants is deemed safer and in the long-term ([Wilkinson 2016](#).) They seem to have a lower propensity for abuse ([Fluyau 2022](#)) but are also associated with

withdrawal symptoms that can be severe and possibly worse than BDZs withdrawal (Fava 2019). Its use is not devoid of problem, as they may even worsen the conditions they are supposed to treat (Fava 2020). Studies where BDZs and antidepressants are assessed in the long term (i.e. longer than a year) are needed for anxiety disorders, as the efficacy of medications in anxiety disorders is less established for longer durations. BDZs may be an alternative to people who do not respond to antidepressants and/or psychotherapy.

Another important question is: are BDZs more helpful and less risky in the long-term if they are only taken intermittently (i.e. a few times per week, as needed) as rescue medications? Studies where regular versus intermittent use of BDZs in anxiety disorders is compared, will be particularly useful to guide the clinician to the optimal course of treatment.

Finally, it will be important to systematically assess the efficacy of medications compared to psychotherapy, perhaps in a NMA. Data from depression seems to show that psychotherapies can lead to a more sustained effect. The same may apply to anxiety disorders in general and panic disorder in particular and needs to be investigated. Psychotherapy can be a valid first-line alternative or add-on treatment in panic disorder (Papola 2022) and needs to be compared to medications in future research trials.

Acknowledgements

Editorial contributions:

Cochrane Common Mental Disorders supported the authors in the development of this systematic review. The following people conducted the editorial process for this article:

Sign-off Editor (final editorial decision): Neil O'Connell, Brunel University, London, UK; **Managing Editor** (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Marwah Anas El-Wegoud, Central Editorial Service; **Editorial Assistant** (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Central Editorial Service; **Copy Editor** (copy editing and production): [NAME, AFFILIATION]

Peer-reviewers (provided comments and recommended an editorial decision): Amir Garakani, M.D., Department of Psychiatry and Behavioral Health, Greenwich Hospital, Greenwich, CT, Department of Psychiatry, Yale School of Medicine, New Haven, CT (**clinical review**); Anton J.L.M. van Balkom, MD, PhD Department of Psychiatry Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands (**clinical review**); Rafael C. Freire - Department of Psychiatry and Center for Neuroscience Studies, Queen's University, Kingston, ON, Canada (**clinical review**); Brian Duncan (**consumer review**); Benjamin Rouse, Research Analyst, ECRI (**methods review**); Sofia Tsokani, Cochrane (**methods review**) Anne Littlewood, Cochrane Oral Health (**search review**). One additional peer reviewer provided clinical peer-review but chose not to be publicly acknowledged.

History

Protocol first published: Issue 7, 2017

Contributions of authors

GG, CB, MK, TAF and AC conceived the review. GG, DC and AC wrote the draft of the protocol. NM, SJCD and DC contributed to the formal analysis of the review. and all authors critically commented on the protocol. HI, AT, AP, IB, LR, SDn and AC selected the studies, appraised their quality and extracted the data. GG and NM wrote the draft of the review. All authors contributed in reviewing and editing the draft.

Declarations of interest

- GG: is a Cochrane Editor. He was not involved in the editorial process of the manuscript. He is a diplomate of the Academy of Cognitive Therapy.

- NM: is a Cochrane Editor. He was not involved in the editorial process of the manuscript.- CB: is a Cochrane Editor. He was not involved in the editorial process of the manuscript.- SJCD: is a Cochrane Editor. He was not involved in the editorial process of the manuscript. He is a member of the European College of Neuropsychopharmacology and co-chair of their Anxiety Disorders research network. He has published opinions in medical journals relevant to the interventions in this review. He is a member of the Anxiety Disorders Research Network of European College of Neuropsychopharmacology (ECNP) and of the British Association of Psychopharmacology (BAP). - TAF: has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Otsuka, Pfizer, Shionogi and Mitsubishi-Tanabe, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha publishers. He has received grant or research support from the Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, the Japan Foundation for Neuroscience and Mental Health, Mitsubishi-Tanabe and Mochida. He is diplomate of the Academy of Cognitive Therapy. TAF has a patent 2018-177688 pending.

- HI: receive a honorarium for a lecture from Otsuka.

- SD: no conflicts of interest,
- DC: no conflicts of interest.
- MK: no conflicts of interest.
- AT: received lecture fees from Sumitomo Dainippon Pharma, Eisai, Janssen Pharmaceutical, Meiji-Seika Pharma, Mitsubishi Tanabe Pharma, Otsuka, and Takeda Pharmaceutical.- IB: is Deputy Co-ordinating Editor of the Cochrane Schizophrenia Group. She was not involved in the editorial process of the current review.- AP: no conflicts of interest.- AC: is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017-08-ST2-006), by the NIHR Oxford and Thames Valley Applied Research Collaboration and by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005). The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health. He has received research, educational and travel support from INCiPiT (Italian Network for Paediatric Trials), CARIPO Foundation, Lundbeck and Angelini Pharma. He is the CI/PI of two trials about seltorexant in depression, sponsored by Janssen.
- SDn: is a Cochrane Editor. She was not involved in the editorial process of the manuscript.
- LR: no conflict of interest

Sources of support

Internal sources

- Western University, Canada
Salary and protected research time for GG
- University of Verona, Italy
Salary for CB, IB
- University of Bristol, UK
Salary for DC
- University of Toronto, Canada
Salary and protected time for SJD
- Kyoto University, Japan
Salary for TAF, HI, AT
- University of Oxford, UK
Salary for AC
- National Institute for Health and Care Research (NIHR), UK
Support to AC (NIHR Research Professorship - grant RP-2017-08-ST2-006, NIHR Oxford Cognitive Health Clinical Research Facility, NIHR Oxford and Thames Valley Applied Research Collaboration and NIHR Oxford Health Biomedical Research Centre - grant BRC-1215-20005)

External sources

- None, Other
No external source of support

Differences between protocol and review

While conducting our systematic review of antidepressants, BDZs and azapirones to treat panic disorder, we identified inconsistency between direct and indirect evidence in the network meta-analyses. We judged it important to explore the sources of this inconsistency. This requires a substantial addition to the methods proposed in the original protocol. Therefore, we have updated our protocol to outline the methods we plan to use to quantify and explore this inconsistency. For example, we had originally proposed to conduct global tests of inconsistency to guide whether to use more intensive methods (node-splitting). However, since we were concerned about potential inconsistency, we decided to conduct node-splitting and did not conduct global tests of inconsistency.

The protocol stated that bias-adjustment models would be conducted as sensitivity analyses. However, given the poor fit of standard models, results from bias-adjustment models were reported as the main analyses as they fitted the data much better.

The protocol stated that we would not include studies using DSM-III criteria. However, since the other Cochrane pairwise meta-analyses on which this NMA is based, have included studies using DSM-III criteria, we decided to include studies using DSM-III criteria.

In addition, we proposed to conduct sensitivity analyses where different doses were treated as separate nodes. However, given the large number of meta-regression analyses and sensitivity analyses conducted we chose not to.

We initially plan to include studies with no useable data, but since they could not be entered in the analysis, we decided to exclude them.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Amore 1999		
Study characteristics		
Methods	Study design: randomised controlled trial	
Participants	<p>Diagnosis: DSM-IV Panic disorder with or without agoraphobia</p> <p>Method of diagnosis: not stated</p> <p>Age, mean (SD) years: fluoxetine 37.0 (7.1); imipramine 37.2 (8.2)</p> <p>Sex: for fluoxetine, 57.89% women, 42.11% men; for imipramine 36.84% women, 63.16% men</p> <p>Location: Italy; setting unclear.</p> <p>Co-morbidities: patients with history of psychosis, current major depression, organic brain syndromes or significant neurological disorders, seizures, clinically relevant cardiovascular, hepatic, renal or haematological diseases were excluded</p> <p>Rescue medication: oxazepam (up to a maximum daily dose of 30 mg) permitted during first four weeks of double-blind treatment</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) fluoxetine arm (n = 19)</p> <p>Duration: 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders</p> <p>Treatment protocol: flexible dosage; range = 10-50 mg, mean 20 mg/day (SD 10) (responder group)</p> <p>(2) imipramine arm (n=19)</p> <p>Duration: 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders</p> <p>Treatment protocol: flexible dosage; range = 2-250 mg, mean 150 mg/day (SD 25) (responder group)</p>	
Outcomes	<p>Time points for assessment: baseline and weekly for 16 weeks, every two weeks between week 17 and 24, later monthly</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Panic-Associated Symptoms Scale (PASS) 2. Hamilton Rating Scale for Anxiety (HAMA) 3. Hamilton Rating Scale for Depression (HRSD) 4. Clinical Global Impression (CGI) 	
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: "they were randomly assigned to fluoxetine or imipramine treatment". No further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	High risk	Data on the scales CGI, PASS and HRSD not reported at endpoint.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.
Amore 1999 bis		

Study characteristics		
Methods	Study design: randomised controlled trial	
Participants	<p>Diagnosis: DSM-IV Panic Disorder with or without agoraphobia</p> <p>Method of diagnosis: Not stated</p> <p>Age: for fluoxetine, M = 37.2 (SD = 7.0); for citalopram, M = 36.7 (SD = 7.4)</p> <p>Sex: for fluoxetine, 57.1% women, 42.9% men; for imipramine 61.9% women, 38.1% men</p> <p>Location: Italy; setting unclear</p> <p>Co-morbidities: patients with history of psychosis, current major depression, organic brain syndromes or significant neurological disorders, seizures, clinically relevant cardiovascular, hepatic, renal or haematological diseases, alcohol or drugs abuse were excluded</p> <p>Rescue medication: Oxazepam (up to a maximum daily dose of 30 mg) permitted</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) fluoxetine arm (n = 21)</p> <p>Duration: 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders</p> <p>Treatment Protocol: flexible dosage; range = 10 - 50 mg, M = 20 mg/day (SD = 10)</p> <p>(2) citalopram arm (n = 21)</p> <p>Duration: 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders</p> <p>Treatment Protocol: flexible dosage; range = 20 - 60 mg, M = 40 mg/day (SD = 10)</p>	
Outcomes	<p>Time points for assessment: baseline and weekly for 16 weeks, every two weeks between week 17 and 24, later monthly</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Panic-Associated Symptoms Scale (PASS) 2. Hamilton Rating Scale for Anxiety (HAMA) 3. Clinical Global Impression (CGI) 4. Dosage Records and Treatment-Emergent Symptoms Scale (DOTES) 	
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: "they were randomly assigned". No further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	High risk	Data on the scales CGI, PASS and HAMA not reported at endpoint.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Asnis 2001

Study characteristics	
Methods	Study design: 8 weeks, multi-centre, double-blind, placebo-controlled outpatient clinical trial, parallel groups, individual randomisation
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: not specified</p> <p>Age (years): fluvoxamine arm mean age (years) 34.2 (SD = 10.2, range 19-65), placebo arm mean age (years) 36.7 (SD = 9.8, range 20-63)</p> <p>Sex: 64 men, 115 women</p> <p>Location: outpatients, 4 centres throughout the USA</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: discouraged, but allowed for night time sedation (lorazepam 1-2 mg or chloral hydrate 1-2 mg)</p>
Interventions	Participants were randomly assigned to either:

	<p>1. fluvoxamine arm (randomised n = 93) Duration: 8 weeks Treatment protocol: flexible dosage; range = 100-300 mg/day, mean 4.2 cps/day (SD = 1.4)</p> <p>2. placebo arm (randomised n = 95) Duration: 8 weeks Treatment protocol: flexible dosage, mean 5.1 cps/day (SD = 1.2)</p>
Outcomes	<p>Timepoints for assessment: at baseline and weekly until week 8</p> <p>Outcomes</p> <ol style="list-style-type: none"> 1. DPAI 2. CAS 3. estimate of Panic Attack frequency and severity (item 7 of the CAS) 4. SDS 5. MADRS 6. CGI-S 7. CGI-I
Notes	<p>Date of study: not specified</p> <p>Funding source: unclear</p> <p>Declarations of interest among the primary researchers: unclear</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as "randomized", however the sequence generation process is not discussed.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study is defined as "double-blind". Quote: "Treatment was started with a daily dosage of one capsule (50 mg fluvoxamine or matching placebo) [...]"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: fluvoxamine group 29/93 (31.2%), placebo group 29/95 (30.5%). There are high dropout rates in each arm. Reasons for leaving the study early are relatively balanced between the two groups (see table 1). Quote: "Conclusions were based on the last observation carried forward (LOCF) to the end of the study analyses for the intention to treat population (all patients randomized to double-blind treatment who provided some on-drug efficacy data)". However, the tables do not report the number of analysed participants.
Selective reporting (reporting bias)	High risk	The primary outcome is clearly reported in the methods, quote: "The primary efficacy measurement, the DPAI, was designed to identify panic attacks". However, the DPAI scores are not reported in the text and tables. All other measurements are reported.
Other bias	High risk	Quote: "The authors thank Drs. R.I.H. and A.M. who were at Solvay Duphar for their help in providing statistical assistance and a thorough review of the manuscript". A risk of sponsorship bias cannot be excluded.

Baker 2003

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-IV panic disorder</p> <p>Method of diagnosis: Structured Clinical Interview for DSM-IV (modified version)</p> <p>Age: clonazepam: mean = 47.3 (SE = 2.76); Placebo: mean = 44.4 (SE = 1.87)</p> <p>Sex: Clonazepam: female 30%; placebo: female 56%</p> <p>Location: Canada (Toronto Western Hospital)</p> <p>Comorbidities: not stated</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Clonazepam (n = 10)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: not stated</p> <p>(2) Placebo (n = 17)</p>

	Duration: 4 weeks	
	Treatment protocol: not stated	
Outcomes	Time points for assessment: baseline, end of trial Primary outcomes: (1) Anxiety: HAMA, weekly (2) Daily diaries (3) General psychiatric symptomatology: SCL-90-R (4) Somatosensory Amplification Scale (5) Illness Intrusiveness Scale (6) Depression: HAMD	
Notes	Date of study: not stated Funding source: supported by a grant from the Heart and Stroke Foundation of Ontario 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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided 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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Unclear risk	The efficacy data of rating scales are not reported. There are data on sleep measures only.
Other bias	Low risk	No evidence of other bias was found.

Bakish 1993

Study characteristics	
Methods	Study design: Randomised controlled trial
Participants	Diagnosis: DSM-III-R panic disorder with or without agoraphobia Method of diagnosis: Not stated Age: Not stated Sex: Not stated Location: Canada; setting: outpatients Co-morbidities: Not stated Rescue medication: Chloral hydrate, up to 1 g at night
Interventions	Participants were randomly assigned to either: (1) brofaromine arm (n = 47) Duration: 8 weeks Treatment Protocol: flexible dosage; range = 50 - 150 mg, M and SD not provided (2) clomipramine arm (n = 46) Duration: 8 weeks Treatment Protocol: flexible dosage; range = 25 - 75 mg, M and SD not provided
Outcomes	Time points for assessment: baseline, every two weeks Outcomes: 1. Number of panic attacks per week 2. Hamilton Rating Scale for Anxiety (HAMA) 3. Hamilton Rating Scales for Depression (HAM-D) 4. Clinician Rated Impairment and Disability Scale (CRIDS) 5. Clinician Rated Global Change Scale (CRGCS) 6. Patient Rating Impairment Disability Scale (PRIDS) 7. Patient Rated Anxiety Scale (PRAS) 8. Marks Matthews Phobia Scale 9. Patient Rated Global Change Scale (PRGCS)

	10. Daily Panic Inventory (DPI)	
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: "randomised". No further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	High risk	Data on the scales HAMD, CRIDS, CRGCS, PRIDS, PRAS, PRCGS, DPI not reported at endpoint; data on the scales HAMA and Mark Matthews Phobia Scale are reported only in graphs; number of patients evaluated not specified.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Ballenger 1998

Study characteristics

Methods	Study design: 10 weeks, double-blind, randomised (cluster randomisation), placebo-controlled, parallel-design, multicentre clinical trial
Participants	Diagnosis: DSM-III-R criteria for panic disorder, with or without agoraphobia Method of diagnosis: not specified Age (years): placebo arm mean age 37.3 (SD = 10.4), paroxetine 10 mg arm mean age 36.1 (SD = 9.1), paroxetine 20 mg arm mean age 35.9 (SD = 10.1) and paroxetine 40 mg mean age 36.3 (SD = 10.8) Sex: 95 men, 183 women Location: outpatients Co-morbidities: excluded Rescue medication: not allowed
Interventions	Participants were randomly assigned to either: 1. paroxetine 10 mg arm (randomised n = 67) Duration: 10 weeks Treatment protocol: fixed dosage 10 mg/day 2. paroxetine 20 mg arm (randomised n = 70) Duration: 10 weeks Treatment protocol: fixed dosage 20 mg/day 3. paroxetine 40 mg arm (randomised n = 72) Duration: 10 weeks Treatment protocol: fixed dosage 40 mg/day 4. placebo arm (randomised n = 69) Duration: 10 weeks Treatment protocol: fixed dosage
Outcomes	Timepoints for assessment: at baseline, week 4 and week 10 Outcomes: <ol style="list-style-type: none"> percentage of subject free of panic attacks at endpoint mean change from baseline in number of full panic attacks percentage of subjects with a 50% reduction from baseline in number of full panic attacks CGI-S mean number and intensity of panic attacks number of unexpected and situational panic attacks severity of anticipatory anxiety CGI-I Marks-Sheehan Phobia Scale

	10. HAMA 11. MADRS 12. SDS 13. Social Adjustment Self-Report Questionnaire
Notes	Date of study: not specified Funding source: sponsored by the drug company marketing the drug Declarations of interest among the primary researchers: apparently connected with the drug company marketing the drug
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk The study is described as "randomized", however the sequence generation process is not discussed.
Allocation concealment (selection bias)	Unclear risk No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk The study is described as "double-blind", however procedures for ensuring the blindness of participants and who administered the intervention are not discussed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk Dropouts: paroxetine 10 mg group 22/67 (32.8%), paroxetine 20 mg group 23/70 (32.8%), paroxetine 40 mg group 22/72 (30.5%), placebo group 23/69 (33.3%). The dropout rate is high in every arm and reasons for leaving the study are apparently balanced between groups as reported in table 2 in the paper. Quote: "Results for the intent-to-treat population were determined on the basis of the data sets for both completer analysis (observed cases) and endpoint analysis (last observation carried forward)". Outcome measures reported are consistent with an ITT analysis (as reported in table 3 in the paper).
Selective reporting (reporting bias)	Low risk Primary and secondary outcomes are clearly pre-specified in the protocol of the study and in the "measurements" paragraph of the paper. All relevant data are clearly reported in tables.
Other bias	Unclear risk A "disclosure of interest" paragraph is not reported.

Bandelow 2004

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM-IV and ICD-10 diagnosis of panic disorder with or without agoraphobia Method of diagnosis: Not stated Age: for sertraline, M = 39.6 (SD = 11.7); for paroxetine, M = 38.1 (SD = 11.7) Sex: for sertraline, 60% women, 40% men; for paroxetine 66% women, 34% men Location: 5 centres in Denmark, 22 centres in Germany, 2 centres in the Netherlands, 2 centres in Switzerland, 2 centres in Turkey; setting: outpatients Co-morbidities: patients with clinically significant and unstable medical illness, bipolar disorder, schizophrenic disorder, delusional disorder, epilepsy, major depressive disorder (MDD), obsessive-compulsive disorder (OCD), social phobia, history of alcoholism or drug abuse were excluded Rescue medication: chloral hydrate, zolpidem or zopiclone allowed if necessary to treat severe insomnia, less than 3 times per week
Interventions	Participants were randomly assigned to either: (1) sertraline arm (n = 112) Duration: 12 weeks Treatment protocol: flexible dosage; range = 25 - 150 mg, M = 84.5, SD = 39.1 (2) paroxetine arm (n = 113) Duration: 12 weeks Treatment protocol: flexible dosage; range = 10 - 60 mg, M = 48.1, SD = 11.2
Outcomes	Time points for assessment: baseline, week 1, 2, 4, 6, 8, 12 and 15 Outcomes: 1. Panic and Agoraphobia Scale (PAS) 2. agoraphobia/avoidance behaviour 3. anticipatory anxiety 4. disability 5. health worries

	<p>6. Clinical Global Impression-Severity of Illness (CGI-S)</p> <p>7. Clinical Global Impression-Improvement (CGI-I)</p> <p>8. Hamilton Rating Scale for Anxiety (HAMA)</p> <p>9. Montgomery-Åsberg Depression Rating Scale (MADRS)</p> <p>10. Sertraline Quality of Life Battery</p> <p>11. Digit Symbol Substitution Task</p> <p>12. Digit Span</p> <p>13. Patient Global Impression (PGI)</p>
Notes	<p>Date of study: data were collected from January 2000 to June 2001</p> <p>Funding source: Funded by Pfizer Inc, New York</p> <p>Declarations of interest among the primary researchers: Dr Bandelow has received grant/research support from GlaxoSmithKline</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "they were randomly assigned". No further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "[...] a secondary analysis was performed on the ITT population, which consisted of all patients who were randomly assigned to study drug and for whom at least one post baseline PAS assessment was available"
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by Pfizer; the role of the funder in planning, conducting and writing the study is not discussed.

Barlow 2000

Study characteristics	
Methods	<p>Study design: 12 weeks and then 6 months, multicentre, randomised, double-blind, placebo-controlled clinical trial, parallel groups, cluster randomisation</p>
Participants	<p>Diagnosis: panic disorder with or without mild agoraphobia</p> <p>Method of diagnosis: ADIS-R (Anxiety Disorder Interview Schedule-Revised, diagnosis confirmed 2 weeks prior to first treatment visit)</p> <p>Age (years): mean 36.1 (SD = 10.7)</p> <p>Sex: 62.5% women</p> <p>Location: not specified</p> <p>Co-morbidities: patients with depression were not excluded, unless suicidal</p> <p>Rescue medication: allowed up to 20 doses of benzodiazepines (or 10 alprazolam equivalent)</p>
Interventions	<p>Participants were randomly assigned to either:</p> <ol style="list-style-type: none"> 1. imipramine arm (randomised n = 83) Duration: 12 weeks Treatment protocol: flexible dosage. "the dose was titrated 10 mg every other day until 50 mg per day and then was flexible, with efforts to reach 100 mg by the end of week 3 and 200 by week 5" 2. CBT alone arm (randomised n = 77) Duration: 12 weeks Treatment protocol: unclear 3. CBT plus imipramine arm (randomised n = 65) Duration: 12 weeks Treatment protocol: flexible dosage; range = 10-60 mg/day 4. CBT plus placebo arm (randomised n = 63) Duration: 12 weeks Treatment protocol: flexible dosage 5. placebo arm (randomised n = 24) Duration: 12 weeks

	Treatment protocol: flexible dosage	
Outcomes	Timepoints for assessment: at baseline, at week 12 and then at month 4, 5, and 6 Outcomes: 1. PDSS 2. Responders based on CGI	
Notes	Date of study: May 1991-April 1998 Funding source: the study was mostly funded by public financial support. Sponsorship bias is unlikely to have occurred. Declarations of interest among the primary researchers: none	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, however details on the random sequence generation are not discussed.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trained independent evaluators were employed (see "Assessment" paragraph)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Trained independent evaluators were employed.
Selective reporting (reporting bias)	Low risk	Primary endpoints are divided in continuous outcome measures (average item score for the PDSS) and categorical outcome measures (responders based on CGI). All relevant data are reported in tables.
Other bias	Unclear risk	Study authors received various financial support from pharmaceutical agencies. Quote: "Imipramine and matching placebo were provided by Teva Pharmaceuticals USA". The study was mostly funded by public financial support.

Beauclair 1994

Study characteristics

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

Bergink 2005

Study characteristics	
Methods	Study design: 9 weeks, randomised (individual randomisation), double-blind, parallel, placebo-controlled clinical trial, parallel groups
Participants	<p>Diagnosis: panic disorder with and without agoraphobia according to the DSM IV criteria</p> <p>Method of diagnosis: PDSS, CGI and number of panic attacks per week</p> <p>Age (years): the mean age was 41 for the metabotropic glutamate (LY354740), 44 for paroxetine and 45 for placebo</p> <p>Sex: 18 men and 27 women</p> <p>Location: University Medical Centre (UMC) in Utrecht, the Netherlands</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: not permitted</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. LY354740 arm (randomised n = 18)</p> <p>Duration: 9 weeks</p> <p>Treatment protocol: flexible dosage; range = 100-200 mg/day</p> <p>2. paroxetine arm (randomised n = 9)</p> <p>Duration: 9 weeks</p> <p>Treatment protocol: flexible dosage; range = 10-60 mg/day</p> <p>3. placebo arm (randomised n = 0)</p> <p>Duration: 9 weeks</p> <p>Treatment protocol: flexible dosage</p>
Outcomes	<p>Timepoints for assessment: at baseline and then at week 3, 6, 9</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. responders (participants that hadn't had a full panic attack during their final 3-week active drug period): 2. number of panic attacks 3. MADRS 4. HAMA 5. PGI-P 6. PDSS 7. CGI-S
Notes	<p>Date of study: not specified</p> <p>Funding source: unclear</p> <p>Declarations of interest among the primary researchers: unclear</p>
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "eligible patients were assigned in a 1:1:1:1 ratio to one of the following four treatment groups: LY354740 100 mg/day, LY354740 200 mg/day, paroxetine, placebo". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is described as "double blind" but no further details are given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number and the reasons for dropouts are specified. Data analysis was performed on the intent-to treat population using the LOCF.
Selective reporting (reporting bias)	Low risk	The primary and secondary outcome data are shown in a table.
Other bias	Unclear risk	It is unclear whether the study authors received a grant for the study.

Black 1993

Study characteristics

Methods	Study design: 8 weeks, double-blind, placebo-controlled trial, parallel groups, individual randomisation
Participants	<p>Diagnosis: DSM-III-R criteria for panic disorder with or without agoraphobia</p> <p>Method of diagnosis: SCID</p> <p>Age (years): fluvoxamine arm mean age 35.1 (SD = 10.4), CBT arm mean age 38.7 (SD = 12.4) and placebo arm mean age 37.0 (SD = 9.9)</p> <p>Sex: 22 men, 53 women</p> <p>Location: outpatient setting, multicentre, USA</p> <p>Co-morbidities: patients with a diagnosis of major depression were also included, medical comorbidities were excluded</p> <p>Rescue medication: not allowed</p>
Interventions	<p>Participants were randomly assigned to either:</p> <ol style="list-style-type: none"> 1. fluvoxamine arm (randomised n = 25) Duration: 8 weeks Treatment protocol: flexible dosage; range = up to 300 mg per day, mean 230 mg (4.6 cps)/day 2. CBT arm (randomised n = 25) Duration: 8 weeks Treatment protocol: psychotherapy sessions 3. placebo arm (randomised n = 25) Duration: 8 weeks Treatment protocol: flexible dosage, 5.5 cps/day
Outcomes	<p>Timepoints for assessment: at baseline and then at week 4 and 8</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. number and severity of attacks 2. CAS 3. CGI 4. SDS 5. MADRS
Notes	<p>Date of study: not specified</p> <p>Funding source: financed by a drug company</p> <p>Declarations of interest among the primary researchers: unclear</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to the drug study (n=50) or to the cognitive therapy (n=25) [...]". The sequence generation process is not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "Investigators and subjects remained "blind" to this assignment (ie, fluvoxamine vs placebo)". However, procedures for ensuring the concealment of allocation are not discussed.
Blinding of participants and personnel	Unclear risk	Quote: "Medications [...] were administered in a double-blind fashion". However, procedures for ensuring the blinding are not discussed.

(performance bias) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Assessments were made by the project coordinator (JG) or a psychiatrist (DWB or RW)". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rate: fluvoxamine group 4/25 (16%), placebo group 7/25 (28%). The rate of dropouts in the placebo group was higher than in the fluvoxamine group, and reasons for leaving the study early are unbalanced, particularly considering dropouts for ineffectiveness. In the "statistical analysis" paragraph both "completer analysis" and ITT analysis with a "last observation carried forward" approach are mentioned, however it is not clear which one has been employed for data reported in tables, since the number of analysed participants is not reported.
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes are not clearly pre-specified in the text. Data from all the rating scales are clearly reported in graphs, with the exception of the frequency of panic attacks.
Other bias	High risk	Quote: "The study was sponsored in part through a grant from Reid-Rowell Pharmaceuticals Inc, Atlanta, Ga". The role of the funder in planning, conducting and writing the study is not discussed.

Bradweijn 2005

Study characteristics

Methods	Study design: 10 weeks, flexible dose, double-blind, randomised (individual randomisation), parallel groups, placebo-controlled study
Participants	Diagnosis: DSM-IV panic disorder with or without agoraphobia Method of diagnosis: DSM-IV and modified Mini International Neuropsychiatric Interview Age (years): 38.9 (SD = 12.4) for the venlafaxine ER arm and 38.8 (SD = 12.1) for the placebo arm Sex: venlafaxine arm, 61 men and 99 women; placebo arm, 69 men, 99 women Location: outpatient setting, 50 sites in Canada, Europe and South Africa Co-morbidities: excluded Rescue medication: not allowed
Interventions	Participants were randomly assigned to either: 1. venlafaxine ER arm (randomised n = 181) Duration: 10 weeks Treatment protocol: flexible dosage; range = 75-225 mg/day, mean = 162.9 mg/day (SD = 60.6) at week 10 2. placebo arm (randomised n = 180) Duration: 10 weeks Treatment protocol: flexible dosage; range = 1-3 capsules
Outcomes	Timepoints for assessment: at baseline and then at 2, 3, 4, 6,8 and 10 weeks Outcomes: 1. PAAS 2. CGI-S 3. CGI-I 4. Phobia Scale (Fear and Avoidance) 5. Covi Anxiety scale 6. Q-LES-Q 7. SDS 8. report of adverse effects 9. physical examinations
Notes	Date of study: not specified Funding source: the study was funded by the company marketing the drug Declarations of interest among the primary researchers: the primary researcher received a funding from drug companies for the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as "randomised". No further info about the random sequence generation is provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is described as double blind but it is unclear whether the investigators were "blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study is described as double blind but it is unclear whether the investigators were "blind".

Incomplete outcome data (attrition bias) All outcomes	High risk	The dropout rate is over 25% and it is reported in the flow chart of the study. The study authors used ITT analysis.
Selective reporting (reporting bias)	Low risk	The results are clearly reported in the tables and in the text.
Other bias	High risk	The study was funded by the company marketing the drug. The primary researcher received funding from drug companies for the study.

Brooks 1998

Study characteristics		
Methods	Study design: 10 weeks, placebo-controlled study, parallel groups, individual randomisation	
Participants	<p>Diagnosis: DSM-III-R and ICD-10 criteria diagnosis of panic disorder and agoraphobia</p> <p>Method of diagnosis: SCID for DSM-III-R</p> <p>Age (years): 18-50; exercise arm mean age 31.8 (SD = 9.5), clomipramine arm mean age 33.9 (SD = 9.2) and placebo arm mean age 34.8 (SD = 6.8)</p> <p>Sex: 23 men, 23 women</p> <p>Location: outpatient setting, Germany</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: promethazine 25-50 mg</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. clomipramine arm (randomised n = 15)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: fixed dosage; range = 37.5-112.5 mg/day</p> <p>2. aerobic exercise-running arm (randomised n = 16)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: running schedule</p> <p>3. placebo arm (randomised n = 15)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: fixed dosage</p>	
Outcomes	<p>Timepoints for assessment: at baseline and then at 10 weeks</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. HAMA 2. Panic & Agoraphobia Scale 3. CGI 4. FQ 5. Beck Anxiety Inventory 6. BDI 7. MADRS 	
Notes	<p>Date of study: unclear</p> <p>Funding source: grant from a car factory</p> <p>Declarations of interest among the primary researchers: none</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The sequence generation process is not described. Moreover the randomisation procedure was divided in 2 steps, quote: "At baseline, patients were randomly assigned to the clomipramine/placebo group (n = 30) or the exercise group (n = 6). The study therapists (A.B., G.P., and A.G.) were not blind to this assignment. Patients in the drug group were further randomly assigned to receive either clomipramine (n = 15) or placebo (n = 15). The assignment was done by the hospital pharmacist; investigators and subjects remained blind to this assignment". This may have altered the balance between the 3 arms, which are however described as comparable.
Allocation concealment (selection bias)	Unclear risk	Selection bias is likely to have occurred due to the lack of description of the sequence generation process and the division of the randomisation procedure.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: exercise group 5/16 (31.2%); clomipramine group 0/15 (0%); placebo group 4/15 (26.7%). Dropout rates are high for 2 groups, with reasons for leaving the study apparently balanced. An ITT analysis was performed and data were imputed with a LOCF approach.
Selective reporting (reporting bias)	Low risk	All relevant outcomes are clearly reported in tables.
Other bias	Low risk	Supported by a grant from a car factory so it is unlikely that a sponsorship bias might have occurred.

Bystritsky 1994

Study characteristics		
Methods	Study design: Randomised controlled trial	
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: Not stated</p> <p>Age: average age of 37 years, no between-group differences</p> <p>Sex: 12 males and 9 females, no between-group differences</p> <p>Location: USA; setting unclear</p> <p>Co-morbidities: lack of significant drug or alcohol history or significant medical illness; patients that had an additional diagnosis of major depression (MD) or generalised anxiety disorder (GAD) were allowed to participate only if they presented a predominant picture of panic disorder and if panic symptoms preceded the onset of the current episode of MD or GAD</p> <p>Rescue medication: Not stated.</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) desipramine arm (n = 11)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible dosage; range = 10 - 300 mg, M = 110, SD = 49</p> <p>(2) fluoxetine arm (n = 11)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible dosage; range = 2.5 - 60 mg, M = 19, SD = 10</p>	
Outcomes	<p>Time points for assessment: weekly</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Hamilton Rating Scale for Anxiety (HAMA) 2. Hamilton Rating Scales for Depression (HAM-D) 3. Four Dimensional Anxiety Scale 4. Clinical Global Impression-Severity of Illness (CGI-S) 5. Clinical Global Impression-Improvement (CGI-I) 	
Notes	<p>Date of study: Not stated</p> <p>Funding source: this research has been supported in part by NIMH grant MH 45342-02 and by an NPI Opportunity Grant</p> <p>Declarations of interest among the primary researchers: None.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "they were assigned randomly". No further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both patients and investigators were blind to the assignment"; "patients were administered identical capsules labeled A, B or C: Capsules A, containing 2,5 mg of fluoxetine or 10 mg of desipramine were administered for one week [...], capsules B (containing) 25 mg of desipramine or 5 mg of fluoxetine, (capsules) C (containing) 50 mg of desipramine or 10 mg of fluoxetine".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both patients and investigators were blind to the assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Unclear risk	Quote: "this research has been supported in part by NIMH grant MH 45342-02 and by an NPI Opportunity Grant".

Caillard 1999

Study characteristics		
Methods	Study design: 8 weeks, multicentre, randomised (individual randomisation), parallel groups, double-blind, three arms, placebo-controlled trial	
Participants	<p>Diagnosis: DSM-III-R criteria for panic disorder with or without agoraphobia</p> <p>Method of diagnosis: participants had to fulfil the DSM-III-R criteria for panic disorder, with a minimum score of 20 on the HAMA), and a minimum of 5 points for the 2 first items (anxious mood and tension), after the 1-week, single-blind period</p> <p>Age (years): clomipramine low-dose arm mean age 38 (SD = 10), clomipramine high-dose arm mean age 35.5 (SD = 11) and placebo arm mean age 37 (SD = 10)</p> <p>Sex: 64 men, 94 women</p> <p>Location: outpatient setting, multicentre (15 sites in France)</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: not allowed</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. clomipramine low-dose arm (randomised n = 61)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage; 60 mg/day</p> <p>2. clomipramine high-dose arm (randomised n = 62)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage; 150 mg/day</p> <p>3. Placebo arm (randomised n = 57)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage</p>	
Outcomes	<p>Timepoints for assessment: at baseline and weekly</p> <p>Outcomes:</p> <ol style="list-style-type: none"> HAMA CGI HDRS 	
Notes	<p>Date of study: not specified</p> <p>Funding source: the sponsor is the drug company marketing clomipramine</p> <p>Declarations of interest among the primary researchers: unclear</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, however details on the sequence generation process are not provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts: clomipramine "low dose" group 15/61 (25%); clomipramine "high dose" group 22/62 (37%); placebo 25/57 (45%). Dropout rates are high (more than 20%), unbalanced between groups both in number and in terms of reasons for leaving the study early. The intention-to-treat analysis included all 180 randomised participants and was applied only for categorical data. Instead, only participants who strictly observed the protocol were included in the explanatory analysis. However, according to Table 2, not all randomised participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Quote: "The aim of this study was to investigate the dose-response relationship for clomipramine in patients with panic disorder [...]". However, the primary outcome measure and time-point employed are not clearly reported. All relevant data are reported in the text and tables.
Other bias	High risk	Quote: "This study was supported in part by the NOVARTIS Company and by the French University Antidepressant Group". The role of the funder in planning, conducting and writing the study is not discussed.

Carter 1995

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM-III-R Panic disorder with agoraphobia

	<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	<p>Participants were randomly assigned to either:</p> <p>(1) Adinazolam SR 30 mg (n = 79)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: fixed dose: 30 mg</p> <p>(2) Adinazolam SR 60 mg (n = 81)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: fixed dose: 60 mg</p> <p>(3) Adinazolam SR 90 mg (n = 72)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: fixed dose: 90 mg</p> <p>(4) Placebo (n = 83)</p> <p>Duration: 4 weeks</p>	
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 provided.
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.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only modified ITT (1 post-baseline 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 1992

Study characteristics

Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia)</p> <p>Method of diagnosis: "patients were evaluated by Structured Clinical Interview for DSM-III Diagnosis, Upjohn (SCID-UP)</p> <p>Age: M = 34, SD not provided</p> <p>Sex: 62 % female, 38 % male</p> <p>Location: 12 centres in USA, Spain, Denmark, Germany, England, Italy, Brazil, Mexico, France, Colombia, Austria, Sweden, Canada, Belgium; setting: inpatients and outpatients</p>

	<p>Co-morbidities: patients with psychotic disorders, dementia, bipolar disorder, alcoholism or drug abuse within the last six months or significant medical problems were excluded. Patients with current major depression were excluded unless the depression was judged to be secondary to the anxiety disorder and did not have melancholic or psychotic features.</p> <p>Rescue medication: Quote "patients taking CNS drugs, including benzodiazepines, were excluded from the study. During the washout period, blood was drawn for benzodiazepines screening".</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) imipramine arm (n = 391)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 25 - 250 mg, M = 155, SD not provided</p> <p>(2) alprazolam arm (n = 386)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 - 10 mg, M = 5.7, SD not provided</p> <p>(3) placebo arm (n = 391)</p> <p>Duration: 8 weeks</p>	
Outcomes	<p>Time points for assessment: baseline, weekly, endpoint</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Physician's and patient's global improvement scales 2. Panic Attack Scale, patient's diary 3. Overall Phobia Scale (Marks & Matthews), Phobic Anxiety Factor of the Symptom Check List (SCL-90) 4. anticipatory anxiety 5. Hamilton Rating Scale for Anxiety (HAMA) 6. social functioning, five-point scale 7. Hamilton Rating Scale for Depression (HRSD) 8. Hopkins SCL-90 patient self-rating scale for presence and intensity of symptoms 	
Notes	<p>Date of study: Data collection: 1984 - 1987</p> <p>Funding source: sponsored by Upjohn Company, Kalamazoo, Michigan</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: "randomly assigned"; "alprazolam, imipramine or placebo were assigned in 12 randomization blocks of the basic three cell random-assignment, parallel treatment-design. [...] At each center patients were blindly and randomly assigned to alprazolam, imipramine or placebo treatment, based on a table of random numbers [...]. Patients removed from the protocol before three weeks had to be replaced; after three weeks, non-completers were not replaced." No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote "double-blind design". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote "double-blind design". No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "of 1168 patients randomized, 1122 met criteria for ITT". No further information provided.
Selective reporting (reporting bias)	High risk	In the primary publication, data on Panic Attack scale are not reported; data on Physician's global Improvement scale are only partially reported, and without the number of patients evaluated; data on other continuous outcomes (HAMA, HRSD) are reported without number of patients evaluated. Other data are partially reported in secondary publication of this study.
Other bias	High risk	Sponsored by Upjohn Company, Kalamazoo, Michigan; the role of the funder in planning, conducting and writing the study is not discussed.

Davidson 1994

Study characteristics	
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> <p>Age: Adinazolam: mean = 36.1 (SD = 10.8); Placebo: mean = 35.5 (SD = 8.9)</p> <p>Sex: Adinazolam: M = 34%, F = 66%; Placebo: M = 33%, F = 67%</p>

	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	Participants were randomly assigned to either: (1) Adinazolam SR (n = 99) Duration: 4 weeks Treatment protocol: flexible dosage; mean = 84.1 (SD = 28.6); range = 3.5 to 7.5 capsules (2) Placebo (n = 103) Duration: 4 weeks Treatment protocol: flexible; mean = 92.3 (SD = 27.3 mg equivalents); range = 4 to 8 tablets	
Outcomes	Time points for assessment: baseline, weeks 1, 2, 4 Primary outcomes: (1) Overall improvement: CGI (2) Frequency/duration/intensity of panic attacks: Sheehan Panic and Anxiety Attack Scale (3) Agoraphobia: Phobia Severity Scale; SCL-90, phobic cluster Secondary outcomes: (1) Anxiety: HAMA; Sheehan Clinician Rated Anxiety Scale (2) Impairment: Sheehan Disability Scale (3) The main phobia of the Phobia Severity Scale	
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: "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 provided.
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 dropout 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

Den Boer 1988

Study characteristics

Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM-III panic disorder without phobic avoidance or panic disorder with severe phobic avoidance behaviour Method of diagnosis: Not stated Age: for maprotiline, M = 35.0 (SD = 7.4); for fluvoxamine, M = 37.3 (SD = 10.6) Sex: for maprotiline, 4 males and 20 females; for fluvoxamine 5 males and 15 females Location: the Netherlands; setting: outpatients Co-morbidities: patients with major affective disorders, schizophrenia, other psychotic disorder or significant medical problems were excluded Rescue medication: Not stated
Interventions	Participants were randomly assigned to either: (1) maprotiline arm ("24 patients were included in the maprotiline group")

	<p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 50 - 150 mg, M and SD not provided (2) fluvoxamine arm ("20 patients were included in the fluvoxamine group")</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 50 - 150 mg, M and SD not provided</p>
Outcomes	<p>Time points for assessment: baseline and weekly</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. SCL-90 2. State Anxiety Inventory (A-STATE) 3. Self Rating Depression Scale (SDS) 4. Hamilton Anxiety Scale (HAS) 5. Hamilton Depression Scale (HDS) 6. panic attack inventory 7. side-effects scale
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: "they were randomly allocated". No further details.
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.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote "double-blind treatment". No further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of patients randomised per group not reported (number of total randomised patients = 47); only number of patients evaluated per group was available, respectively 24 in maprotiline group and 20 in fluvoxamine.
Selective reporting (reporting bias)	High risk	Continuous outcome data are reported only in graphs.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Den Boer 1990

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R</p> <p>Method of diagnosis: not stated</p> <p>Age: for fluvoxamine M = 37, for ritanserin M = 35, for placebo M = 37</p> <p>Sex: the female to male ratio was almost 3 to 1 in all groups</p> <p>Location: the Netherlands; setting: outpatients</p> <p>Co-morbidities: patients with a primary diagnosis other than panic disorder were excluded</p> <p>Rescue medication: none</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) fluvoxamine arm</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage = 150 mg</p> <p>(2) ritanserin arm</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage = 20 mg</p> <p>(3) placebo arm</p> <p>Duration: 8 weeks</p> <p>Total number of randomised patients = 60. The number of patients randomised for each arm is not provided.</p>
Outcomes	<p>Time points for assessment: baseline, weekly</p> <p>Outcomes:</p>

	<ol style="list-style-type: none"> 1. SCL-90 2. Hamilton Rating Scale for Anxiety (HAMA) 3. State-Trait Anxiety Inventory (STAI) 4. Fear Questionnaire (FQ) 5. panic inventory 	
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: "randomised". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided about management of incomplete outcome data.
Selective reporting (reporting bias)	High risk	Data are reported in graphs (HAMA, FQ); other data only partially reported.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Gentil 1993

Study characteristics

Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: semi-structured interview</p> <p>Age: for imipramine, M = 36.35 (SEM = 2.12); for clomipramine, M = 34.1 (SEM = 1.89)</p> <p>Sex: for imipramine, 70% women, 30% men; for clomipramine 50% women, 50% men</p> <p>Location: Brazil; setting: outpatients</p> <p>Co-morbidities: patients with other medical condition, drug abuse, OCD, primary major depression or psychoses were excluded; major depression without melancholia, secondary to panic disorder, could still be included</p> <p>Rescue medication: Not stated</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) imipramine arm (n = 20)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 25 - 200 mg, M = 113.8, SD = 9.5</p> <p>(2) clomipramine arm (n = 20)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 10 - 80 mg, M = 50, SD = 4.2</p> <p>(3) placebo arm (propranolol) (n = 20)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; M = 85.5, SD = 5.7</p>
Outcomes	<p>Time points for assessment: baseline, week 2, 4, 6 and 8</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Clinical Global Impression Scale (CGI) 2. Sheehan Anxiety Scales 3. Hamilton Rating Scale for Depression (HRSD) 4. Beck Depression Inventory (BDI)
Notes	<p>Date of study: Not stated</p> <p>Funding source: grants from FAPESP and FINEP, donations from Rhodia SA, Metalurgica Matarazzo, Itautec, Soft Consultoria an Industrias Bardella SPA, Fundacao Zerbini and Fundacao Faculdade de Medicina</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: "they were randomly allocated". Dropouts before completing the fourth week of treatment were replaced (therefore we considered only data before replacing: number of

		dropouts at fourth week). No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "double-blind treatment"; "Capsules were in the hospital pharmacy with tablets of the commercially available TCAs or propranolol (placebo) and filled up with lactose. The dose range of propranolol was selected to give mild to moderate peripheral anticholinergic effects".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "double-blind treatment"; "Capsules were in the hospital pharmacy with tablets of the commercially available TCAs or propranolol (placebo) and filled up with lactose. The dose range of propranolol was selected to give mild to moderate peripheral anticholinergic effects".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 patients left the trial before completing the first four weeks of treatment and were replaced. No information provided on incomplete outcome data management.
Selective reporting (reporting bias)	High risk	Data on the scales HAM-D and BDI not reported at endpoint. Data on the scales CGI and Sheehan are reported only in graphs; number of patients evaluated not specified.
Other bias	Low risk	Quote: "this study was not supported by the manufacturers of the drugs tested".

GSK 1994/04

Study characteristics

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> <p>Sex: Paroxetine: M = 28; Alprazolam: M = 29; Placebo: M = 23</p> <p>Location: 16 centres in the 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) Paroxetine (n = 77)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible dosage; range: 10 to 60 mg/day</p> <p>(2) Alprazolam (n = 77)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible dosage; range: 1 to 6 mg/day</p> <p>(3) Placebo (n = 72)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible</p>
Outcomes	<p>Time points for assessment: not stated</p> <p>Primary outcomes:</p> <p>(1) Percentage of participants having zero full panic attacks during the last 2 weeks of treatment phase</p> <p>(2) Mean change from baseline in the number of full panic attacks during the last 2 weeks of treatment phase</p> <p>(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</p> <p>(4) Overall improvement: CGI severity of illness score</p> <p>Secondary outcomes:</p> <p>(1) Mean number of full and limited symptoms (all) panic attacks, and full situational and full unexpected panic attacks, per 2-week period</p> <p>(2) Mean intensity of all and full panic attacks per 2-week period</p> <p>(3) Per cent of time engaged in, and intensity of, anticipatory anxiety per 2 weeks</p> <p>(4) Agoraphobia: Marks Sheehan Phobia Scale, Fear and Avoidance Scores</p> <p>(5) Overall improvement: CGI Global improvement score</p> <p>(6) Anxiety: HAMA</p> <p>(7) Depression: MADRS</p> <p>(8) Disability: Sheehan Disability Scale, Social Adjustment Self-Report Scale</p>
Notes	<p>Date of study: November 1992 to April 1994</p> <p>Funding source: GlaxoSmithKline</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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
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	Low risk	No evidence of other bias was found.

GSK 29060 525

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: Panic disorder; no further details provided</p> <p>Method of diagnosis: Not stated</p> <p>Age: for paroxetine, M = 37.12 (SD = 9.92); for clomipramine, M = 40.13 (SD = 11.34)</p> <p>Sex: for paroxetine, 14 women, 23 men, 1 unknown; for clomipramine 17 women, 14 men</p> <p>Location: China; setting unclear</p> <p>Co-morbidities: patients with current major depression were excluded. No other co-morbidities mentioned</p> <p>Rescue medication: Not stated</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) paroxetine arm (n = 38)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible dosage; range = 10 - 50 mg, M and SD not provided</p> <p>(2) clomipramine arm (n = 35)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: flexible dosage; range = 50 - 100 mg, M and SD not provided</p>
Outcomes	<p>Time points for assessment: baseline, endpoint (10 weeks)</p> <p>Outcomes:</p> <ol style="list-style-type: none"> mean change from baseline in the number of full panic attacks Hamilton Rating Scale for Anxiety (HAMA) Panic Associated Symptoms Scale Clinical Global Impression Severity of Illness Score (CGI-S) Patient Global Evaluation (PGE)
Notes	<p>Date of study: September 1998 to September 1999</p> <p>Funding source: GSK</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: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "ITT population consisted of all subjects who received treatment and have one post treatment evaluation". No further information provided.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by GSK; the role of the funder in planning, conducting and writing the study is not discussed.

Hoehn-Saric 1993

Study characteristics	
Methods	Study design: 8 weeks, double-blind, placebo-controlled outpatient clinical trial, parallel groups, individual randomisation
Participants	Diagnosis: DSM-III-R panic disorder with or without agoraphobia Method of diagnosis: SCID Age (years): mean age 38.0 (SD = 9.6) Sex: 16 men, 20 women Location: outpatient department at Johns Hopkins Hospital (Baltimore, Maryland, USA) Co-morbidities: excluded Rescue medication: not allowed
Interventions	Participants were randomly assigned to either: 1. fluvoxamine arm (randomised n = 25) Duration: 8 weeks Treatment protocol: flexible dosage; range = 100-300 mg/day, mean 206.8 mg/day 2. placebo arm (randomised n = 25) Duration: 8 weeks Treatment protocol: flexible dosage, mean = 5.6 cps/day
Outcomes	Timepoints for assessment: at baseline and then weekly until week 8 Outcomes: 1. CAS 2. MADRS 3. SDS 4. severity and the number of panic attacks/week
Notes	Date of study: not stated Funding source: cps of fluvoxamine or placebo were provided by the drug company marketing the drug Declarations of interest among the primary researchers: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The sequence generation procedure is not discussed. 50 patients were randomised (25 for each group), however only those who were still eligible after the single-blind phase took the medication. This procedure may have affected the effect of randomisation. The balance between the two arms is not discussed or reported in graphs.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts: fluvoxamine group 6/25 (24%); placebo group 7/25 (28%), which are high dropout rates. However, 25 is the number originally allocated to each arm (see above, selection bias). Among the original 50 participants, some (not clear how many) were excluded after a single-blind phase. 37 participants completed the study, however only those who had complete sets of data (36 participants) were analysed, which seems to be consistent with a 'per protocol' analysis.
Selective reporting (reporting bias)	High risk	Quote: "[...] we predicted that treatment with fluvoxamine would be more effective than placebo in reducing the frequency and severity of panic attacks". However, it is not clear which exactly is the primary outcome and how it was assessed. Mean scores and SDs are clearly reported for the baseline assessment (figure 1), but only graphically reported for weekly assessments.
Other bias	High risk	Cps of fluvoxamine or placebo were provided by Solvay Co. The role of the funder in planning and conducting the study is not discussed.

Holland 1999

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM-III-R panic disorder with or without agoraphobia Method of diagnosis: Not stated Age: for adinazolam, M = 36.5; for clomipramine, M = 35.8; SD not provided

	<p>Sex: for adinazolam, 36% male; for clomipramine 38% male</p> <p>Location: UK; setting unclear</p> <p>Co-morbidities: patients with psychiatric co-morbidities were excluded</p> <p>Rescue medication: Not stated</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) adinazolam arm (n = 166)</p> <p>Duration: 24 weeks</p> <p>Treatment protocol: flexible dosage; range = 30 - 90 mg, M and SD not provided</p> <p>(2) clomipramine arm (n = 149)</p> <p>Duration: 24 weeks</p> <p>Treatment protocol: flexible dosage; range = 50 - 150 mg, M and SD not provided</p>	
Outcomes	<p>Time points for assessment: weeks 1, 2, 4, 8, 12, 16, 20 and 24</p> <p>Outcomes:</p> <ol style="list-style-type: none"> total number of panic attacks (Panic Attack and Anticipatory Anxiety scale) Clinical Global Impression Improvement Score (CGI-I) SCL - 90, Phobic Anxiety Dimension Sheehan Disability Scale 	
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: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF data are reported, but without specifying number of patients evaluated.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported, but without specifying number of patients evaluated.
Other bias	Unclear risk	Authors' affiliations refer to pharmaceutical companies.

Johnston 1995

Study characteristics	
Methods	Study design: 28 weeks, placebo-controlled, double-blind clinical trial, parallel groups, individual randomisation
Participants	<p>Diagnosis: DSM-III agoraphobia</p> <p>Method of diagnosis: unclear</p> <p>Age (years): 18-70 (mean = 37, SD = 10)</p> <p>Sex: women</p> <p>Location: unclear</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: unclear</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. clomipramine arm (randomised n = 16)</p> <p>Duration: 28 weeks</p> <p>Treatment protocol: flexible/fixed dosage; range = 25-300 mg/day, mean = 68.3 mg/day (SD = 39.7)</p> <p>2. clomipramine + CBT arm (randomised n = 17)</p> <p>Duration: 28 weeks</p> <p>Treatment protocol: flexible dosage; range = 25-300 mg/day, mean = 133.3 mg/day (SD = 58.7)</p> <p>3. placebo arm (randomised n = 16)</p> <p>Duration: 28 weeks</p> <p>Treatment protocol: flexible/fixed dosage; range = 25-300 mg/day, mean = 154.41 mg/day (SD = 51.7)</p> <p>4. placebo + CBT (randomised n = 15)</p> <p>Duration: 28 weeks</p> <p>Treatment protocol: flexible/fixed dosage; range = 25-300 mg/day, mean = 139.3 mg/day (SD = 73.7)</p>

Outcomes	<p>Timepoints for assessment: at baseline, week 1, 2, 3, 4, and then at 4 weekly intervals thereafter for a total of 28 weeks</p> <p>Outcomes:</p> <p>Daily Anxiety Scale (self administered)</p> <p>behavioural diary (self administered)</p> <p>FQ</p> <p>Fear Survey Schedule III (FSS III)</p> <p>Social Adjustment Scale Self Report</p> <p>Symptom Check List (SCL-90)</p> <p>Gambrill-Richey Assertion Inventory (G-R)</p> <p>BAT (behavioural approach test)</p>
Notes	<p>Date of study: not specified</p> <p>Funding source: the drug was supplied by the drug company that produces it and by Health and Welfare Canada</p> <p>Declarations of interest among the primary researchers: none</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about the sequence generation is provided. Quote: "random sequential assignment of patients to each of the four groups was carried out"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the participants and the personnel administering the drug are described as blinded. Quote: "the study was double blind for medication status with the principal investigator, therapists and subjects being unaware of whether placebo or clomipramine was being administered to individuals" and "study medications were supplied in coded vials with sealed keys to be consulted in emergency".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors are described as blinded. Quote: "the study was double blind for medication status with the principal investigator, therapists and subjects being unaware of whether placebo or clomipramine was being administered to individuals".
Incomplete outcome data (attrition bias) All outcomes	High risk	The number of dropouts is reported and it seems that there were some significant differences between dropouts and participants. Quote: "mean scores on 45 of the 48 outcome and demographic measures were higher for the drop-out group than for those who completed the clinical trial".
Selective reporting (reporting bias)	Unclear risk	Data are only graphically reported (in box and whisker plot) so their interpretation is not easy. The only table reported doesn't specify the differences between clomipramine and placebo.
Other bias	High risk	The study was supported by the drug company marketing clomipramine.

Klosko 1990

Study characteristics

Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III -R 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) Alprazolam (n = 17)</p> <p>Duration: 15 weeks</p> <p>Treatment protocol: flexible dosage; mean = 4.60 (SD = 1.82)</p> <p>(2) Panic control treatment (PCT) (behaviour therapy treatment group) (n = 18)</p> <p>Duration: 15 weeks</p> <p>Treatment protocol: 15 individual sessions of an integrated CBT in weekly meetings</p> <p>(3) Waiting list (n = 16)</p> <p>Duration: 15 weeks</p> <p>Treatment protocol: no treatment</p> <p>(4) Placebo arm (n = 18)</p> <p>Duration: 15 weeks</p> <p>Treatment protocol: flexible dosage; mean = 5.08 (SD = 2.65)</p>

Outcomes	<p>Time points for assessment: clinical assessment before and after treatment; self monitoring measures throughout treatment</p> <p>Primary outcomes:</p> <p>(1) Anxiety episodes and panic attacks: diary</p> <p>(2) Anxiety: HAMA</p> <p>(3) Depression: HAMD</p> <p>(4) Global clinical severity ratings</p>	
Notes	<p>Date of study: not stated</p> <p>Funding source: This research was supported in part by a grant from the National Institute of Mental Health (MH-36800) and 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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
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 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.

Koszycki 2011

Study characteristics

Methods	<p>Study design: 12 weeks randomised (individual randomisation), parallel groups, double-blind, placebo-controlled, multicentre clinical trial. The "acute phase" lasted 12 weeks. Participants who showed adequate response were eligible to enter a 12-week extension treatment.</p>
Participants	<p>Diagnosis: DSM-IV criteria for panic disorder with or without agoraphobia</p> <p>Method of diagnosis: psychiatric interview and a Structured Clinical Interview for DSM-IV (SCID)</p> <p>Age (years): sertraline arm mean age 36.40 (SD = 10.0), placebo arm mean age 35.24 (SD = 9.9), sertraline + SCBT arm mean age 36.22 (SD = 10.9), placebo + SCBT arm mean age 36.80 (SD = 12.2)</p> <p>Sex: 90 men, 161 women</p> <p>Location: outpatient, 15 academic health centres in Canada</p> <p>Co-morbidities: "co-morbid depression, generalized anxiety disorder, social phobia, somatization disorder and specific phobia were allowed as long as these conditions were secondary to and not clinically more prominent than the PD with or without agoraphobia"</p> <p>Rescue medication: oxazepam up to 60 mg/week allowed. It was used at least once by the 55.9% of the participants and the weekly mean dose range was 24.8 mg/week (SD = 30.9) to 33.7 mg/week (SD = 18)</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. sertraline arm (randomised n = 63)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage; range = 25-200 mg/day, mean = 116.1 mg/day (SD = 59.6)</p>

	<p>2. sertraline + SCBT arm (randomised n = 61)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage; range = 25-200 mg/day, mean = 95.8 mg/day (SD = 57.6)</p> <p>3. placebo + SCBT arm (randomised n = 65)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage; mean = 138.3 mg/day (SD=59.5)</p> <p>4. placebo arm (randomised n = 62)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage, mean = 138.3 mg/day (SD = 59.5)</p>	
Outcomes	<p>Timepoints for assessment: at baseline at week 1, 2, 3, 4, 6, 8, 10 and 12</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. frequency of panic attacks and anticipatory anxiety 2. Mobility Inventory for Agoraphobia (MI-AAL) 3. Body Sensations Questionnaire (BSQ) and Agoraphobic Cognitions Questionnaire (ACQ) 4. SDS 5. CGI-S 6. CGI-I 	
Notes	<p>Date of study: not specified</p> <p>Funding source: the study was supported by the drug company marketing sertraline</p> <p>Declarations of interest among the primary researchers: one of the primary researchers declared a conflict of interest with several drug companies.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to one of four groups by a computer generated randomization code [...]".
Allocation concealment (selection bias)	Low risk	Quote: "Investigators at each site were provided with a sealed envelope that contained the identification of the study drug being administered to the patient. In a medical emergency, the investigator was authorized to break the code for that subject only".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and sertraline were provided as matching capsules and administered double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome assessments were made by investigators who were blind to allocation of the drug and who were not told whether the patient was assigned to SCBT. Patients were instructed not to divulge their SCBT assignment to the investigators".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: placebo arm (30.6%); sertraline arm (25.4%). Dropout rates are high. Reasons for leaving the study early are apparently balanced between groups, with the exception of adverse effects (9 in placebo arms versus 5 in antidepressant arm). An ITT was performed. Quote: "The mixed model methodology, as opposed to conventional repeated-measures ANOVA, allows all available observations on each patient to be used without having to use an imputation procedure such as last-observation carried forward". Only those who had no post-baseline assessment were excluded from the ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Data are poorly reported.
Other bias	High risk	The study was supported by the drug company marketing sertraline; the role of the funder in planning, conducting and writing the study is not discussed.

Krueger 1999

Study characteristics

Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM - III - R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: SCID Axis I, Roche edition</p> <p>Age: for moclobemide, M = 35.0 (SD = 8.9); for clomipramine, M = 36.0 (SD = 9.5)</p> <p>Sex: for moclobemide, 41.8% males, 58.2 females; for clomipramine 39.7% males, 60.3% females</p> <p>Location: Norway, Sweden, the Netherlands; setting unclear</p> <p>Co-morbidities: none, except of generalised anxiety disorders and social phobia of less than moderate severity</p> <p>Rescue medication: chloral hydrate as an occasional night time hypnotic</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) moclobemide arm (n = 67)</p>

	<p>Duration: 8 weeks</p> <p>Treatment protocol: fixed-flexible dosage, range = 300 - 600 mg, M and SD not provided (2) clomipramine arm (n = 68)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed-flexible dosage, range = 100 - 200 mg, M and SD not provided</p>
Outcomes	<p>Time points for assessment: week 1, 2, 4, and 8</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. number of panic attacks 2. Patients' Clinical Global Impression of Change (P-CGI-C) 3. Investigators' rating of Clinical Global Impression of the Severity of the patients' panic disorder (I-CGI-S) 4. Patients' rating of Clinical Global Impression of Severity (P-CGI-S) 6. Sheehan Disability Scale (SDS) 7. Hamilton Rating Scale for Anxiety (HAMA) 8. Montgomery-Åsberg Depression Rating Scale (MADRS)
Notes	<p>Date of study: Not stated</p> <p>Funding source: Hoffmann - La Roche</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: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "it was estimated that the ITT population with two-sided significance level of 0.05 and a power of at least 0.8 had to be at least 66 patients in each treatment group"; "the ITT population comprised 135 patients who had received treatment and at least one assessment after baseline".
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by Hoffmann-La Roche; the role of the funder in planning, conducting and writing the study is not discussed.

Lecrubier 1997

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: not stated</p> <p>Age: for paroxetine, M = 34.7 (SD = 9.3); for clomipramine, M = 35.1 (SD = 9.2)</p> <p>Sex: for paroxetine, 53 males, 70 females; for clomipramine 46 males, 75 females</p> <p>Location: 39 centres in Belgium, Denmark, France, Hungary, Ireland, Israel, Italy, the Netherlands, Norway, Spain, Switzerland, UK, Yugoslavia; setting: outpatients</p> <p>Co-morbidities: none</p> <p>Rescue medication: chloral hydrate for night time sedation allowed</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) paroxetine arm (n = 123)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage, range = 10 - 60 mg, M and SD not provided</p> <p>(2) clomipramine arm (n = 122)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage, range = 10 - 150 mg, M and SD not provided</p> <p>(3) placebo arm (n = 123)</p> <p>Duration: 12 weeks</p>
Outcomes	Time points for assessment: weeks 3, 6, 9, 12

	Outcomes: 1. change in number of panic attacks 2. proportion of subjects with zero panic attacks 3. proportion of subjects with a > 50% reduction in the number of panic attacks 4. change in intensity of panic attacks 5. Hamilton Rating Scale for Anxiety (HAMA) 6. Clinical Global Impression Scale (CGI) 7. Montgomery-Åsberg Depression Rating Scale (MADRS) 8. Mark Sheehan Phobia Scale 9. Patient Global Evaluation (PGE) 10. Sheehan Disability Scale	
Notes	Date of study: October 1991 - November 1993 Funding source: Sponsored by GSK Declarations of interest among the primary researchers: Department of Clinical Research, Development and Medical Affairs, SmithKline Beecham Pharmaceuticals	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the primary and secondary efficacy analysis were performed on the ITT population, which included all subjects who were randomized, who received their randomized treatment and for whom at least one assessment was available after active treatment. Safety assessment were performed on the ITT population. Dropouts rates were around 30% in both treatment arms."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by GSK; the role of the funder in planning, conducting and writing the study is not discussed.

Lepola 1990

Study characteristics	
Methods	Study design: Randomised controlled trial
Participants	Diagnosis: DSM-III panic disorder with or without agoraphobia Method of diagnosis: Not stated Age: M = 37.4, SD not provided Sex: not stated Location: Finland; setting: inpatients Co-morbidities: patients with psychiatric co-morbidities were excluded; medical co-morbidities are not mentioned; six patients suspected cases of epilepsy Rescue medication: "the patients did not receive any other treatment during the trial period"
Interventions	Participants were randomly assigned to either: (1) alprazolam arm (n = 27) Duration: 9 weeks Treatment Protocol: flexible dosage, range = 1.5 - 8 mg, M = 4.9, SD not provided (2) imipramine arm (n = 28) Duration: 9 weeks Treatment Protocol: flexible dosage, range = 30 - 225 mg, M = 130, SD not provided
Outcomes	Time points for assessment: baseline, 3 weeks, 9 weeks Outcomes: 1. panic attack frequency 2. Hamilton Rating Scale for Anxiety (HAMA)

	3. Montgomery-Åsberg Depression Rating Scale (MADRS) 4. seven-point evaluation scale of the clinical state (not better specified)	
Notes	Date of study: Not stated Funding source: Not stated Declarations of interest among the primary researchers: None (but authors' affiliations refer to pharmaceutical companies).	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Authors' affiliations refer to pharmaceutical companies.

Liebowitz 2009

Study characteristics		
Methods	Study design: 10 weeks, randomised (individual), parallel groups, double-blind, placebo-controlled, multicentre clinical trial	
Participants	Diagnosis: DSM-IV criteria for panic disorder with or without agoraphobia Method of diagnosis: not specified Age (years): venlafaxine ER arm mean age 36 (SD = 12.4) and placebo arm mean age 36.7 (SD = 12.0) Sex: 107 men, 203 women Location: outpatient setting, in 56 sites (7 in Canada and 49 in USA) Co-morbidities: people with a secondary major depression or GAD were eligible. Any other clinically significant Axis I or Axis II disorders, or HAM-D score ≥ 18 at baseline were excluded Rescue medication: unclear	
Interventions	Participants were randomly assigned to either: 1. venlafaxine ER arm (randomised n = 175) Duration: 10 weeks Treatment protocol: flexible dosage; range = 37.5 to 225 mg/day 2. placebo arm (randomised n = 168) Duration: 10 weeks Treatment protocol: flexible dosage	
Outcomes	Timepoints for assessment: at baseline and then at week 1, 2, 3, 4, 6, 8 and 10 Outcomes: <ol style="list-style-type: none"> 1. percentage of participants free of panic attacks, measured with the PAAS 2. PDSS 3. CGI-I 4. PAAS 5. HAMA 6. Phobia Scale 7. Q-LES-Q 8. SDS 	
Notes	Date of study: the study was conducted from April 2001-December 2002 Funding source: drug company marketing the drug is likely to have sponsored the study Declarations of interest among the primary researchers: declared	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as randomised, however the process of sequence generation is not clearly reported.

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is described as double-blind, however methods for ensuring blindness of both participants and who administered the intervention are not discussed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates: venlafaxine arm 55/175 (31.4%); placebo arm 43/168 (25.6%). Dropout rates are high in both arms and reasons for leaving the study early are apparently balanced, according with Figure 1. Quote: "The primary analysis population for efficacy variables was the intent-to-treat (ITT) population". However, as reported in Figure 1, the ITT population does not match with participants randomly assigned at baseline. Quote: "Patients in the ITT population were those who had a baseline PAAS evaluation and at least 1 double-blind, on-therapy evaluation of the primary efficacy variable during visits 3 to 10 and within 3 days of stopping the study medication before taper". This is consistent with an 'as treated' analysis. In the ITT population imputations were performed with a LOCF approach.
Selective reporting (reporting bias)	Low risk	The primary outcome measure is defined as "the percentage of patients free of full-symptom panic attacks as measured with the Panic and Anticipatory Anxiety Scale (PAAS)", however the precise time point of interest is not clearly specified. All relevant data are clearly reported in the text and tables.
Other bias	High risk	Quote: "This clinical trial and analysis were sponsored by Wyeth Research, Collegeville, Pa". No other details on the role of funder in planning and conducting the study are provided.

Londborg 1998

Study characteristics		
Methods	Study design: multisite, double-blind, parallel and fixed-dose design, randomised (individual randomisation) controlled trial	
Participants	<p>Diagnosis: DSM-III-R diagnosis of panic disorder with or without agoraphobia</p> <p>Method of diagnosis: SCID (Structured Clinical interview for DSM-III-R)</p> <p>Age (years): 18.9-74.5 (the average age of participants was 38.8 years)</p> <p>Sex: 53% men, 47% women</p> <p>Location: outpatient setting, 7 sites in USA (6 western USA and 1 in West Virginia)</p> <p>Co-morbidities: participants with a secondary diagnosis of an affective disorder, anxiety states including generalised anxiety disorder, social or simple phobia, obsessive-compulsive disorder or post-traumatic stress disorder or personality disorder were permitted to participate</p> <p>Rescue medication: choral hydrate for sleep</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. sertraline 50 mg arm (randomised n = 43)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage 50 mg/day</p> <p>2. sertraline 100 mg arm (randomised n = 44)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage 100 mg/day</p> <p>3. sertraline 200 mg arm (randomised n = 45)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage 200 mg/day</p> <p>3. placebo arm (randomised n = 45)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage, number of tablets not specified</p>	
Outcomes	<p>Timepoints for assessment: at the end of weeks 1, 2, 3, 4, 6, 8, 10 and 12</p> <p>Outcomes:</p> <p>1. PAAS</p> <p>2. HAMA</p> <p>3. CGI-S</p> <p>4. CGI-I</p>	
Notes	<p>Date of study: not specified</p> <p>Funding source: drug company marketing sertraline</p> <p>Declarations of interest among the primary researchers: RW is a Senior Associate Medical Director at the drug company marketing sertraline</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned by site, with a blocking factor of four". No further information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "the subjects were randomly assigned by site". No further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "study medication was taken with the evening meal as a single dose of two capsules contained in a blister pack". No further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The dropout rate is high (> 20%). Quote: "of the 177 safety-evaluable subjects, 63 (36%) withdrew from the study, 28 due to adverse experiences and 12 because of insufficient clinical response [...]" The difference among the groups was not statistically significant when subjects in the placebo group were compared with pooled subjects taking sertraline (31% and 37%)" The investigators used the LOCF. Quote: "parallel analyses of efficacy parameters were performed both for end-point with last observation carried forward"
Selective reporting (reporting bias)	Low risk	The data related to primary outcomes are reported in the text, in tables and graphs.
Other bias	High risk	The study was funded by the drug company marketing sertraline. RW is a Senior Associate Medical Director at the drug company marketing sertraline.

Lydiard 1992

Study characteristics

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) Alprazolam 2 mg (n = 30)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: fixed = 2 mg</p> <p>(2) Alprazolam 6 mg (n = 31)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: fixed = 6 mg</p> <p>(2) Placebo arm (n = 33)</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> <p>(4) Avoidance: 4-point scale</p> <p>(5) Anxiety: HAMA</p> <p>(6) Disability: 5-point Work and Social Disability Scale</p> <p>(7) Global improvement: 11-point scale</p> <p>Secondary outcome:</p> <p>(1) Adverse events</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	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
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	Low risk	No evidence of other bias was found.

Lydiard 1993

Study characteristics

Methods	Study design: 12-week, placebo-controlled, parallel groups, individual randomisation, double-blind study
Participants	Diagnosis: DSM-III-R diagnosis of panic disorder with or without agoraphobia Method of diagnosis: structured interview for DSM-III-R Age (years): DMI arm mean age = 38.1 SD = 6.9, placebo arm mean age = 35.1 SD = 1.3 Sex: sex distribution between the 2 arms is unclear Location: primary care setting, South Carolina (USA) Co-morbidities: excluded Rescue medication: apparently not permitted, but this is not explicit
Interventions	Participants were randomly assigned to either: 1. desipramine arm (randomised n = 28) Duration: 12 weeks Treatment protocol: flexible dosage; range = 50-200 mg/day, mean = 177 mg (SD = 81) 2. placebo arm (randomised n = 28) Duration: 12 weeks Treatment protocol: flexible dosage; range = 50-200 mg/day, mean = 242 mg/day (SD = 54)
Outcomes	Timepoints for assessment: at baseline, 8 and 12 weeks Outcomes: 1. HAMA 2. Phobia Scale 3. CGI-I
Notes	Date of study: not specified Funding source: unclear Declarations of interest among the primary researchers: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as "randomised", but no information about the random sequence generation is provided. Quote: "the patients were randomly assigned to either DMI or placebo".
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double blind", no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double blind", no further information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The dropout rate in the DMI group is around 7%, while the dropout rate in the placebo group is 39%, so it is high. Investigators used a data imputation technique. Quote: "we calculated the 12-week outcome for all patients completing at least 8 weeks' treatment by bringing the last observed value forward, expressing these as 12-week outcome".
Selective reporting (reporting bias)	Low risk	All the outcomes are reported in a table in a clear way.
Other bias	Unclear risk	It is unclear whether the study was funded by a drug company marketing desipramine or not. No declaration of interest is mentioned.

Michelson 2001

Study characteristics		
Methods	Study design: 12 weeks, randomised (individual randomisation), parallel groups, double-blind, placebo-controlled	
Participants	<p>Diagnosis: DSM-IV criteria for panic disorder with or without agoraphobia</p> <p>Method of diagnosis: SCID</p> <p>Age (years): mean age in fluoxetine arm 36.5 (SD = 10.3), mean age in placebo arm 34.8 (SD = 9.8)</p> <p>Sex: in fluoxetine arm 48% (n = 43) men, 52% (n = 47) women; in placebo arm 41% (n = 37) men, 59% (n = 53) women (overall number: 80 men and 100 women)</p> <p>Location: outpatients, psychiatric clinics, 9 sites in Europe</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: unclear</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. fluoxetine arm (randomised n = 90)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage; range = 20-60 mg/day, mean = 29.8 mg/day (SD is not specified)</p> <p>2. placebo arm (randomised n = 90)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: flexible dosage (the number of tablets is not specified)</p>	
Outcomes	<p>Time points for assessment: at baseline, 6, 12 weeks (endpoint)</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. PDSS 2. number of full panic attacks per week 3. CGI-S 4. HAMA 5. State Anxiety Inventory 6. HDRS 7. SDS 	
Notes	<p>Date of study: not reported in the primary publication</p> <p>Funding source: unclear</p> <p>Declarations of interest among the primary researchers: some authors are employees of the company marketing the drug, others are paid consultants</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is reported as randomised, but no information is provided about the random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described just as quote: "double blind trial". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>The dropout rate is reported in the text. Quote: "among randomised patients, the number of patients reaching the final visit after 12 weeks of fluoxetine or placebo therapy was similar for both groups (fluoxetine n = 75, 83.3%); placebo n = 80 (88.8%). The total number of discontinuations due to adverse effects was similar for both groups (fluoxetine n = 5, 5.5%), (placebo n = 3, 3.3%)... other reasons for discontinuation included lack of efficacy (fluoxetine n = 5, 5.5%), (placebo n = 3, 3.3%)... patients lost to follow up... patient decision... and protocol requirement..."</p> <p>Despite the dropouts the groups still seem comparable.</p> <p>Data imputation was performed (ITT analysis).</p>
Selective reporting (reporting bias)	Low risk	The data of all the outcome measures are clearly reported in tables as mean scores and mean changes from baseline. Standard deviations are specified.
Other bias	High risk	Sponsorship bias: some study authors are employees of the company marketing the drug, other are paid consultants.

Moroz 1999

Study characteristics		
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 and a psychiatric interview</p> <p>Age: Clonazepam: mean = 36.7 (SD = 11.3); Placebo: mean = 36.8 (SD = 11.4)</p> <p>Sex: Clonazepam: F = 141, M = 81; Placebo: F = 140, M = 76</p> <p>Location: not stated (USA); setting: outpatients</p> <p>Comorbidities: psychiatric (major depression, social phobia, obsessive-compulsive disorder, generalised anxiety disorder) were excluded.</p> <p>Rescue medication: none</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Clonazepam (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) Placebo (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, HAMD: 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	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
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	High 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 1989

Study characteristics	
Methods	Study design: Randomised controlled trial
Participants	<p>Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks</p> <p>Method of diagnosis: not stated</p> <p>Age: mean = 31 (range = 18 to 62)</p>

	<p>Sex: M = 17; F = 38</p> <p>Location: California, USA (psychiatric outpatients clinic)</p> <p>Comorbidities: not stated</p> <p>Rescue medication: none</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Alprazolam (n = 20)</p> <p>Duration: 5 weeks</p> <p>Treatment protocol: flexible dosage; range = 1.5 to 6 mg, mean = 3.62 (7.24 capsules, SD = 4.09)</p> <p>(2) Placebo (n = 21)</p> <p>Duration: 5 weeks</p> <p>Treatment protocol: flexible; mean = 9.90 capsules, SD = 3.74</p>	
Outcomes	<p>Time points for assessment: weekly</p> <p>Primary outcomes:</p> <p>(1) Panic: Panic and Anxiety Attack Scales (Sheehan)</p> <p>(2) Avoidance: Phobia Scale (Marks-Sheehan)</p> <p>(3) Anxiety: HAMA</p> <p>(4) Depression: HAMD</p> <p>Secondary outcome:</p> <p>(1) Adverse events: Side Effects Checklist</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	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
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	Low risk	No evidence of other bias was found.

Nair 1996

Study characteristics

Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: not stated</p> <p>Age: for fluvoxamine, M = 34.5; for imipramine, M = 34.5, SD not provided</p> <p>Sex: for fluvoxamine 56% females 44% males; for imipramine 50% females 50% males</p> <p>Location: Canada; setting: outpatients</p> <p>Co-morbidities: patients with a history of bipolar disorder, organic brain syndrome, schizophrenia or other psychotic disorders were excluded</p> <p>Rescue medication: oxazepam up to 60 mg daily or chloral hydrate up to 2000 mg daily were permitted during first four weeks of treatment</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) fluvoxamine arm (n = 50)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage, range = 50 - 300 mg, M = 171.4, SD not provided</p> <p>(2) imipramine arm (n = 48)</p> <p>Duration: 8 weeks</p>

	Treatment protocol: flexible dosage, range = 50 - 300 mg, M = 164.7, SD not provided (3) placebo arm (n = 50) Duration: 8 weeks	
Outcomes	Time points for assessment: weekly Outcomes: 1. Sheehan Panic and Anticipatory Anxiety Scale 2. Clinical Global Impression Scale (CGI) 3. Montgomery-Åsberg Depression Rating Scale (MADRS) 4. Sheehan Disability Scale (SDS) 5. Sheehan Panic Attack Diary (intensity and number of panic attacks) 6. Sheehan Phobia Scale 7. Hopkins Symptom Checklist	
Notes	Date of study: Not stated Funding source: Orto McNeil Ltd. 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: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study medication was in the form of identically appearing capsules each containing either placebo, 50 mg of fluvoxamine or 50 mg of imipramine".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the study medication was in the form of identically appearing capsules each containing either placebo, 50 mg of fluvoxamine or 50 mg of imipramine".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "two patient samples were identified for analysis and reporting purposes prior to unblinding: an all patients analysis and an ITT. The all patients sample was defined as those randomised to double blind treatment and who provided at least some drug safety and tolerance data [...] the main efficacy analysis of the study was based on the LOCF of the ITT sample".
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by Orto McNeil Ltd; the role of the funder in planning, conducting and writing the study is not discussed.

Noyes 1996

Study characteristics

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 Age: M = 36.6; SD = 10.5 Sex: women = 157, men = 84 Location: USA, Australia; setting: outpatients Co-morbidities: patients with major psychiatric co-morbidities, head trauma or seizures were excluded Rescue medication: none
Interventions	Participants were randomly assigned to either: (1) diazepam arm (n = 81) Duration: 8 weeks Treatment protocol: flexible dosage, range = 10 - 100 mg, M = 43, SD not provided (2) alprazolam arm (n = 78) Duration: 8 weeks Treatment protocol: flexible dosage, range = 1 - 10 mg, M = 4.9, SD not provided (3) placebo arm (n = 79) Duration: 8 weeks
Outcomes	Time points for assessment: baseline, 4 weeks, 8 weeks Outcomes: 1. frequency of panic attacks

	<ol style="list-style-type: none"> 2. Sheehan Self Rated Scale for Anxiety 3. Hamilton Rating Scale for Anxiety (HAMA) 4. Marks and Mathews Agoraphobia Scale 5. Profile of Mood States 6. Hamilton Rating Scale for Depression (HRSD) 7. Work and Social Disability Scale 8. Systematic Assessment for Treatment-Emergent Events 	
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	Quote: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "to examine differences in treatment groups over time we completed ITT analysis using logistic regression procedures. The results of analysis using the completer sample were very similar to those using the III subjects".
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Supported by a grant from the Upjohn Company; the role of the funder in planning, conducting and writing the study is not discussed.

Pecknold 1994

Study characteristics

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) Alprazolam CT (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) Alprazolam XR (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) Placebo (n = 70*)</p> <p>Duration: 6 weeks</p> <p>Treatment protocol: flexible dosage; range = 2 to 7(?) mg; mean = 5.46 (SD = 2.26)</p> <p>*The number of participants in the different arms is inconsistently reported. We used the number of participants of the LOCF analyses.</p>
Outcomes	<p>Time points for assessment: at baseline and weekly thereafter for 6 weeks</p> <p>Primary outcomes:</p> <ol style="list-style-type: none"> (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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
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"
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	High risk	The study was supported by the Upjohn Company.

Pfizer 2008

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	Diagnosis: Panic disorder with or without agoraphobia according to DSM IV Method of diagnosis: no information provided Age: range = 18 - 64 years, mean and SD not provided Sex: sertraline: female = 113, male = 44; paroxetine: female = 109, male = 53 Location: Japan; setting unclear Co-morbidities: "patients with bipolar disorder, schizophrenia, delusional disorder, epilepsy, MDD, OCD, seasonal affective disorder or GAD were excluded; patients who concurrently have depression/depressive state, anxiety disorder and generalized anxiety disorder may be included if the primary diagnosis is identified to be panic disorder" Rescue medication: none
Interventions	Participants were randomly assigned to either: (1) sertraline arm (n = 157) Duration: 12 weeks Treatment protocol: flexible dosage, range = 25 - 100 mg (2) paroxetine arm (n = 164) Duration: 12 weeks Treatment protocol: flexible dosage, range = 10 - 30 mg
Outcomes	Time points for assessment: Outcomes: 1. Panic and Agoraphobia Scale 2. Clinical Global Impression Improvement Score (CGI-I) 3. frequency of panic attacks 4. Hamilton Rating Scale for Anxiety (HAMA)

Notes	Date of study: May 2008 - February 2010 Funding source: Pfizer 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: "Allocation: randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Masking: double-blind (subject, investigator)".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Masking: double-blind (subject, investigator)".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Last Observation Carried Forward". No further information provided.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by Pfizer; the role of the funder in planning, conducting and writing the study is not discussed.

Pohl 1989b

Study characteristics		
Methods	Study design: 8 weeks, randomised controlled trial, individual randomisation, parallel groups	
Participants	Diagnosis: DSM-III Panic disorder or agoraphobia with panic attacks Method of diagnosis: not stated Age (years): for buspirone, mean = 31.1 (SD = 2.1); for placebo, mean = 31.6 (SD = 2.2); for imipramine, M = 29.2 (SD = 2.2) Sex: for buspirone, 44% women, 56% men; for placebo 50% women, 50% men Location: outpatients, USA Co-morbidities: excluded Rescue medication: none	
Interventions	Participants were randomly assigned to either: 1. buspirone arm (randomised n = 18) Duration: 8 weeks Treatment protocol: flexible dosage; range = 10-60 mg, mean = 29.5 (SD = 4.0) 2. imipramine arm (randomised n = 20) Duration: 8 weeks Treatment protocol: flexible dosage; range = 50-300 mg, mean = 140 (SD = 17.5) 3. placebo arm (randomised n = 22) Duration: 8 weeks Treatment protocol: flexible	
Outcomes	Timepoints for assessment: weekly for the first 4 weeks, and biweekly for the last 4 weeks Outcomes: 1. 7-point scale for the degree of global psychopathology 2. CGI-I 3. Global phobic disability 4. Symptom Check List (SCL-90) 5. HAMA	
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 eligible patients were randomized to 8 weeks of double-blind treatment with buspirone, imipramine or placebo following an initial 4-7 days of single blind placebo wash-out." No further details about randomisation are provided
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules were used.

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of the assessors is not described even though the trial is described as "double blind".
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rate.
Selective reporting (reporting bias)	High risk	The measures of primary outcome are specified in the text (in the "efficacy measures" chapter under the "methods" section) but the results are reported in graphs and not in a table or in the text as numbers.
Other bias	Unclear risk	No information is provided about a possible sponsorship of the study.

Pollack 1998

Study characteristics		
Methods	Study design: 10 weeks, flexible dose, multicentre trial, random assignment (individual), parallel groups, placebo-controlled	
Participants	Diagnosis: DSM-III-R criteria for panic disorder with or without agoraphobia Method of diagnosis: SCID Age (years): mean age in sertraline arm 37.8 (SD = 11.6), mean age in placebo arm 34.9 (SD = 9.6) Sex: 115 women, 63 men Location: outpatient setting, 10 sites, USA and Brazil Co-morbidities: "patients with comorbid dystimic, personality, or other anxiety disorders could be included if the panic disorder was judged to be the principal diagnosis" Rescue medication: not allowed	
Interventions	Participants were randomly assigned to either: 1. sertraline arm (randomised n = 88) Duration: 10 weeks Treatment protocol: flexible dose, range 25-200 mg/day, mean 118.1 mg/day (SD = 62.9) 2. placebo arm (randomised n = 88) Duration: 10 weeks Treatment protocol: flexible dose, range unknown, mean 147.5 mg/day (SD = 55.5)	
Outcomes	Timepoints for assessment: at baseline and at weeks 1, 2, 3, 4, 6, 8 and 10 Outcomes: <ol style="list-style-type: none"> 1. Sheehan PAAS 2. CGI-S 3. CGI-I 4. PGE 5. PDSS 6. HAMA 7. Hamilton Rating Scales for Depression (HAM-D) 8. Q-LES-Q 	
Notes	Date of study: not specified Funding source: supported by the company marketing the drug Declarations of interest among the primary researchers: one of the primary researcher is an employee of the company marketing the drug.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random sequence generation is explained. Quote: "patients were randomly assigned by computer-generated numbers to 10 weeks of double blind treatment with either sertraline or placebo".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate is less than 20%. They apparently imputed missing data. Quote: "patients who took at least one dose of double blind medication and completed any additional assessment were included in the analysis for safety and efficacy".
Selective reporting (reporting bias)	Low risk	Outcomes are clearly reported in tables.

Other bias	High risk	The study was financially supported by the drug company marketing the drug and one of the primary researchers was an employee of the company itself.
------------	-----------	--

Pollack 2007a

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-IV panic disorder with or without agoraphobia</p> <p>Method of diagnosis: Mini-International Neuropsychiatric Interview</p> <p>Age: for venlafaxine 75 mg, M = 35.8, SD = 9.97; for venlafaxine 225 mg, M = 37.1, SD = 11.8, for paroxetine M = 37.5, SD = 11</p> <p>Sex: for venlafaxine 75 mg, females = 65%, males = 35%; for venlafaxine 225 mg, females = 68%, males = 33%; for paroxetine females = 68%, males = 32%</p> <p>Location: Argentina, Mexico, Chile, Costa Rica; setting: outpatients</p> <p>Co-morbidities: patients with other predominant Axis I or II disorders and important medical conditions were excluded</p> <p>Rescue medication: zaleplon or zolpidem permitted up to 3 times per week for the first 2 weeks of randomised treatment</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) venlafaxine 75 mg arm (n = 163)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage = 75 mg/day</p> <p>(2) venlafaxine 225 mg arm (n = 167)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage = 225 mg/day</p> <p>(3) paroxetine arm (n = 161)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage = 40 mg/day</p> <p>(4) placebo arm (n = 162)</p> <p>Duration: 12 weeks</p>
Outcomes	<p>Time points for assessment: baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. patients free of panic attacks at endpoint 2. Panic Disorder Severity Scale (PDSS) 3. panic attacks frequency 4. Clinical Global Impression Improvement Score (CGI-I)
Notes	<p>Date of study: not stated</p> <p>Funding source: Wyeth Research, Collegeville, Pennsylvania</p> <p>Declarations of interest among the primary researchers: members of advisory boards, and research support received by many pharmaceutical companies, including AstraZeneca, GlaxoSmithKline, Eli Lilly, Pfizer, Roche, Wyeth</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...they were randomly assigned to receive venlafaxine 75 mg/day, venlafaxine 225 mg/day, paroxetine or placebo once daily in identically appearing capsules".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...they were randomly assigned to receive venlafaxine 75 mg/day, venlafaxine 225 mg/day, paroxetine or placebo once daily in identically appearing capsules".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "statistical analysis on the primary and secondary outcome measures were performed for an ITT population of patients who had at least one post randomisation visit on therapy using LOCF values".
Selective reporting (reporting bias)	Unclear risk	Continuous data at endpoint are reported only in graphs.
Other bias	High risk	Sponsored by Wyeth; the role of the funder in planning, conducting and writing the study is not discussed.

Pollack 2007b

Study characteristics

Methods	Study design: randomised controlled trial	
Participants	<p>Diagnosis: DSM-IV panic disorder with or without agoraphobia</p> <p>Method of diagnosis: Mini-International Neuropsychiatric Interview</p> <p>Age: for venlafaxine 75 mg, M = 36.2, SD = 10.7; for venlafaxine 150 mg, M = 37.7, SD = 11.5, for paroxetine M = 37.6, SD = 10.5</p> <p>Sex: for venlafaxine 75 mg, females = 66%, males = 34%; for venlafaxine 150 mg, females = 70%, males = 30%; for paroxetine females = 64%, males = 36%</p> <p>Location: Europe; setting: outpatients</p> <p>Co-morbidities: patients with other predominant Axis I or II disorders and important medical conditions were excluded</p> <p>Rescue medication: zaleplon or zolpidem permitted up to 3 times per week for the first 2 weeks of randomised treatment</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) venlafaxine 75 mg arm (n = 166)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage = 75 mg/day</p> <p>(2) venlafaxine 150 mg arm (n = 168)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage = 150 mg/day</p> <p>(3) paroxetine arm (n = 166)</p> <p>Duration: 12 weeks</p> <p>Treatment protocol: fixed dosage = 40 mg/day</p> <p>(4) placebo arm (n = 163)</p> <p>Duration: 12 weeks</p>	
Outcomes	<p>Time points for assessment: baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. frequency of panic attacks from the Panic and Anticipatory Anxiety Scale 2. patients free of panic attacks at endpoint 3. Panic Disorder Severity Scale (PDSS) 4. PDSS: anticipatory anxiety 5. Phobia Scale 6. Hamilton Rating Scale for Anxiety (HAMA) 7. Sheehan Disability Scale (SDS) 8. Quality of Life Enjoyment and Satisfaction Questionnaire 9. Clinical Global Impression Improvement Score (CGI-I) 	
Notes	<p>Date of study: not stated</p> <p>Funding source: sponsored by Wyeth Research</p> <p>Declarations of interest among the primary researchers: members of advisory boards, and research support received by many pharmaceutical companies, including AstraZeneca, GlaxoSmithKline, Eli Lilly, Pfizer, Roche, Wyeth; some authors' affiliations refer to Wyeth.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study medication was provided as identical appearing capsules and was to be taken once daily with food".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Study medication was provided as identical appearing capsules and was to be taken once daily with food".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "statistical analysis on the primary and secondary outcome measures were performed for an ITT population of patients who had at least one post randomisation visit on therapy using LOCF values". No further information provided.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by Wyeth; the role of the funder in planning, conducting and writing the study is not discussed.

Ribeiro 2001

Study characteristics		
Methods	Study design: Randomised controlled trial	
Participants	Diagnosis: DSM-IV panic disorder with or without agoraphobia Method of diagnosis: not stated Age: for mirtazapine, M = 36.1, SD = 10.9; for fluoxetine, M = 36.4, SD = 10.1 Sex: for mirtazapine, 86.7% females, for fluoxetine 66.7% females Location: Brasil; setting: outpatients Co-morbidities: patients with psychiatric and physical disorders were excluded Rescue medication: none	
Interventions	Participants were randomly assigned to either: (1) mirtazapine arm (n = 15) Duration: 8 weeks Treatment Protocol: flexible dosage, range = 15 - 30 mg, M = 17.9, SD = 4.3 (2) fluoxetine arm (n = 15) Duration: 8 weeks Treatment Protocol: flexible dosage, range = 10 - 20 mg, M = 13.1, SD = 3.2	
Outcomes	Time points for assessment: Baseline, week 1, 2, 4, 6 and 8 Outcomes: 1. Panic Diary 2. Clinical Global Impression Severity of Illness Score (CGI-S) 3. Clinical Global Impression Improvement Score (CGI-I) 4. Hamilton Rating Scale for Anxiety (HAMA) 5. Sheehan Phobic Scale	
Notes	Date of study: November 1998 - March 1999 Funding source: research supported by FIPE-HCPA (FUNDO DE INCENTIVO À PESQUISA E EVENTOS) 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: "patients were randomised to mirtazapine or fluoxetine using a computer program which assigned 15 patients to each group".
Allocation concealment (selection bias)	Low risk	Quote: "a person who was not participating in the study labeled flasks containing enough medications for periods between visits"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the analysis included all patients who took at least one dose of medication during the double-blind phase and who provided any follow-up data". No further information provided.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Unclear risk	Quote: "Organon Pharmaceutical kindly provided mirtazapine for the trial". No more information provided.

Robinson 1989

Study characteristics	
Methods	Study design: Randomised controlled trial
Participants	Diagnosis: DSM-III Panic disorder Method of Diagnosis: Not stated Age: for buspirone, M = 34.4 (SD = 1.8); for placebo, M = 33.1 (SD = 1.9); for imipramine, M = 30.1 (SD = 1.0) Sex: for buspirone, 64% women, 36% men; for placebo 62% women, 38% men; imipramine 75% women, 25% men Location: United States of America Co-morbidities: unclear Rescue medication: none
Interventions	Participants were randomly assigned to either:

	<p>(1) Buspirone arm (n = 34) Duration: 8 weeks Treatment Protocol: flexible dosage; range = not stated, M = 43 (SD = 3)</p> <p>(2) Placebo arm (n = 29) Duration: 8 weeks Treatment Protocol: Flexible</p> <p>(3) Imipramine arm (n = 28) Duration: 8 weeks Treatment Protocol: flexible dosage; range = not stated, M = 221 (SD = 18)</p>
Outcomes	<p>Timepoints for assessment: at 0, 2, 4, 6, 7, 8 weeks</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Hamilton Anxiety rating scale 2. Number of panic attacks 3. Global ratings of social disability
Notes	<p>Date of study: Not stated</p> <p>Funding source: Not stated</p> <p>Declarations of interest among the primary researchers: One of the authors belonged to Bristol-Myers Company Pharmaceutical Research and Development Division. The authors were advised by employees from Bristol-Myers Company.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules were used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This is a double-blind trial. No other information.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rate.
Selective reporting (reporting bias)	Unclear risk	No information provided.
Other bias	High risk	All the authors were employed by the drug company marketing the drug

Rosenbaum 1997

Study characteristics	
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) Clonazepam 0.5 mg (n = 68) Duration: 9 weeks (+ discontinuance phase: 7 weeks) Treatment protocol: fixed dose = 0.5 mg</p> <p>(2) Clonazepam 1.0 mg (n = 68) Duration: 9 weeks (+ discontinuance phase: 7 weeks) Treatment protocol: fixed dose = 1.0 mg</p> <p>(3) Clonazepam 2.0 mg (n = 69) Duration: 9 weeks (+ discontinuance phase: 7 weeks) Treatment protocol: fixed dose = 2.0 mg</p> <p>(4) Clonazepam 3.0 mg (n = 67) Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p>

	<p>Treatment protocol: fixed dose = 3.0 mg (5) Clonazepam 4.0 mg (n = 72) Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed dose = 4.0 mg (6) Placebo arm (n = 69) Duration: 9 weeks (+ discontinuance phase: 7 weeks)</p> <p>Treatment protocol: fixed</p>	
Outcomes	<p>Time points for assessment: at each visit (CGI-S, mean duration of anticipatory anxiety); at each postbaseline visit (CGI-C); at baseline, week 9, week 16 (severity of fear associated with the main phobia)</p> <p>Primary outcomes:</p> <p>(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</p> <p>Secondary outcomes:</p> <p>(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</p>	
Notes	<p>Date of study: October 1992 to June 1995</p> <p>Funding source: This clinical trial was supported by Hoffmann-La Roche.</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)	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 provided.
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	High risk	This clinical trial was supported by Hoffmann-La Roche.

Savoldi 1990

Study characteristics	
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) Etizolam (n = 15)</p> <p>Duration: 4 weeks</p> <p>Treatment protocol: fixed dosage = 0.50 mg</p> <p>(2) Placebo arm (n = 15)</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>

	(2) Agoraphobia: HAMA, item 2 (3) Frequency of panic attacks: not stated (4) Depression: HAMD Secondary outcome: (1) Tolerability: 4-point scale, semi-structured interview
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: "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 provided.
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	Low risk No evidence of other bias was found.

Schweizer 1992

Study characteristics		
Methods	Study design: randomised controlled trial	
Participants	Diagnosis: DSM-III-R panic disorder, either uncomplicated, with limited phobic avoidance, or with agoraphobia Method of diagnosis: not stated Age: mean = 35 Sex: 3 males, 2 females Location: not stated Comorbidities: social phobia (n = 1) Rescue medication: none (besides midazolam when necessary)	
Interventions	Participants were randomly assigned to either: (1) Midazolam (n = 3 + 2) Duration: 3 + 3 weeks Treatment protocol: flexible dosage; range = 0.25 to 1 mg; mean number of doses (week 3) = 6.1 (0.44 mg/day) (2) Placebo (n = 2 + 3) Duration: 3 + 3 weeks Treatment protocol: flexible	
Outcomes	Time points for assessment: baseline, week 1, 2, 3, 4, 5, 6 Primary outcomes: (1) Number of panic attacks: participants' diaries (2) Global phobia: 11-point Global Phobia Scale (3) Anxiety: HAMA; Sheehan Patient Rated Anxiety Scale (4) Overall improvement: 7-point CGI-I	
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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.

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". No further information provided.
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". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual participant data available. No evidence of selective outcome report.
Selective reporting (reporting bias)	Unclear risk	No side effects reported.
Other bias	Unclear risk	Very small pilot cross-over trial.

Schweizer 1993

Study characteristics

Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM - III panic disorder Method of diagnosis: Structured Clinical Interview for DSM-III, Upjohn Version Age: M = 33, SD = 7 Sex: female = 75%, male = 25% Location: USA; setting: in and outpatients Co-morbidities: none Rescue medication: Quote: "no concomitant centrally active medication therapy was permitted during the study"
Interventions	Participants were randomly assigned to either: (1) alprazolam arm (n = 37) Duration: 8 weeks short term, 32 weeks long term Treatment protocol: flexible dosage, range = 2 - 10 mg, M = 5.4, SD = 2.1 (2) imipramine arm (n = 34) Duration: 8 weeks short term, 32 weeks long term Treatment protocol: flexible dosage, range = 50 - 250 mg, M = 152, SD = 65 (3) placebo arm (n = 35) Duration: 8 weeks short term, 32 weeks long term
Outcomes	Time points for assessment: weekly until week 6, week 8, monthly for 6 months Outcomes: 1. panic attack frequency and severity 2. Hamilton Rating Scale for Anxiety (HAMA) 3. phobias 4. disability resulting from the phobic anxiety 5. global assessment of improvement 6. safety questionnaire (SAFTEE) 7. benzodiazepines plasma levels
Notes	Date of study: not stated Funding source: sponsored by Upjohn Co. 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: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients were dispensed identical capsules containing either 1 mg of alprazolam or 25 mg of imipramine".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients were dispensed identical capsules containing either 1 mg of alprazolam or 25 mg of imipramine".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "ITT endpoint analysis, including all patients with at least one week of treatment and 'evaluable patients' or 'decreasing N' analysis, using only those patients available at each visit, were the primary set of analysis conducted. Supplementary completers analysis using only patients who completed either 8 weeks or 32 weeks of treatment were also conducted". "While the high attrition rate in the imipramine and placebo treatment groups posed a problem for the statistical analysis of the various outcome measures, attrition rates themselves constituted an important and independent outcome measures. Survival analysis was performed for on-study treatment".

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	High risk	Sponsored by Upjohn Co; the role of the funder in planning, conducting and writing the study is not discussed.

Sharp 1990

Study characteristics	
Methods	Study design: randomised (individual randomisation), parallel groups, double-blind, fixed-dose design, 12 weeks + 6 months of follow-up
Participants	<p>Diagnosis: DSM-III-R panic disorder with or without agoraphobia</p> <p>Method of diagnosis: not specified</p> <p>Age (years): 18-70, 36.62 in fluvoxamine arm, 42.28 in placebo arm, 37.27 in fluvoxamine + placebo arm, 38.81 in placebo + CBT arm, 33.23 in CBT arm</p> <p>Sex: 115 women, 32 men</p> <p>Location: general practice/primary care, Scotland, UK</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: not allowed</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>1) fluvoxamine arm (randomised n = 36)</p> <p>Treatment protocol: fixed dose, range 50-150 mg/day, mean = 150 mg/day</p> <p>Duration: 12 weeks</p> <p>2. placebo arm (randomised n = 37)</p> <p>Treatment protocol: fixed dose; range not stated</p> <p>Duration: 12 weeks</p> <p>3. fluvoxamine + CBT (randomised n = 38)</p> <p>Treatment protocol: fixed dose; 150 mg/day</p> <p>Duration: 12 weeks</p> <p>4. placebo + CBT arm (randomised n = 36)</p> <p>Treatment protocol: fixed dose; range not stated</p> <p>Duration: 12 weeks</p> <p>(5) CBT arm (randomised n = 43)</p> <p>Treatment protocol: 30-60-min sessions</p> <p>Duration: 12 weeks</p>
Outcomes	<p>Timepoints for assessment: at baseline and at weeks 1, 2, 4, 6, 8, 10 and 12</p> <p>Outcomes:</p> <ol style="list-style-type: none"> 1. Clinical Global Impression-Severity of Illness (CGI-S) 2. HAMA 3. Kellner and Sheffield Symptom Rating Test (SRT) 4. MADRS 5. FQ 6. frequency of panic attacks 7. SDS
Notes	<p>Date of study: not specified</p> <p>Funding source: funded by the company marketing the drug</p> <p>Declarations of interest among the primary researchers: not specified</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no further information about random sequence generation is provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The active and the placebo tablets seem to be identical. Quote: "medication was supplied in 50 mg tablets, patients receiving placebo were given the equivalent number of tablets at each appointment, thus maintaining the double blind status".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	There was an independent assessor monitoring the data collection. Quote: "JA acted as independent monitor; data collected were monitored at monthly intervals throughout the duration of study"
Incomplete outcome data (attrition bias)	Unclear risk	Dropout rate is around 19% in the fluvoxamine group and around 24% in the placebo group. It is not clear whether missing data were imputed.

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Scores of the scales used for the treatment evaluation are poorly reported.
Other bias	High risk	Funded by the company marketing the drug.

Sheehan 1993

Study characteristics		
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>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Alprazolam (n = 34)</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) Buspirone (n = 34)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 15 to 100 mg, mean = 61 (SD = 26.5)</p> <p>(2) Placebo (n = 33)</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 provided.
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) All outcomes	Unclear risk	Double-blind; no further information.
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.
------------	--------------	---

Sheehan 2005

Study characteristics		
Methods	Study design: pooled analysis of 3 identical, double-blind, placebo-controlled, parallel-group, individually randomised, 10-week clinical trials	
Participants	Diagnosis: DSM-IV panic disorder with or without agoraphobia Method of diagnosis: DSM-IV Age (years): 18-65, mean 37.6 (SD = 10.22) in paroxetine CR group, 37.8 (SD = 10.61) in placebo group Sex: 356 men, 543 women Location: USA and Canada, outpatient setting Co-morbidities: inclusion of people with secondary Axis I disorders Rescue medication: not allowed	
Interventions	Participants were randomly assigned to either: 1. paroxetine CR arm (randomised n = 444) Duration: 10 weeks Treatment protocol: flexible dosage; range = 12.5-75 mg/day, mean = 50 mg/day (SD = not specified) 2. Placebo arm (randomised n = 445) Duration: 10 weeks Treatment protocol: flexible dosage	
Outcomes	Timepoints for assessment: at baseline and at weekly and bi-weekly intervals Outcomes: <ol style="list-style-type: none"> percentage of participants free of panic attacks number of full panic attacks for 2 weeks CGI-S HAMA Marks Sheehan Phobia Scale CGI-I 	
Notes	Date of study: November 1996-September 1997 Funding source: the studies were sponsored by the company marketing paroxetine CR Declarations of interest among the primary researchers: the study author declares to have financial associations with many companies that produce psychoactive pharmaceutical agents	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The studies are described as "randomised", but no information about the random sequence generation is provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The studies are described as "double blind", no other information is provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of dropouts and the reasons of withdrawals are clearly reported. The study authors use the data imputation. Quote: "Efficacy and safety analysis were carried out on the modified intention-to-treat (ITT) population, defined as all patients who were randomly assigned to treatment, received at least 1 dose of study medication, and had at least 1 postbaseline assessment".
Selective reporting (reporting bias)	Low risk	The results of the primary and secondary efficacy outcomes are reported in tables and graphs.
Other bias	High risk	The studies were sponsored by the company marketing paroxetine CR; the role of the funder in planning, conducting and writing the study is not discussed.

Sheikh 1999

Study characteristics		
------------------------------	--	--

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 - Patient version (SCID-P) Age: mean = 61.24 (SD = 5.27), range = 55 to 73 Sex: M = 2; F = 32 Location: USA Comorbidities: none Rescue medication: none
Interventions	Participants were randomly assigned to either: (1) Alprazolam (n = 8) Duration: 8 weeks Treatment protocol: flexible dosage; range = 1 to 6 mg, mean = 2.87 (SD = 1.66) (2) Imipramine (n = 10) Duration: 8 weeks Treatment protocol: flexible dosage; range = 10 to 200 mg, mean = 77.5 (SD = 59.4) (3) Placebo arm (n = 7) Duration: 8 weeks Treatment protocol: flexible
Outcomes	Time points for assessment: baseline, at each subsequent medication visit Primary outcomes: (1) Number/intensity of panic attacks: participant's diary (2) Anxiety: HAMA (3) Depression: HAMD (4) Overall improvement: CGI; PGI
Notes	Date of study: 2-year period (1988-90) 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. 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: "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 provided.
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.

Stahl 2003

Study characteristics

Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM - IV panic disorder Method of diagnosis: not stated Age: for escitalopram, M = 37.5, for citalopram M = 37.1 Sex: for escitalopram 57.6 % female, for citalopram 61.6% female Location: USA; setting: outpatients Co-morbidities: patients with bipolar disorder, schizophrenia, obsessive-compulsive disorder or other psychotic disorder,

	psychoactive substance use disorder, clinically significant abnormalities in laboratory evaluations or electrocardiographic readings were excluded Rescue medication: zolpidem	
Interventions	Participants were randomly assigned to either: (1) escitalopram arm (n = 129) Duration: 10 weeks Treatment protocol: flexible dosage, range = 5 - 20 mg, M = 10.8 SD not provided (2) citalopram arm (n = 126) Duration: 10 weeks Treatment protocol: flexible dosage, range = 10 - 40 mg, M = 21.3, SD not provided (3) placebo arm (n = 125) Duration: 10 weeks	
Outcomes	Time points for assessment: baseline, weeks 1, 2, 4, 6, 8 and 10 Outcomes: 1. Panic and Anticipatory Anxiety Scale (PAAS) 2. panic attack frequency 3. Panic & Agoraphobia Scale 4. Clinical Global Impression Improvement Score (CGI-I) 5. Clinical Global Impression Severity of Illness Score (CGI-S) 6. Hamilton Rating Scale for Anxiety (HAMA) 7. Patient Global Evaluation (PGE) 8. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) 9. Hamilton Rating Scale for Depression (HAM-D)	
Notes	Date of study: 1999 - 2001 Funding source: sponsored by Forest Laboratories Declarations of interest among the primary researchers: one of the authors has received research support from many drug companies; other authors are employees of Forest Laboratories.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The ITT set consisted of 351 patients, 125 treated with escitalopram, 112 with citalopram and 114 with placebo". Dropout rates were different between treatment groups (escitalopram = 24.2%, citalopram = 31.9%).
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	High risk	Sponsored by Forest Laboratories; the role of the funder in planning, conducting and writing the study is not discussed.

Taylor 1990

Study characteristics

Methods	Study design: Randomised controlled trial
Participants	Diagnosis: panic disorder with phobic avoidance Method of diagnosis: Structured Clinical Interview for Diagnoses-Upjohn version (SCID-UP) Age: Alprazolam: mean = 35.0; Imipramine: mean = 34.1; Placebo: mean = 34.9 Sex: Alprazolam: Male = 19%, Imipramine: 30%, Placebo: 31% Location: USA Comorbidities: none Rescue medication: none
Interventions	Participants were randomly assigned to either: (1) Alprazolam (n = 26) Duration: 8 weeks

	<p>Treatment protocol: flexible dosage; range = 1 to 8 mg, mean = 3.7 (2) Imipramine (n = 27)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: flexible dosage; range = 1 to 9 mg, mean = 4.9 (3) Placebo (n = 26)</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 (2) Anxiety: HAMA (3) Depression: Beck Depression Inventory (4) Overall psychiatric symptomatology: SCL-90 (5) Global improvement: 7-point scale (6) Work and social disability: 5-point scale (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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	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.
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

Study characteristics

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) Alprazolam (n = 24)</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) Clonazepam (n = 26)</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) Placebo arm (n = 22)</p>

	Duration: 6 weeks	
	Treatment protocol: flexible	
Outcomes	Time points for assessment: baseline, week 3 and 6 Primary outcomes: (1) Number/intensity/duration of panic attacks: participant's diary (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 provided.
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	High risk	Supported in part by a grant from the Upjohn Corporation, Kalamazoo, Michigan

Tiller 1999

Study characteristics

Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM-III-R panic disorder Method of diagnosis: Structured Clinical Interview (SCID) Age: M = 35 Sex: 67% female Location: not stated; setting: unclear Co-morbidities: not stated Rescue medication: not stated; "there was not extensive co-prescription of hypnotics, sedatives or beta-blockers".
Interventions	Participants were randomly assigned to either: (1) moclobemide arm (n = 182) Duration: 8 weeks Treatment protocol: flexible dosage, range = 300 - 600 mg, M = 498, SD = 68 (2) fluoxetine arm (n = 184) Duration: 8 weeks Treatment protocol: flexible dosage, range = 10 - 30 mg, M = 20.5, SD = 2.7
Outcomes	Time points for assessment: Outcomes: 1. number of adverse events 2. severe adverse events

	3. clinical global impression of tolerability 4. panic-free patients 5. Clinical Global Impression Scale (CGI)
Notes	Date of study: not stated Funding source: sponsored by Hoffmann-La Roche Declarations of interest among the primary researchers: none.
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Quote: "randomly allocated". No further information provided.
Allocation concealment (selection bias)	Unclear risk No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk Quote: "double blind". No further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk Quote: "double blind". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk No information provided about management of incomplete outcome data; number of total dropouts not reported.
Selective reporting (reporting bias)	Unclear risk All relevant outcomes mentioned in the methods section were reported.
Other bias	High risk Sponsored by Hoffmann-La Roche; the role of the funder in planning, conducting and writing the study is not discussed.

Tsutsui 1997

Study characteristics	
Methods	Study design: 12 weeks, randomised (cluster randomisation), parallel design, placebo-controlled, double-blind
Participants	Diagnosis: DSM-III-R panic disorder Method of diagnosis: not specified Age (years): some participants > 65, range unclear Sex: they show the ratio of gender, however, it is not for the randomised population, but for the population included in the analysis. Location: inpatient, multicentre trial all over Japan Co-morbidities: excluded Rescue medication: lorazepam
Interventions	Participants were randomly assigned to either: 1. sertraline low-dose arm (randomised n = 59) Duration: 12 weeks Treatment protocol: fixed dosage; 75 mg/day 2. sertraline high-dose arm (randomised n = 54) Duration: 12 weeks Treatment protocol: fixed dosage; 150 mg/day 3. placebo arm randomised n = 56) Duration: 12 weeks Treatment protocol: fixed dosage; number of tablets not specified
Outcomes	Timepoints for assessment: baseline and at 12 weeks Outcomes: 1. response rate (Global Improvement 5-point scale) 2. frequency of panic attacks
Notes	Date of study: not specified Funding source: unclear Declarations of interest among the primary researchers: unclear
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Cluster randomisation. The method is not specified.
Allocation concealment (selection bias)	Low risk An independent researcher randomly allocated participants. He passed identical tablets to clinician.
Blinding of participants and personnel (performance bias) All outcomes	Low risk Both the participants and the physician were blinded.

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts from analysis were over 20%, no imputation for missing data was performed.
Selective reporting (reporting bias)	Unclear risk	There is no protocol of this study, so we cannot decide on the selective reporting.
Other bias	Unclear risk	Researcher conflicts of interest are unclear.

Tsutsui 2000a

Study characteristics	
Methods	Study design: 8 weeks, randomised controlled trial (cluster randomisation), parallel design, double-blind
Participants	<p>Diagnosis: DSM-IV panic disorder</p> <p>Method of diagnosis: not stated</p> <p>Age (years): inclusion criteria included 65 years. They showed the age range of population included into their analysis. It was from 18-60, however, this is not the age range of population randomised. So we cannot decide if randomised population included 65 years persons = "unclear".</p> <p>Sex: They show the ratio of gender, however, it is not for the randomised population, but for the population included in the analysis</p> <p>Location: in and outpatient setting, all over Japan. (multicentre trial)</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: lorazepam, zopiclone, brotizolam, lormetazepam, rilmazafone</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. paroxetine arm (randomised n = 87)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage 30 mg/day</p> <p>2. placebo arm (randomised n = 84)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: fixed dosage</p>
Outcomes	<p>Timepoints for assessment: at baseline, at 8 weeks</p> <p>Outcomes:</p> <p>1. response rate</p> <p>2. number of panic attacks</p>
Notes	<p>Date of study: not specified</p> <p>Funding source: the study was sponsored by the company marketing the drug</p> <p>Declarations of interest among the primary researchers: conflict of interest among primary researchers</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster randomisation trial. No further details are provided about the random sequence generation.
Allocation concealment (selection bias)	Low risk	An independent researcher randomly allocated participant. He passed identical tablets to clinician.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the participants and the personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is unclear whether the researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts from analysis were over 20%, no imputation for missing data was performed.
Selective reporting (reporting bias)	Unclear risk	There is no protocol of this study, so we cannot decide the selective reporting.
Other bias	High risk	The study was sponsored by the company marketing the drug. Conflict of interest among primary researchers.

Tsutsui 2000b

Study characteristics	
Methods	Study design: 8 weeks, randomised (cluster randomisation), parallel design, placebo-controlled, double-blind trial
Participants	Diagnosis: DSM-IV panic disorder

	<p>Method of diagnosis: not stated</p> <p>Age (years): range 18-72</p> <p>Sex: distribution of gender in randomised population not reported</p> <p>Location: in and outpatient setting, all over Japan</p> <p>Co-morbidities: excluded</p> <p>Rescue medication: lorazepam</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>1. paroxetine low-dose arm (randomised n = 38)</p> <p>Treatment protocol: fixed dosage 20 mg/day</p> <p>Duration: 8 weeks</p> <p>2. paroxetine high-dose arm (randomised n = 45)</p> <p>Treatment protocol: fixed dosage 30 mg/day</p> <p>Duration: 8 weeks</p> <p>3. placebo arm (randomised n = 37)</p> <p>Treatment protocol: fixed dosage</p> <p>Duration: 8 weeks</p>
Outcomes	<p>Timepoints for assessment: baseline and 8 weeks</p> <p>Outcomes:</p> <p>1. response rate (Global Improvement 5-point scale)</p> <p>2. number of panic attacks</p>
Notes	<p>Date of study: not specified</p> <p>Funding source: the study was sponsored by the company marketing the drug</p> <p>Declarations of interest among the primary researchers: conflict of interest among the primary researchers</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster randomisation. No further details are provided about the random sequence generation.
Allocation concealment (selection bias)	Low risk	An independent researcher randomly allocated participants. He passed identical tablets to clinician.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and the physicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is unclear whether the assessors were blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts from analysis were over 20%. ITT analysis was used, but the method of imputation was not mentioned.
Selective reporting (reporting bias)	Unclear risk	There is no protocol of this study, so we cannot decide the selective reporting.
Other bias	High risk	The study was sponsored by the company marketing the drug. Conflict of interest among the primary researchers.

Uhlenhuth 1989

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM - III panic disorder or agoraphobia with panic attacks</p> <p>Method of diagnosis: SCID-UP</p> <p>Age: M = 31.54, SD = 7.12</p> <p>Sex: 58% female</p> <p>Location: USA; setting: outpatients</p> <p>Co-morbidities: patients with another primary psychiatric disorder or a physical disorder judged likely to interfere with the study were excluded</p> <p>Rescue medication: not stated</p>
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>

	Treatment protocol: fixed dosage 6 mg (3) imipramine arm (n = 20) Duration: 8 weeks Treatment protocol: fixed dosage 225 mg (4) placebo arm (n = 20) Duration: 8 weeks	
Outcomes	Time points for assessment: weeks 1, 2, 3, 4, 6, 8 Outcomes: 1. number of panic attacks (major, spontaneous, minor, situational) 2. Marks & Matthews Phobia Scale 3. disability 4. Hamilton Rating Scale for Anxiety (HAMA) 5. Hamilton Rating Scale for Depression (HRSD) 6. SAFTEE-UP for adverse effects	
Notes	Date of study: not stated Funding source: sponsored by 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	Quote: "random". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients received two identical appearing capsules four times daily".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patients received two identical appearing capsules four times daily".
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	High risk	Sponsored by Upjohn Company; the role of the funder in planning, conducting and writing the study is not discussed.

Valenca 2000

Study characteristics

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

	(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 provided.
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).

Van Vliet 1993

Study characteristics

Methods	Study design: 12-week, double-blind, placebo-controlled, individual randomisation, parallel groups
Participants	Diagnosis: DSM-III-R panic disorder with or without agoraphobia Method of diagnosis: SCL-90 Age (years): 26-49 (mean = 32 SD = 6.4) Sex: 27 women, 3 men Location: outpatient clinic of the department of Biological Psychiatry of the University Hospital in Utrecht, Netherlands Co-morbidities: excluded Rescue medication: oxazepam to a maximum of 30 mg daily, if required
Interventions	Participants were randomly assigned to either: 1. brofaromine arm (randomised n = 15) Duration: 12 weeks Treatment protocol: flexible dosage; range = 50-150 mg/day, mean = not stated (SD = not stated) 2. placebo arm (randomised n = 14) Duration: 12 weeks Treatment protocol: flexible dosage; range = not stated, mean = not stated (SD = not stated)
Outcomes	Timepoints for assessment: weekly for 12 weeks (some outcomes were evaluated at the baseline and at the endpoint only) Outcomes: 1. HAMA 2. MADRS 3. FQ 4. number of panic attacks 5. HDRS 6. SCL-90 7. UPI (Utrecht Panic Inventory) 8. STAI
Notes	Date of study: not specified Funding source: none declared Declarations of interest among the primary researchers: none declared
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to one of the two treatment groups". No further details are provided. The number of participants randomised per arm is unclear.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	The only information reported about dropout is that one participant in the placebo group was withdrawn from the study at week 8 because of lack of efficacy. Other reasons for withdrawal are not discussed. Thus it is not clear whether the 2 groups are still comparable or not after the dropout. Data imputation is not clearly discussed, however apparently only completers were analysed (consistent with 'per protocol analysis').
Selective reporting (reporting bias)	High risk	The measures of primary outcome are not clearly specified and mean scores of the scales are graphically reported in figures and only partially reported in the text.
Other bias	Low risk	It is unlikely that sponsorship bias could have influenced the results. Quote: "The authors wish to thank Mrs M de Wol-Ferdinandusse, director of the Dutch Foundation of Phobic Disorders, and the Laboratory of Biological Psychiatry of the University Hospital Utrecht, head Mr A Klompmakers"

Van Vliet 1996

Study characteristics		
Methods	Study design: randomised controlled trial	
Participants	Diagnosis: DSM-III-R panic disorder with or without agoraphobia Method of diagnosis: open interview Age: M = 35, SD = 7.46 Sex: 26 women, 6 men Location: the Netherlands; setting: outpatients Co-morbidities: patients with another anxiety disorder, major affective disorders or psychotic disorder, alcohol or drug abuse and medical problems were excluded Rescue medication: oxazepam maximum 30 mg daily	
Interventions	Participants were randomly assigned to either: (1) brofaromine arm (n = 15) Duration: 12 weeks Treatment protocol: fixed dosage 150 mg (2) fluvoxamine arm (n = 15) Duration: 12 weeks Treatment protocol: fixed dosage 150 mg	
Outcomes	Time points for assessment: weekly Outcomes: 1. Hamilton Rating Scale for Anxiety (HAMA) 2. Montgomery-Åsberg Depression Rating Scale (MADRS) 3. Fear Questionnaire 4. number of panic attacks 5. Hamilton Rating Scale for Depression (HAM-D) 6. SCL-90	
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: "randomly". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided about management of incomplete outcome data.
Selective reporting (reporting bias)	High risk	Continuous outcomes are reported incompletely (number of evaluated patients is not reported), so that they cannot be entered in a meta-analysis; Fear Questionnaire data for agoraphobia are only reported in graphs.
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Versiani 2002

Study characteristics		
Methods	Study design: 8 weeks, multicentre, placebo-controlled, randomised (individual) parallel-group, double-blind clinical trial	
Participants	Diagnosis: DSM-III-R panic disorder with or without agoraphobia Method of diagnosis: not specified Age (years): mean age in reboxetine arm 36.5 (SD = 10.4), mean age in placebo arm 35.1 (SD = 10.9) Sex: 50 women, 25 men Location: Brazil and Italy Co-morbidities: excluded Rescue medication: unclear	
Interventions	Participants were randomly assigned to either: 1. reboxetine arm (randomised n = 42) Duration: 8 weeks Treatment protocol: flexible dosage; range = 2-8 mg/day 2. placebo arm (randomised n = 40) Duration: 8 weeks Treatment protocol: flexible dosage	
Outcomes	Timepoints for assessment: weekly for 8 weeks Outcomes: <ol style="list-style-type: none"> 1. Sheehan panic Attack and Anxiety Scale 2. Phobia Scale 3. CGI 4. Hamilton Rating Scales for Depression (HAM-D) 5. SCL-90 6. SDS 7. DOTES (Dosage Record and Treatment Emergent Symptom Scale) 	
Notes	Date of study: not specified Funding source: not specified Declarations of interest among the primary researchers: not mentioned	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomised" but not further information is given about the random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts. Quote: "a last observation carried forward analysis was conducted and included all patients who received at least 3 weeks of treatment".
Selective reporting (reporting bias)	Unclear risk	The outcomes are reported in the graphs and in the text. For some data they don't specify the SD.

Other bias	Unclear risk	Sponsorship bias cannot be ruled out.
------------	--------------	---------------------------------------

Wade 1997

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	<p>Diagnosis: DSM-III-R panic disorder</p> <p>Method of diagnosis: not stated</p> <p>Age: M = 38, SD not provided</p> <p>Sex: 70% female, 30 % male</p> <p>Location: not stated; setting unclear</p> <p>Co-morbidities: patients with depression, organic brain damage, drug/alcohol misuse and other severe psychiatric or somatic disorders were excluded</p> <p>Rescue medication: treatment with oxazepam was permitted during weeks 1 and 2 (maximum dose 20 mg daily), discontinued during weeks 3 and 4, and prohibited during weeks 5 to 8.</p>
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) citalopram 10-15 mg arm (n = 97)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: 10 mg, with the option of increasing to 15 mg if efficacy was not seen</p> <p>(2) citalopram 20-30 mg arm (n = 95)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: 20 mg, with the option of increasing to 30 mg if efficacy was not seen</p> <p>(3) citalopram 40-60 arm (n = 89)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: 40 mg, with the option of increasing to 60 mg if efficacy was not seen</p> <p>(4) clomipramine (n = 98)</p> <p>Duration: 8 weeks</p> <p>Treatment protocol: 60 mg, with the option of increasing to 90 mg if efficacy was not seen</p> <p>(5) placebo (n = 96)</p>
Outcomes	<p>Time points for assessment: baseline, last assessment (no further details provided)</p> <p>Outcomes:</p> <ol style="list-style-type: none"> number of panic attacks - Clinical Anxiety Scale (CAS) general improvement (Physician's Global Improvement Scale, Patient's Global Improvement Scale) Hamilton Anxiety Rating Scale (HAS) Montgomery-Åsberg Depression Rating Scale (MADRS)
Notes	<p>Date of study: not stated</p> <p>Funding source: not stated</p> <p>Declarations of interest among the primary researchers: None (but authors' affiliations refer to pharmaceutical companies).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind". No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the primary analysis of efficacy was based upon the relative number of responding patients for the ITT population and by use of the LOCF".
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported; data on CAS are reported only in graphs.
Other bias	Unclear risk	One of the authors' affiliation refer to Lundbeck.

Zhang 2000

Study characteristics	
Methods	Study design: randomised controlled trial
Participants	Diagnosis: DSM III - R

	<p>Method of diagnosis: no available information</p> <p>Age: not stated</p> <p>Sex: not stated</p> <p>Location: China; setting: in and outpatients</p> <p>Co-morbidities: none</p> <p>Rescue medication: not stated</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) paroxetine arm (n = 38)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: week 1: 20 mg, week 2: 30 mg, week 3: 40 mg, week 4-10: 40-50 mg; M = 43.5, SD = 4.8</p> <p>(2) clomipramine arm (n = 35)</p> <p>Duration: 10 weeks</p> <p>Treatment protocol: week 1: 50 mg, week 2: 100 mg, week 3: 150 mg, week 4-10: 150-200 mg; M = 159.7, SD = 20.1</p>	
Outcomes	<p>Time points for assessment: not stated</p> <p>Outcomes: not stated</p>	
Notes	<p>Date of study: not stated</p> <p>Funding source: sponsored by the drug company marketing the drug</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 provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Unclear risk	No information provided.
Other bias	High risk	Sponsored by the drug company marketing the drug; the role of the funder in planning, conducting and writing the study is not discussed.

BDI: Beck Depression Inventory

CBT: cognitive behavioural therapy

CGI: Clinical Global Impression

DSM III/IV: Diagnostic and Statistical Manual of Mental Disorders (third/fourth revision)

GAD: generalised anxiety disorder

HAMA: Hamilton Rating Scale for Anxiety

HRSD: Hamilton Rating Scale for Depression

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

ITT: intention-to-treat

LOCF: last observation carried forward

M: mean

MADRS: Montgomery-Åsberg Depression Rating Scale

mg: milligram

MDD: major depressive disorder

MHPG: 3-methoxy-4-hydroxyphenylglycol

n: number

OCD: obsessive compulsive disorder

PASS: Panic-Associated Symptoms Scale

SCID: Structured Clinical Interview for DSM

SCL-90: Anxiety Subscale of Symptom Checklist-90-Revised

SD: standard deviation

SDS: Self Rating Depression Scale

SEM: standard error of the mean

TCA: tricyclic antidepressants

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ananth 1979	Wrong diagnosis (anxiety neurosis)
Bakish 1994	Wrong study design (single case)
Baldini Rossi 2000	Wrong diagnosis (participants were not primarily diagnosed with panic disorder)
Ballenger 1988	Wrong diagnosis (the main diagnosis is agoraphobia, and less than 30% of participants suffer from panic disorder)
Balon 1991	Wrong study design (panicogenic)
Balon 1993	Wrong study design (panicogenic)
Barbosa 1980	Wrong diagnosis (anxiety disorder)
Bernardi 1998	Wrong comparator (comorbidity of anxiety and depression)
Bueno 1988	Wrong diagnosis (anxiety disorder)
Bystritsky 1990	Wrong study design (not double-blind)
Charney 1986	Wrong study design (not randomised)
Chen 1997	Wrong comparator (buspirone)
Chen 1998	Wrong comparator (buspirone)
Chen 2003	Wrong diagnosis (anxiety)
Chouinard 1983	Wrong diagnosis (psychoneurotic patients)
Chouinard 1982	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 usable data
Dasberg 1974	Wrong diagnosis (anxiety disorder)
Davis 1981	Wrong study design (not a RCT)
De Candia 2009	Wrong diagnosis (mild to moderate anxiety disorder)
de Jonghe 1989	Wrong diagnosis (participants were diagnosed with anxiety disorders including panic disorder, but the randomisation was not stratified by diagnosis)
De Rosa 1980	Wrong diagnosis (anxiety disorder)
Dell'Erba 2006	Wrong study design (not randomised)
den Boer 1987	Wrong diagnosis (participants were diagnosed with anxiety disorders including panic disorder, but the randomisation was not stratified by diagnosis)
Downing 1978	Wrong diagnosis (anxiety disorder)
Downing 1979	Wrong diagnosis (anxiety disorder)
Downing 1983	Wrong diagnosis (anxiety disorder)
Dunner 1986	Wrong diagnosis (participants were diagnosed with anxiety disorders including panic disorder, but the randomisation was not stratified by diagnosis)
Dyukova 1992	Wrong study design (not randomised)
Dyukova 1993	Wrong diagnosis (autonomic crisis)
Evans 1986	Wrong study comparator (concomitant psychotherapy)
Fahy 1992	Wrong study comparator (concomitant psychotherapy)
Fava 1989	No usable data
Filip 1981	Wrong diagnosis (anxiety disorder)
Franulic 1989	Wrong study design (not randomised)
Furukawa 2009	Wrong study design (review)
Greiss 1980	Wrong diagnosis (anxiety disorder)
Grilo 1988	Wrong intervention (combined therapy with cognitive behaviour therapy)
Hare 1974	Wrong diagnosis (anxiety and depression)
Hofmeijer-Sevink 2017	Wrong intervention (D-Cycloserine Enhancement)
Hu 2002	Wrong comparator (psychotherapy and drug)
Huppert 2004	Wrong comparator (CBT and medication)
Kahn 1986	Wrong diagnosis (depressive and anxiety disorder)
Kaplan 2000	Wrong study design (comparison with healthy people)
Keller 1993	Wrong diagnosis (participants were not primarily diagnosed with panic disorder)
Kerry 1983	Wrong diagnosis (neurotic anxiety)
Klein 1988	Wrong study design (not a RCT)
Klerman 1990	Wrong study design (not a RCT)
Knijnenik 1990	Wrong diagnosis (anxiety neurosis)
Laakmann 1980	Wrong diagnosis (anxiety neurosis)
Lapierre 1975	Wrong diagnosis (anxiety neurosis)
Lepola 1989	Wrong study design (not randomised)
Lorch 1995	Wrong intervention (concomitant psychotherapy)
Marks 1993	Wrong intervention (concomitant psychotherapy)
Mavissakalian 1982	Wrong study design (review)
Mavissakalian 2003	Wrong study design (long-term phase of a discontinuation/maintenance open-label study)

Study	Reason for exclusion
McCurdy 1978	Wrong diagnosis (anxiety neurosis and depressive symptomatology)
McEvilly 1981	Wrong diagnosis (anxiety disorder)
McHugh 2007	Wrong intervention (concomitant psychotherapy)
Mellman 1986	Wrong study design (withdrawal study)
Miretzky 1992	Wrong intervention (concomitant psychotherapy)
Mueller 1986	Wrong diagnosis (anxiety neurosis)
Muncy 1981	Wrong comparator (imipramine compared with two psychotherapeutic modalities plus no treatment; no placebo or other intervention arm)
Nair 1982	Wrong diagnosis (participants were diagnosed with anxiety disorders including panic disorder, but the randomisation was not stratified by diagnosis)
Nanivadekar 1973	Wrong diagnosis (anxiety neurosis)
Nardi 2011	Wrong study design (not double-blind)
Ogunremi 1973	Wrong diagnosis (healthy participants)
Padron 1974	Wrong comparator (no placebo group)
Pareek 2014	Wrong comparison (clonazepam-CR versus clonazepam)
Pasini 1972	Wrong diagnosis (anxiety disorder)
Pfizer 2002	No data available
Pfizer 2005	Wrong study design (not double-blind)
Piedade 1987	Wrong diagnosis (anxious status)
Pohl 1989a	Wrong intervention (concomitant psychotherapy)
Pollack 2002	Wrong study design (review)
Pollack 2003	Wrong intervention (combined therapy with different drugs)
Pols 1996	Wrong study design (induced panic attacks)
Porta 1974	Wrong diagnosis (anxiety disorder)
Predescu 1969	Wrong study design (not a RCT)
Pyke 1989	Wrong study design (panicogenic)
Raffaele 2002	Wrong study design (only one group)
Rapaport 2000	Wrong intervention (concomitant psychological therapy)
Rifkin 1991	Wrong study design (not a RCT)
Rizley 1986	No usable data
Roll 2004	Wrong intervention (concomitant psychotherapy)
Roy-Byrne 2001	Wrong comparator (paroxetine versus usual care)
Rynn 2003	Wrong population (patient discontinuing benzodiazepine therapy)
Saiz-Ruiz 1992	No usable data
Scieghe 1986	Wrong diagnosis (neurotic anxiety)
Sheehan 1980	Wrong diagnosis (participants were not diagnosed with panic disorder)
Sladka 1979	Wrong diagnosis (anxiety neurosis)
Sonne 1986	Wrong diagnosis (all anxiety disorders)
Surman 1986	Wrong study design (not randomised)
Sveback 1990	Wrong study design (not randomised)
Taylor 1982	Wrong intervention (concomitant psychological therapy)
Telch 1985	Wrong intervention (concomitant psychotherapy)
Terra 1971	Wrong diagnosis (anxiety disorder)
Tesar 1990	Wrong study design (not a RCT)
Tyrer 1984	Wrong diagnosis (generalised anxiety disorder)
Tyrer 1988	Wrong diagnosis (participants with different diagnoses, and randomisation was not stratified according to diagnosis)
van Apeldoorn 2008	Wrong intervention (concomitant psychotherapy)
Van Balkom 1996	Wrong comparator (concomitant exposure in vivo)
Van Boeijen 2007	Wrong comparator (psychotherapy)
Versiani 1983	Wrong diagnosis (anxiety disorder)
Wiesner 1993	Wrong intervention (benzodiazepine agonist)
Woods 1988	Wrong intervention (benzodiazepine antagonist)
Yang 2005	Wrong study design (not double-blind)
Yang 2006	Wrong study design (not double-blind)
Yeragani 1992	Wrong study design (panicogenic)
Zajacka 1996	Wrong diagnosis (participants were not diagnosed with panic disorder)
Zmorski 1985	Wrong diagnosis (anxiety disorder)

CBT: cognitive behavioural therapy

RCT: randomised controlled trial

Appendices

Appendix 1. Cochrane Specialized Register

The Cochrane Common Mental Disorders Group (CCMD) maintains an archived controlled trials register known as the CCMDCTR. This specialized register contains over 40,000 reference records (reports of RCTs) for anxiety

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

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

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

The CCMDCTR-Studies Register was searched for a suite of panic reviews on condition alone.
Condition = panic

Records will be manually screened for drug therapy trials.

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

CCDANCTR-Refs Search 1 (panic):

#1. panic or agoraphobi*

#2. (antidepress* or anti-depress* or "anti depress*" or MAOI* or RIMA* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) NEAR (uptake or reuptake or re-uptake or "re uptake")) or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or pharmacotherap* or psychotropic* or "drug therapy")

#3. (agomelatine or alaproclate or amoxapine or amineptine or amitriptylin* or amitriptylinoxide or atomoxetine or bexloxtone or benactyzine or binospirone or brofaromine or (bupropion or amfebutamone) or butriptyline or caroxazone or cyanopramine or cilobamine or cimoxatone or citalopram or (chlorimipramin* or clomipramin* or chlomipramin* or clomipramine) or clorgyline or clovoxamine or (cx157 or tyrima) or demexiptiline or deprenyl or (desipramine* or pertofrane) or desvenlafaxine or dibenzepin or diclofensine or dimetacrin* or dosulepin or dothiepin or doxepin or duloxetine or desvenlafaxine or dvs-233 or escitalopram or etoperidone or femoxetine or fluotracen or fluoxetine or fluvoxamine or (hyperforin or hypericum or "st john*") or imipramin* or iprindole or iproniazid* or ipsapirone or isocarboxazid* or levomilnacipran or lofepramine* or ("lu aa21004" or vortioxetine) or "lu aa24530" or (ly2216684 or edivoxetine) or maprotiline or melitracen or metapramine or mianserin or milnacipran or minaprine or mirtazapine or moclobemide or nefazodone or nialamide or nitroxazepine or nomifensine or norfenfluramine or nortriptylin* or noxiptilin* or opipramol or oxaflozane or paroxetine or

phenelzine or pheniprazine or pipofezine or pirlindole or pivagabine or pizotyline or propizepine or protriptylin* or quinupramine or reboxetine or rolipram or scopolamine or selegiline or sertraline or setiptiline or teciptiline or thozalinone or tianeptin* or toloxatone or tranlycypromin* or trazodone or trimipramine or venlafaxine or viloxazine or vilazodone or viqualine or zalospirone)

#4. (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or "ethyl loflazepate" or "cm 6912" or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or 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-drugs or "z drugs") or *pam or *lam or nonbenzo*)

#5. (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or *piron* or or gabapentin* or pregabalin or mirogabalin or imagabalin)

#6. (#1 and (#2 or #3 or #4 or #5))

CCDANCTR-Refs Search 2 (ADNOS):

#7. ((anxiety or anxious):ti or ADNOS) and not (agoraphobi* or panic or (social NEAR (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or "post trauma*" or posttrauma*)

#8. (#7 and (#2 or #3 or #4 or #5))

The search of the CCMDCTR was conducted at several different time points, across a suite of associated panic reviews:

- Benzodiazepines versus placebo for panic disorder in adults (all years to 26 March 2014, 11 September 2015 and 29 May 2018)
- Antidepressants and benzodiazepines for panic disorder in adults (all years to 11 September 2015)
- Antidepressants versus placebo for panic disorder in adults (all years to May 2017)

Hence for this review, the search in January 2021 was date limited, 2014 onwards.

Appendix 2. Other database searches

Panic NMA search (22-Jan-2021)

Ovid Embase (2014 to 2021 Week 03), n=600

Ovid MEDLINE (2014 to to January 22, 2021), n=133

Ovid PsycINFO (2014 to January Week 2 2021), n=239

CLib:CENTRAL (2014 to Issue 1 of 12, 2021), n=412

CCMDCTR (2014-2016), n=223

Total=1607

Duplicates removed=408

To screen, n=1199

Database: Embase <1980 to 2021 Week 03>

Search Strategy:

1 Panic/ (23677)

2 Agoraphobia/ (6204)

3 (panic or agoraphobi* or agrophobi*).mp. (30012)

4 or/1-3 (30012)

5 exp antidepressant agent/ (428171)

6 exp serotonin uptake inhibitor/ (261582)

7 exp serotonin noradrenalin reuptake inhibitor/ (177554)

8 exp noradrenalin uptake inhibitor/ (220773)

9 (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 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or 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* or Opipramol or Oxafozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp. (230665)

10 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp. (332300)

11 exp Benzodiazepine derivative/ (217044)

12 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl lofazepate 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 lofazepate 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).mp. (240315)

13 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone).mp. (10678)

14 (placebo* or dummy or sugar pill*).mp. (458097)

15 or/5-14 (1174248)

16 major clinical study/ (3666712)

17 Randomized controlled trial/ (637112)

18 Controlled clinical study/ (465662)

19 double blind procedure/ (177381)

20 randomization/ (89576)

21 (RCT or randomi#ed).ti,ab,kw. (952346)

22 ((at random or random*) adj2 (allocat* or assign* or divide* or division or number)).ti,ab,kw. (289159)

23 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw. (233577)

24 or/16-23 (4754094)

25 ((animal or nonhuman) not (human and (animal or nonhuman))).de. (5727997)

26 24 not 25 (4613841)

27 4 and 15 and 26 (2703)

28 elsevier.cr. (25284730)

29 27 and 28 (2625)

30 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).yr,dc,dd. (11982917)

31 29 and 30 (685)

32 (random\$ adj sampl\$ adj7 ("cross section\$" or questionnaire\$1 or survey\$ or database\$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8318)

33 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group\$1.ti,ab.) (258041)

34 (((case adj control\$) and random\$) not randomi?ed controlled).ti,ab. (18055)

35 (Systematic review not (trial or study)).ti. (163799)

36 (review.ab. and review.pt.) not trial.ti. (856407)

37 or/32-36 (1233786)

38 31 not 37 (600)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily
<1946 to January 22, 2021>

Search Strategy:

1 (panic or agoraphobi*).mp. (17630)

2 exp Antidepressive Agents/ (150189)

3 exp Neurotransmitter Uptake Inhibitors/ (147746)

4 exp Monoamine Oxidase Inhibitors/ (21782)

5 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp. (254597)

6 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxadone or Benactyzine or Binspirone 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 or Escitalopram or Etoperidone or Femoxetine or Fluotraceron 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* or Opipramol or Oxaflazane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viquiline or Zalospirone).mp. (103692)

7 exp Benzodiazepines/ (65890)

8 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl lofazepate 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 lofazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metacclazepam 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 tofisolam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).mp. (95432)

9 (azapirone or alnespirone or binspirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone).mp. (3696)

10 (placebo* or dummy or sugar pill*).mp. (240983)

11 or/2-10 (716304)

12 randomized controlled trial.pt. (521298)

13 randomi#ed.ti,ab,kf. (660246)

14 controlled clinical trial.pt. (94034)

15 Double-Blind Method/ (161967)

16 clinical trials as topic.sh. (194395)

17 randomly.ab. (351007)

18 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,kf. (235272)

19 trial.ti,kf. (249466)

20 (animals not (humans and animals)).sh. (4746234)

21 or/12-19 (1389632)

22 21 not 20 (1286054)

23 1 and 11 and 22 (1221)

24 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).yr,dc,ed,ez. (9248835)

25 23 and 24 (133)

Database: APA PsycInfo <1806 to January Week 2 2021>

Search Strategy:

1 Panic Attack/ or Panic/ or Panic Disorder/ (9720)

2 Agoraphobia/ (2901)

3 (panic or agoraphobi*).mp. (19403)

4 adnos.ti,ab,id. (5)

5 (anxiety disorder* adj2 otherwise specified).ti,ab,id. (72)

6 or/1-5 (19447)

7 exp Antidepressant Drugs/ (39143)

8 Neurotransmitter Uptake Inhibitors/ or exp serotonin norepinephrine reuptake inhibitors/ or exp serotonin reuptake inhibitors/ (13726)

9 exp Monoamine Oxidase Inhibitors/ (2253)

10 exp Tricyclic Antidepressant Drugs/ (6412)

11 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp. (81357)

12 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binspirone 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 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or 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* or Opipramol or Oxaflorazone or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viquiline or Zalospiroline).mp. (38204)

13 exp benzodiazepines/ (10824)

14 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethylidiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethylidiazepam 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 premapazepam 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).mp. (25520)

15 (azapirone or alnespirone or binspirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone).mp. (1905)

16 (placebo* or dummy or sugar pill*).mp. (43421)

17 or/7-16 (149294)

18 (RCT or at random or (random* adj3 (administ* or allocat* or assign* or class* or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or substitut* or treat*)):ti,ab,id. (107013)

19 trial.ti,id. (36775)

20 randomi#ed.ti,ab,id. (88005)

21 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$ or dummy)).ti,ab,id. (26947)

22 (placebo* or dummy or sugar pill*).mp. (43421)

23 or/18-22 (174540)

24 6 and 17 and 23 (1090)

25 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).yr,an. (1307557)

26 24 and 25 (101)

27 (anxiety disorder? not (agoraphobi* or panic or (social adj3 (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or post trauma* or posttrauma*)):ti,id,hw. (15437)

28 17 and 23 and 27 (596)

29 25 and 28 (153)

30 26 or 29 (239)

Search Name:

Date Run: 24/01/2021 16:49:05

Comment:

ID Search Hits

#1 MeSH descriptor: [Panic] this term only 264

#2 MeSH descriptor: [Panic Disorder] this term only 946

#3 MeSH descriptor: [Agoraphobia] this term only 433

#4 (panic or agoraphobi*):ti,ab,kw 3120

#5 (#1 or #2 or #3 or #4) 3120

#6 MeSH descriptor: [Antidepressive Agents] explode all trees 5773

#7 MeSH descriptor: [Neurotransmitter Uptake Inhibitors] explode all trees 3466

#8 MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees 385

#9 (antidepress* or "anti depress*" or MAOI* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) near (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*):ti,ab,kw 26071

#10 (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 or Escitalopram or Etoferidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or "St John*") or Imipramin* or lprindole or lproniazid* 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* or Opipramol or Oxafozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setipitiline or Tecipitiline or Thozalinone or Tianeptin* or Toloxatone or Tranlycypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone):ti,ab,kw 24856

#11 MeSH descriptor: [Benzodiazepines] explode all trees 9637

#12 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or "cm 6912" or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or

meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchloridiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs or nonbenzo*):ti,ab,kw 23211

#13 (azapirone or alnespirone or binspirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or gabapentin* or pregabalin or mirogabalin or imagabalin):ti,ab,kw 5116

#14 (placebo* or dummy or "sugar pill*"):ti,ab,kw 320034

#15 (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14) 357277

#16 #5 and #15 1560

Limit 2014-CLib:CENTRAL, Issue 1 of 12, 2021 =421 trials

Appendix 3. Node-splitting for response: direct, indirect and network estimates

Table below summarises the direct, indirect and network estimates for each comparison. P-values <.05 reflect a statistically significant difference between direct and indirect estimates, these comparisons are in bold:

Comparison	Direct estimate: log OR (95% CrI)	Indirect estimate: log OR (95% CrI)	Network estimate: log OR (95% CrI)	p-value
Citalopram vs placebo	-0.62 (-1.50 to 0.27)	-0.16 (-2.30 to 2.00)	-0.64 (-1.40, 0.10)	0.69
Desipramine vs placebo	-0.93 (-2.50 to 0.60)	0.12 (-2.3 to 2.8)	-0.65 (-1.9, 0.64)	0.48
Brofaromine vs placebo	-27.00 (-64.00 to -3.90)	-1.60 (-3.60 to 0.29)	-2.40 (-4.20 to -0.89)	0.01
Fluoxetine vs placebo	-1.10 (-2.40, 0.19)	-0.99 (-2.30 to 0.23)	-1.00 (-1.90, -0.18)	0.90
Sertraline vs placebo	-0.36 (-1.10 to 0.38)	-0.72 (-1.70 to 0.21)	-0.51 (-1.10 to 0.06)	0.53
Fluvoxamine vs placebo	-1.00 (-1.70 to -0.37)	-40.00 (-96.00 to -3.70)	-1.10 (-1.80 to -0.50)	0.008
Clomipramine vs placebo	-0.98 (-1.80 to -0.33)	-1.30 (-2.70 to 0.16)	-0.93 (-1.50 to -0.38)	0.70
Paroxetine vs placebo	-0.58 (-0.96 to -0.16)	-0.49 (-1.50 to 0.39)	-0.62 (-0.98 to -0.25)	0.85
Citalopram vs Fluoxetine	-0.80 (-2.70 to 0.99)	-0.22 (-1.50 to 1.00)	-0.39 (-1.40 to 0.60)	0.60
Citalopram vs Clomipramine	0.06 (-1.20 to 1.30)	-0.69 (-2.00 to 0.54)	-0.28 (-1.10 to 0.51)	0.37
Desipramine vs Fluoxetine	-1.10 (-3.60 to 1.20)	-0.04 (-1.80 to 1.70)	-0.39 (-1.80 to 0.98)	0.48
Brofaromine vs Fluvoxamine	0.59 (-1.20 to 2.50)	33.00 (2.90 to 88.00)	1.30 (-0.18 to 3.00)	0.01
Alprazolam vs Imipramine	0.06 (-1.50 to 1.60)	0.08 (-1.10 to 1.20)	0.06 (-0.83 to 0.94)	0.98
Alprazolam vs Paroxetine	-0.08 (-1.40 to 1.20)	0.82 (0.17 to 1.50)	0.60 (0.01 to 1.20)	0.21
Moclobemide vs Fluoxetine	-0.10 (-1.20 to 1.00)	1.10 (-0.66 to 2.90)	0.24 (-0.72 to 1.20)	0.24
Paroxetine vs Sertraline	0.07 (-0.78 to 0.91)	-0.29 (-1.10 to 0.55)	-0.11 (-0.69 to 0.48)	0.53
Paroxetine vs Venlafaxine	-0.04 (-0.91 to 0.81)	-0.21 (-1.20 to 0.75)	-0.03 (-0.62 to 0.56)	0.78
Imipramine vs Fluvoxamine	-0.75 (-2.10 to 0.58)	0.23 (-0.98 to 1.50)	-0.05 (-0.97 to 0.89)	0.28
Paroxetine vs Clomipramine	-0.75 (-2.10 to 0.58)	0.23 (-0.98 to 1.50)	-0.05 (-0.97 to 0.89)	0.07
Moclobemide vs Clomipramine	0.66	-0.58	0.13	0.24

Appendix 4. Node splitting for dropout: direct, indirect and network estimates

Table below summarises the direct, indirect and network estimates for each comparison. P-values <.05 reflect a statistically significant difference between direct and indirect estimates, these comparisons are in bold:

Comparison	Direct estimate: log OR (95% CrI)	Indirect estimate: log OR (95% CrI)	Network estimate: log OR (95% CrI)	p-value
Citalopram vs placebo	-0.25 (-0.62 to 0.12)	0.080 (-3.7 to 3.8)	-0.29 (-0.63 to 0.05)	0.84
Desipramine vs placebo	-2.3 (-4.40 to -0.77)	1.3 (-1.60 to 4.9)	-1.5 (-2.90 to -0.23)	0.03
Adinazolam vs placebo	-0.07 (-0.62 to 0.49)	0.32 (-0.25 to 0.90)	0.12 (-0.28 to 0.52)	0.33
Fluoxetine vs placebo	0.48 (-0.38 to 1.40)	-1.6 (-3.6 to 0.08)	0.041 (-0.72 to 0.81)	0.03
Sertraline vs placebo	0.13 (-0.23 to 0.49)	-0.45 (-0.88 to -0.02)	-0.11 (-0.38 to 0.17)	0.04
Fluvoxamine vs placebo	-0.09 (-0.49 to 0.32)	0.13 (-3.70 to 3.90)	0.01 (-0.37 to 0.40)	0.90
Clomipramine vs placebo	-0.33 (-0.66 to -0.01)	-0.09 (-0.73 to 0.55)	-0.26 (-0.54 to 0.02)	0.51
Imipramine vs placebo	-0.54 (-0.78 to -0.31)	1.10 (-1.7 to 4.80)	-0.49 (-0.71 to -0.27)	0.24
Paroxetine vs placebo	-0.02 (-0.19 to 0.16)	0.24 (-0.25 to 0.74)	0.03 (-0.13 to 0.19)	0.34
Citalopram vs Fluoxetine	0.01 (-3.70 to 3.70)	0.36 (-0.49 to 1.20)	0.33 (-0.49 to 1.20)	0.84
Citalopram vs Clomipramine	0.12 (-0.42 to 0.65)	0.02 (-0.59 to 0.62)	0.03 (-0.35 to 0.42)	0.79
Desipramine vs Fluoxetine	-1.00 (-4.60 to 1.70)	2.50 (0.82 to 4.80)	1.50 (0.13 to 3.00)	0.03
Brofaromine vs Fluvoxamine	0.01 (-3.70 to 3.80)	-0.12 (-1.10 to 0.84)	-0.11 (-1.00 to 0.78)	0.94
Brofaromine vs Clomipramine	-0.40 (-1.20 to 0.43)	-0.27 (-4.00 to 3.50)	-0.39 (-1.20 to 0.40)	0.94
Alprazolam vs Clonazepam	0.98 (-0.84 to 3.20)	-1.10 (-1.50 to -0.66)	-0.88 (-1.30 to -0.50)	0.03
Clomipramine vs Adinazolam	-0.53 (-1.00 to -0.03)	-0.13 (-0.77 to 0.49)	-0.38 (-0.77 to 0.01)	0.34
Buspirone vs Alprazolam	3.10 (1.20 to 6.40)	1.60 (0.76 to 2.50)	2.00 (1.30 to 2.70)	0.19
Imipramine vs Alprazolam	0.85 (0.54 to 1.20)	0.68 (0.14 to 1.20)	0.74 (0.48 to 0.99)	0.60
Paroxetine vs Alprazolam	0.77 (0.06 to 1.50)	1.3 (1.10 to 1.60)	1.3 (1.00 to 1.50)	0.16
Imipramine vs Buspirone	-0.56 (-1.60 to 0.43)	-1.90 (-3.20 to -0.73)	-1.20 (-1.90 to -0.55)	0.10
Imipramine vs Fluoxetine	0.95 (-1.70 to 4.50)	-0.68 (-1.50 to 0.14)	-0.53 (-1.30 to 0.25)	0.25
Paroxetine vs Sertraline	0.43 (0.04 to 0.83)	-0.16 (-0.56 to 0.24)	0.14 (-0.14 to 0.42)	0.04
Paroxetine vs Venlafaxine	0.12 (-0.22 to 0.45)	-0.15 (-0.53 to 0.23)	0.11 (-0.13 to 0.35)	0.30
Imipramine vs Clomipramine	-1.2 (-2.1 to -0.38)	-0.26 (-0.77 to 0.26)	-0.50 (-0.93 to -0.08)	0.05
Imipramine vs Clomipramine	-0.24 (-1.60 to 1.10)	-0.21 (-0.58 to 0.15)	-0.23 (-0.58 to 0.13)	0.97
Paroxetine vs Clomipramine	-0.14 (-0.65 to 0.38)	0.49 (0.10 to 0.88)	0.29 (-0.01 to 0.59)	0.06

Appendix 5. WinBUGS and OpenBUGS code

Non-response – bias adjusted model (run in OpenBUGS)

- Placebo 1
- Fluoxetine 2
- Sertraline 3
- Venlafaxine 4
- Fluvoxamine 5
- Clomipramine 6
- Imipramine 7
- Paroxetine 8
- Moclobemide 9
- Citalopram 10
- Desipramine 11
- Clonazepam 12
- Adinazolam 13
- Alprazolam 14
- Escitalopram 15
- Diazepam 16
- Buspirone 17

Reboxetine 18

Etizolam 19

Ritanserin 20

```
model{
for(i in 1:ns){
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
beta[i,1] <- 0 # no bias term in baseline arm
V[i,1] <- 0 # no variance term in baseline arm
Z[i,1] <- 0 # no bias term in baseline arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) {
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] + beta[i, k]* V[i,k] * Z[i,k] # model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
#Summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) {
# calculate variance of log odds ratio for comparisons with arm 1
# check for zero or 100% events in arm k
aux.a[i,k] <- equals(r[i,k],0)+equals(r[i,k],n[i,k])
# check for zero or 100% events in arm 1
aux.b[i,k] <- equals(r[i,1],0)+equals(r[i,1],n[i,1])
aux[i,k] <- max(aux.a[i,k],aux.b[i,k]) # any zero or 100% events?
# add 0.5 if zero or 100% events
V[i,k] <- 1/(r[i,k]+(0.5*aux[i,k])) + 1/(r[i,1]+(0.5*aux[i,k])) + 1/(n[i,k]-r[i,k]+(0.5*aux[i,k])) + 1/(n[i,1]-r[i,1]+(0.5*aux[i,k]))
# model for bias parameter beta
beta[i,k] ~ dnorm(mb[i,k], Pkappa)
mb[i,k] <- A[C[i,k]]
delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm trial correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
} }
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# mean bias: assumptions
A[1] <- 0 # Placebo v Placebo
A[2] <- b # Placebo v Any Drug
A[3] <- 0 #Drug vs Drug
```

```

# bias model prior for variance
kappa ~ dunif(0,5)
kappa.sq <- pow(kappa,2)
Pkappa <- 1/kappa.sq
# bias model prior for mean
b~dnorm(0,.001)
#prediction intervals
delta.new[1] <- 0
w.new[1] <- 0
for (k in 2:nt){
delta.new[k] ~dnorm(m.new[k], tau.new[k])
m.new[k] <- d[k] + sw.new[k]
tau.new[k] <- tau *2*(k-1)/k
w.new[k] <- delta.new[k] - d[k]
sw.new[k] <- sum(w.new[1:k-1])/(k-1)
}
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}}
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
# Provide estimates of treatment effects T[k] on the natural (probability) scale given a Mean Effect, meanA, for
#'standard' treatment A, with precision (1/variance) precA
E ~ dnorm(meanE,precE)
for (k in 1:nt) { logit(T[k]) <- E + (d[k] - d[3]) }
# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
rr[c,k] <-(T[k]/T[c])
logrr[c,k] <-log(T[k]/T[c])
}}
#pairwise prediction intervals: ORs and LORs
for (c in 1: (nt-1)) {
for (k in (c+1) :nt) {
lor.new[c,k] <- delta.new[k] - delta.new[c]
or.new[c,k] <- exp(lor.new[c,k])
}
}
}
list(ns=48, nt=20, meanE=0.496, precE=1.267)
t[,1] t[,2] t[,3] r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] na[] C[,1] C[,2] C[,3] Z[,1] Z[,2] Z[,3] #Name

```

2 10 NA 4 21 7 21 NA NA 2 NA 3 NA NA 0 NA #Amore 1999 bis
1 5 NA 52 92 33 87 NA NA 2 NA 2 NA NA 1 NA #Asnis 2011
1 8 NA 20 69 54 209 NA NA 2 NA 2 NA NA 1 NA #Ballenger 1998
3 8 NA 62 112 64 113 NA NA 2 NA 3 NA NA 0 NA #Bandelow 2004
1 7 NA 19 24 45 83 NA NA 2 NA 2 NA NA 1 NA #Barlow 2000
1 8 NA 5 10 6 9 NA NA 2 NA 2 NA NA 1 NA #Bergink 2005
1 5 NA 10 18 9 21 NA NA 2 NA 2 NA NA 1 NA #Black 1993
1 4 NA 87 180 72 181 NA NA 2 NA 2 NA NA 1 NA #Bradwejn 2005
1 6 NA 14 15 2 15 NA NA 2 NA 2 NA NA 1 NA #Broocks 1998
2 11 NA 2 11 4 11 NA NA 2 NA 3 NA NA 0 NA #Bystritsky 1995
1 6 NA 42 51 63 107 NA NA 2 NA 2 NA NA 1 NA #Caillard 1999
1 3 NA 22 62 18 63 NA NA 2 NA 2 NA NA 1 NA #Koszycki 2011
9 6 NA 15 67 9 68 NA NA 2 NA 3 NA NA 0 NA #Krueger 1999
1 4 NA 81 168 71 175 NA NA 2 NA 2 NA NA 1 NA #Liebowitz 2009
1 11 NA 15 28 9 28 NA NA 2 NA 2 NA NA 1 NA #Lydiard 1993
1 2 NA 35 90 16 90 NA NA 2 NA 2 NA NA 1 NA #Michelson 2001
3 8 NA 51 157 56 164 NA NA 2 NA 3 NA NA 0 NA #Pfizer 2008
1 3 NA 73 88 62 88 NA NA 2 NA 2 NA NA 1 NA #Pollack 1998
1 5 NA 24 37 9 36 NA NA 2 NA 2 NA NA 1 NA #Sharp 1990
1 8 NA 226 421 149 413 NA NA 2 NA 2 NA NA 1 NA #Sheehan 2005
9 2 NA 44 182 48 184 NA NA 2 NA 3 NA NA 0 NA #Tiller 1999
1 3 NA 32 56 63 113 NA NA 2 NA 2 NA NA 1 NA #Tsutsui 1997
1 8 NA 57 84 43 87 NA NA 2 NA 2 NA NA 1 NA #Tsutsui 2000a
1 8 NA 21 37 44 83 NA NA 2 NA 2 NA NA 1 NA #Tsutsui 2000b
1 18 NA 31 40 23 42 NA NA 2 NA 2 NA NA 1 NA #Versiani 2002
8 6 NA 5 38 4 35 NA NA 2 NA 3 NA NA 0 NA #Zhang 2000
1 12 NA 10 17 5 10 NA NA 2 NA 2 NA NA 1 NA #Baker 2003
1 6 8 52 123 49 121 36 123 3 NA 2 2 NA 1 1 #Lecrubier 1997
1 4 8 68 162 67 330 36 161 3 NA 2 2 NA 1 1 #Pollack 2007a
1 4 8 76 163 87 334 37 166 3 NA 2 2 NA 1 1 #Pollack 2007b
1 10 15 104 125 96 126 90 129 3 NA 2 2 NA 1 1 #Stahl 2003
1 6 10 64 96 49 98 136 281 3 NA 2 2 NA 1 1 #Wade 1997
1 5 20 18 19 5 20 18 20 3 NA 2 2 NA 1 1 #Den Boer 1990
1 5 7 37 50 41 50 33 48 3 NA 2 2 NA 1 1 #Nair 1996
1 8 14 15 72 14 77 15 77 3 NA 2 2 NA 1 1 #GSK 1994/04
1 7 14 17 20 11 20 22 41 3 NA 2 2 NA 1 1 #Uhlenhuth 1989
1 12 NA 15 16 2 13 NA NA 2 NA 2 NA NA 1 NA #Beauclair 1994
1 13 NA 43 83 107 232 NA NA 2 NA 2 NA NA 1 NA #Carter 1995
1 13 NA 63 103 30 99 NA NA 2 NA 2 NA NA 1 NA #Davidson 1994
1 14 NA 13 18 9 17 NA NA 2 NA 2 NA NA 1 NA #Klosko 1990
1 12 NA 140 225 80 230 NA NA 2 NA 2 NA NA 1 NA #Moroz 1999
1 14 16 57 79 29 78 32 81 3 NA 2 2 NA 1 1 #Noyes 1996
1 12 NA 41 69 134 344 NA NA 2 NA 2 NA NA 1 NA #Rosenbaum 1997
1 12 NA 7 10 4 14 NA NA 2 NA 2 NA NA 1 NA #Valenca 2000
1 14 NA 28 70 26 139 NA NA 2 NA 2 NA NA 1 NA #Pecknold 1994
1 19 NA 10 15 3 15 NA NA 2 NA 2 NA NA 1 NA #Savoldi 1990
1 14 17 28 33 10 34 28 34 3 NA 2 2 NA 1 1 #Sheehan 1993
1 14 NA 59 108 28 109 NA NA 2 NA 2 NA NA 1 NA #Schweizer 1993

END

Drop out – bias adjusted model (run in winBUGS)

Placebo 1

Fluoxetine 2

Sertraline 3

Venlafaxine 4

Fluvoxamine 5

Clomipramine 6

Imipramine 7

Paroxetine 8

Moclobemide 9

Citalopram 10

Desipramine 11

Brofaromine 12

Clonazepam 13

Adinazolam 14

Alprazolam 15

Escitalopram 16

Diazepam 17

Buspirone 18

Reboxetine 19

Etizolam 20

Mirtazapine 21

model{

for(i in 1:ns){

w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm

beta[i,1] <- 0 # no bias term in baseline arm

V[i,1] <- 0 # no variance term in baseline arm

Z[i,1] <- 0 # no bias term in baseline arm

delta[i,1] <- 0 # treatment effect is zero for control arm

mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

for (k in 1:na[i]) {

r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

logit(p[i,k]) <- mu[i] + delta[i,k] + beta[i,k] * V[i,k] * Z[i,k] # model for linear predictor

rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

#Deviance contribution

dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))

+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }

#Summed residual deviance contribution for this trial

resdev[i] <- sum(dev[i,1:na[i]])

for (k in 2:na[i]) {

calculate variance of log odds ratio for comparisons with arm 1

check for zero or 100% events in arm k

aux.a[i,k] <- equals(r[i,k],0)+equals(r[i,k],n[i,k])

check for zero or 100% events in arm 1

aux.b[i,k] <- equals(r[i,1],0)+equals(r[i,1],n[i,1])

aux[j,k] <- max(aux.a[i,k],aux.b[i,k]) # any zero or 100% events?

```

# add 0.5 if zero or 100% events
V[i,k] <- 1/(r[i,k]+(0.5*aux[i,k])) + 1/(r[i,1]+(0.5*aux[i,k])) + 1/(n[i,k]-r[i,k]+(0.5*aux[i,k])) + 1/(n[i,1]-r[i,1]+(0.5*aux[i,k]))
# model for bias parameter beta
beta[i,k] ~ dnorm(mb[i,k], Pkappa)
mb[i,k] <- A[C[i,k]]
delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm trial correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
} }
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# mean bias: assumptions
A[1] <- 0 # Placebo v Placebo
A[2] <- b # Placebo v Any Drug
A[3] <- 0 #Drug vs Drug
# bias model prior for variance
kappa ~ dunif(0,5)
kappa.sq <- pow(kappa,2)
Pkappa <- 1/kappa.sq
# bias model prior for mean
b~dnorm(0,.001)
#prediction intervals
delta.new[1] <- 0
w.new[1] <- 0
for (k in 2:nt){
delta.new[k] ~dnorm(m.new[k], tau.new[k])
m.new[k] <- d[k] + sw.new[k]
tau.new[k] <- tau *2*(k-1)/k
w.new[k] <- delta.new[k] - d[k]
sw.new[k] <- sum(w.new[1:k-1])/(k-1)
}
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
} }
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best

```



```

}
# Provide estimates of treatment effects T[k] on the natural (probability) scale given a Mean Effect, meanA, for
#'standard' treatment A, with precision (1/variance) precA
E ~ dnorm(meanE,precE)
for (k in 1:nt) { logit(T[k]) <- E + (d[k] - d[3]) }
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
rr[c,k] <- (T[k]/T[c])
logrr[c,k] <- log(T[k]/T[c])
}}
#pairwise prediction intervals: ORs and LORs
for (c in 1: (nt-1)) {
for (k in (c+1) :nt) {
lor.new[c,k] <- delta.new[k] - delta.new[c]
or.new[c,k] <- exp(lor.new[c,k])
}
}
}
list(ns=64, nt=21, meanE=-0.76, precE=2.303)
t[,1] t[,2] t[,3] r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] na[] C[,2] C[,3] Z[,2] Z[,3] #Name
2 7 NA 1 19 2 19 NA NA 2 3 NA 0 NA #Amore 1999
2 10 NA 1 21 1 21 NA NA 2 3 NA 0 NA #Amore 1999 bis
1 5 NA 29 95 29 93 NA NA 2 2 NA 1 NA #Asnis 2011
6 12 NA 22 46 27 47 NA NA 2 3 NA 0 NA #Bakish 1993
1 8 NA 23 69 67 209 NA NA 2 2 NA 1 NA #Ballenger 1998
3 8 NA 31 112 37 113 NA NA 2 3 NA 0 NA #Bandelow 2004
1 7 NA 10 24 32 83 NA NA 2 2 NA 1 NA #Barlow 2000
1 8 NA 3 10 2 9 NA NA 2 2 NA 1 NA #Bergink 2005
1 5 NA 7 25 4 25 NA NA 2 2 NA 1 NA #Black 1993
1 4 NA 45 180 51 181 NA NA 2 2 NA 1 NA #Bradwejn 2005
1 6 NA 4 15 0 15 NA NA 2 2 NA 1 NA #Broocks 1998
2 11 NA 1 11 2 11 NA NA 2 3 NA 0 NA #Bystritsky 1995
1 6 NA 25 57 37 123 NA NA 2 2 NA 1 NA #Caillard 1999
6 8 NA 4 35 1 38 NA NA 2 3 NA 0 NA #GSK 29060 525
1 5 NA 7 25 6 25 NA NA 2 2 NA 1 NA #Hoehn-Saric 1993
6 14 NA 36 149 58 166 NA NA 2 3 NA 0 NA #Holland 1999
1 3 NA 19 62 16 63 NA NA 2 2 NA 1 NA #Koszycki 2011
6 9 NA 15 68 17 67 NA NA 2 3 NA 0 NA #Krueger 1999
1 4 NA 43 168 55 175 NA NA 2 2 NA 1 NA #Liebowitz 2009
1 3 NA 14 45 49 132 NA NA 2 2 NA 1 NA #Londborg 1998
1 11 NA 11 28 2 28 NA NA 2 2 NA 1 NA #Lydiard 1993
1 2 NA 10 90 15 90 NA NA 2 2 NA 1 NA #Michelson 2001
3 8 NA 25 157 42 164 NA NA 2 3 NA 0 NA #Pfizer 2008
1 7 18 3 22 4 20 5 18 3 2 2 1 1 #Pohl 1989
1 3 NA 15 88 17 88 NA NA 2 2 NA 1 NA #Pollack 1998
2 21 NA 3 15 2 15 NA NA 2 3 NA 0 NA #Ribeiro 2001
1 5 NA 9 37 7 36 NA NA 2 2 NA 1 NA #Sharp 1990
1 8 NA 117 445 133 444 NA NA 2 2 NA 1 NA #Sheehan 2005
1 3 NA 23 56 54 113 NA NA 2 2 NA 1 NA #Tsutsui 1997

```

1 8 NA 34 84 41 87 NA NA 2 2 NA 1 NA #Tsutsumi 2000a
 1 8 NA 18 37 38 83 NA NA 2 2 NA 1 NA #Tsutsumi 2000b
 5 12 NA 1 15 1 15 NA NA 2 3 NA 0 NA #Van Vliet 1996
 1 19 NA 21 40 11 42 NA NA 2 2 NA 1 NA #Versiani 2002
 6 8 NA 4 35 1 38 NA NA 2 3 NA 0 NA #Zhang 2000
 1 6 NA 12 15 10 16 NA NA 2 2 NA 1 NA #Johnston 1995
 1 6 7 2 20 7 20 6 20 3 2 2 1 1 #Gentil 1993
 1 6 8 44 123 33 121 36 123 3 2 2 1 1 #Lecrubier 1997
 1 4 8 42 162 53 330 35 161 3 2 2 1 1 #Pollack 2007a
 1 4 8 42 163 67 334 30 166 3 2 2 1 1 #Pollack 2007b
 1 10 16 47 125 38 126 31 129 3 2 2 1 1 #Stahl 2003

Non-remission (run in winBUGS)

Placebo 1

Fluoxetine 2

Sertraline 3

Venlafaxine 4

Fluvoxamine 5

Clomipramine 6

Imipramine 7

Paroxetine 8

Moclobemide 9

Citalopram 10

Desipramine 11

Clonazepam 12

Alprazolam 13

Escitalopram 14

Diazepam 15

Buspirone 16

model{

for(i in 1:ns){

w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm

delta[i,1] <- 0 # treatment effect is zero for control arm

mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

for(k in 1:na[i]) {

r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor

rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

#Deviance contribution

dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])))

+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }

#Summed residual deviance contribution for this trial

resdev[i] <- sum(dev[i,1:na[i]])

for(k in 2:na[i]) {

delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions

md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm trial correction)

taud[i,k] <- tau * 2*(k-1)/k # precision of LOR distributions (with multi-arm trial correction)

w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs

```

sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}}
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
# Provide estimates of treatment effects T[k] on the natural (probability) scale given a Mean Effect, meanA, for
#'standard' treatment A, with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + (d[k] - d[3]) }
# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
for (k in 2:nt) {
NNT[k] <- 1/(T[1]- T[k]) # assumes events are "bad"
RD[k] <- T[k] - T[1]
RR[k] <- T[k]/T[1]
}
}
list(ns=32, nt=16, meanA=0.5624, precA=3.7355)
t[,1] t[,2] t[,3] r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] na[] #trial
2 7 NA 5 19 6 19 NA NA 2 #Amore 1999
1 5 NA 53 95 33 93 NA NA 2 #Asnis 2011
1 8 NA 40 69 112 209 NA NA 2 #Ballenger 1998
1 4 NA 92 180 93 181 NA NA 2 #Bradwejn 2005
2 11 NA 4 11 5 11 NA NA 2 #Bystritsky 1995
1 5 NA 21 25 14 25 NA NA 2 #Hoehn-Saric 1993
1 4 NA 126 168 117 175 NA NA 2 #Liebowitz 2009
1 3 NA 27 45 57 132 NA NA 2 #Londborg 1998
1 11 NA 15 28 6 28 NA NA 2 #Lydiard 1993
1 2 NA 65 90 52 90 NA NA 2 #Michelson 2001
1 3 NA 47 88 38 88 NA NA 2 #Pollack 1998
1 5 NA 20 37 16 36 NA NA 2 #Sharp 1990
1 8 NA 209 445 164 444 NA NA 2 #Sheehan 2005
2 9 NA 80 184 85 182 NA NA 2 #Tiller 1999
END

```

Frequency of Panic attacks

Placebo 1

Fluvoxamine 2

Paroxetine 3

Sertraline 4

Venlafaxine 5

Clomipramine 6

Maprotiline 7

Adinazolam 8

Moclobemide 9

Alprazolam 10

Imipramine 11

Desipramine 12

Fluoxetine 13

Reboxetine 14

Clonazepam 15

Diazepam 16

Normal likelihood, identity link

Random effects model for multi-arm trials

```
model{ # *** PROGRAM STARTS
```

```
for(i in 1:ns){ # LOOP THROUGH STUDIES
```

```
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
```

```
delta[i,1] <- 0 # treatment effect is zero for control arm
```

```
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
```

```
for (k in 1:na[i]) { # LOOP THROUGH ARMS
```

```
var[i,k] <- pow(se[i,k],2) # calculate variances
```

```
prec[i,k] <- 1/var[i,k] # set precisions
```

```
y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
```

```
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
```

```
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k] #Deviance contribution
```

```
}
```

```
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
```

```
for (k in 2:na[i]) { # LOOP THROUGH ARMS
```

```
delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
```

```
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of treat effects distributions (with multi-arm trial correction)
```

```
taud[i,k] <- tau *2*(k-1)/k # precision of treat effects distributions (with multi-arm trial correction)
```

```
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
```

```
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
```

```
}
```

```
}
```

```
totresdev <- sum(resdev[]) #Total Residual Deviance
```

```
d[1]<-0 # treatment effect is zero for reference treatment
```

```
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
```

```
sd ~ dunif(0,5) # vague prior for between-trial SD.
```

```
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
```

```
# ranking on relative scale
```

```
for (k in 1:nt) {
```

```
rk[k] <- rank(d[],k) # assumes events are "bad"
```

```

best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
list(ns=40, nt=16)
t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] na[] #Study#
1 2 NA 2.1 1.2 NA 0.43788027 0.246585883 NA 2 #Asnis 2011
1 3 NA 9.8 6.37 NA 2.118791014 0.87086851 NA 2 #Ballenger 1998
4 3 NA -1.82 -2.13 NA 1.174833708 1.189814663 NA 2 #Bandelow 2004
1 5 NA -3.7 -5 NA 0.105697795 0.10830801 NA 2 #Bradwejn 2005
1 6 NA 1.1 0.55 NA 0.266053216 0.112141433 NA 2 #Caillard 1999
7 2 NA 5 1.6 NA 0.40824829 0.402492236 NA 2 #Den Boer 1988
3 6 NA 0.38 0.16 NA 1.310002864 0.450001084 NA 2 #GSK 29060 525
1 2 NA 1.9 0.8 NA 4.735258411 1.42128463 NA 2 #Hoehn-Saric 1993
8 6 NA 3.1 1.5 NA 0.624500541 0.499522781 NA 2 #Holland 1999
16 6 NA 3.7 3.4 NA 1.099524999 1.103537094 NA 2 #Krueger 1999
9 10 NA 4.7 2.4 NA 2.863295573 1.407124728 NA 2 #Lepola 1990
1 5 NA -1.56 -1.82 NA 0.110397746 0.110397746 NA 2 #Liebowitz 2009
1 4 NA 8.8 2.17 NA 3.028681456 0.535075975 NA 2 #Londborg 1998
1 11 NA 1.6 0.9 NA 0.62364138 0.491353815 NA 2 #Lydiard 1993
1 12 NA -2.2 -2.9 NA 0.337309617 0.337309617 NA 2 #Michelson 2001
4 3 NA -4.07 -4.59 NA 0.543062184 0.667292095 NA 2 #Pfizer 2008
1 10 NA 14 13 NA 0.63107412 0.436033256 NA 2 #Pohl 1989
1 4 NA 1.31 0.74 NA 2.141601196 0.646483859 NA 2 #Pollack 1998
1 4 NA 4.47 4.39 NA 0.828571429 1.170574176 NA 2 #Tsutsui 1997
1 3 NA 0 0 NA 1.688749537 1.78991886 NA 2 #Tsutsui 2000a
1 13 NA 5.8 1.2 NA 1.103105664 0.279478278 NA 2 #Versiani 2002
1 6 3 -8.5 -8.7 -12.2 1.258881491 1.227755341 1.475052479 3 #Lecrubier 1997
1 5 3 -5.1 -6.9 -7.6 0.109337903 0.077068521 1.342750957 3 #Pollack 2007a
1 5 3 -4.8 -6.25 -6 0.109687785 0.078070178 1.30038217 3 #Pollack 2007b
1 2 10 4.6 5.8 2.5 0.431760375 0.297372212 0.300891532 3 #Nair 1996
1 3 9 -8.6 -10.1 -11.3 1.499996438 1.29499611 1.900413489 3 #GSK 1994/04
1 10 9 2.8 1.3 0.9 0.654073773 0.38340579 0.312358076 3 #Schweizer 1993b
1 10 9 0 0.13 0 0.01 0.116666667 0.003535534 3 #Sheikh 1999
1 10 9 -3.3 -5.9 -7.5 2.437314095 1.00623059 1.510518675 3 #Taylor 1990
1 10 9 20.05 8.85 4.12 0.661876121 1.030827338 0.877696542 3 #Uhlenhuth 1989
1 15 NA 10.8 2.4 NA 1.725 0.610170216 NA 2 #Beauclair 1994
1 8 NA -1.23 -2.3 NA 0.45 0.285436723 NA 2 #Carter 1995
1 8 NA 1.8 1.3 NA 0.299540101 0.299501269 NA 2 #Davidson 1994
1 9 NA 0.56 0.51 NA 0.256284643 0.2025 NA 2 #Klosko 1990
1 9 NA 5.36 1.93 NA 1.086244573 0.540315633 NA 2 #Lydiard 1992
1 15 NA 2.2 1.5 NA 0.000686803 0.000677285 NA 2 #Moroz 1999
1 9 14 4.9 1.8 1.4 0.956324716 0.837885005 0.288888889 3 #Noyes 1996
1 9 NA 2.7 1.35 NA 0.590442933 0.246822979 NA 2 #Pecknold 1994
1 9 NA -0.5 -2.7 NA 0.59426608 0.415861968 NA 2 #Schweizer 1993
1 15 9 -2 -5.6 -5.3 5.820379557 2.431840076 2.653613888 3 #Tesar 1991

```

END

Panic scales, endpoint (run in WinBUGS)

```
1 Placebo
2 Fluvoxamine
3 Paroxetine
4 Imipramine
5 Venlafaxine
6 Clomipramine
7 Adinazolam
8 Brofaromine
9 Reboxetine
10 Alprazolam
11 Clonazepam
12 Moclobemide
# Normal likelihood, identity link: SMD with arm-based means
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]){
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
phi[i,k] <- theta[i,k] * Pooled.sd[i] # theta is SMD
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])/var[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]){ # LOOP THROUGH ARMS
# trial-specific RE distributions
delta[i,k] ~ dnorm(md[i,k], taud[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of RE distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]
# cumulative adjustment for multi-arm trials
sw[i,k] <-sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,10) # vague prior for for between-trial SD
```

```

tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# pairwise differences
for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- d[k] - d[c] } }
# rank treatments
for (k in 1:nt) {
rk[k] <- rank(d[,k])
best[k] <- equals(rk[k],1) # Smallest is best (i.e. rank 1)
# prob treat k is h-th best, prob[1,k]=best[k]
for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
}
} # *** PROGRAM ENDS
DATA
#nt=no. treatments, ns=no. studies;
list(nt=12,ns=19)
t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] Pooled.sd[] na[] #Study#
1 2 NA 0.9 0.5 NA 0.093831486 0.085769003 NA 0.852878145 2 #Asnis 2011
1 3 NA 3 2.86 NA 0.156501609 0.090614595 NA 1.307543332 2 #Ballenger 1998
1 4 NA 0.9 1.05 NA 0.183711731 0.08451848 NA 0.800284473 2 #Barlow 2000
1 2 NA 14.8 8.1 NA 3.488393454 4.997189686 NA 19.59859344 2 #Black 1993
1 5 NA 1.27 2.71 NA 0.097982627 0.099611746 NA 1.265132574 2 #Bradwejn 2005
1 6 NA 3.9 2.85 NA 0.210042013 0.145010473 NA 1.5 2 #Caillard 1999
7 6 NA 2.7 1.7 NA 0.160695825 0.103479296 NA 1.407631354 2 #Holland 1999
12 6 NA 3.1 2.9 NA 0.200003597 0.199994876 NA 1.643206626 2 #Krueger 1999
1 3 NA 3.21 2.83 NA 0.059946532 0.059540208 NA 1.22013713 2 #Sheehan 2005
1 8 NA 12.8 6.6 NA 0.347439614 0.490577891 NA 1.638766474 2 #Van Vliet 1993
1 9 NA 3.8 2.5 NA 0.206021205 0.207142724 NA 1.265078372 2 #Versiani 2002
3 6 NA 3.32 3.1 NA 0.212074694 0.176013196 NA 1.159412077 2 #Zhang 2000
1 11 NA 6.6 2.5 NA 0.45 0.332820118 NA 1.562049935 2 #Beauclair 1994
1 7 NA 3.6 3.2 NA 0.100503586 0.099498744 NA 1.005411856 2 #Davidson 1994
1 11 NA 3.5 1.5 NA 0.4 0.221880078 NA 0.979795897 2 #Valenca 2000
1 10 NA 3.6 2.75 NA 0.169722463 0.099238105 NA 1.25886192 2 #Pecknold 1994
1 5 3 9.2 5.44 6.2 0.626498204 0.668302213 0.964339324 10.98180467 3 #Pollack 2007a
1 2 4 3.3 3.4 2.6 0.218797487 0.192148199 0.231455025 1.415371448 3 #Nair 1996
1 3 10 2.3 2 1.9 0.100399203 0.099484975 0.200140362 1.203177189 3 #GSK 1994/04
END

```

Panic scales, change from baseline (run in WinBUGS)

- 1 Placebo
- 2 Paroxetine
- 3 Sertraline
- 4 Imipramine
- 5 Venlafaxine
- 6 Clomipramine
- 7 Fluoxetine
- 8 Desipramine
- 9 Adinazolam
- 10 Citalopram
- 11 Escitalopram

12 Alprazolam

13 Clonazepam

14 Diazepam

Normal likelihood, identity link: SMD with arm-based means

Random effects model for multi-arm trials

model{ # *** PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES

w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm

delta[i,1] <- 0 # treatment effect is zero for control arm

mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

for (k in 1:na[i]){

var[i,k] <- pow(se[i,k],2) # calculate variances

prec[i,k] <- 1/var[i,k] # set precisions

y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood

phi[i,k] <- theta[i,k] * Pooled.sd[i] # theta is SMD

theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor

#Deviance contribution

dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])/var[i,k]

}

summed residual deviance contribution for this trial

resdev[i] <- sum(dev[i,1:na[i]])

for (k in 2:na[i]){ # LOOP THROUGH ARMS

trial-specific RE distributions

delta[i,k] ~ dnorm(md[i,k], taud[i,k])

md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]

precision of RE distributions (with multi-arm trial correction)

taud[i,k] <- tau *2*(k-1)/k

#adjustment, multi-arm RCTs

w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]

cumulative adjustment for multi-arm trials

sw[i,k] <-sum(w[i,1:k-1])/(k-1)

}

}

totresdev <- sum(resdev[]) #Total Residual Deviance

d[1]<-0 # treatment effect is zero for control arm

vague priors for treatment effects

for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,10) # vague prior for between-trial SD

tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

pairwise differences

for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- d[k] - d[c] } }

rank treatments

for (k in 1:nt) {

rk[k] <- rank(d[],k)

best[k] <- equals(rk[k],1) # Smallest is best (i.e. rank 1)

prob treat k is h-th best, prob[1,k]=best[k]

for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }

}

```

}
} # *** PROGRAM ENDS
DATA
#nt=no. treatments, ns=no. studies;
list(nt=14,ns=16)
t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] Pooled.sd[] na[] #Study#
1 6 NA -0.3 -3.1 NA 0.25819889 0.180739223 NA 0.863133825 2 #Broocks 1998
1 5 NA -7.5 -9.28 NA 0.449889616 0.459763915 NA 5.476326989 2 #Liebowitz 2009
1 8 NA -7.2 -8.4 NA 0.396862697 0.321269802 NA 1.910497317 2 #Lydiard 1993
1 7 NA -7.6 -11.5 NA 0.664078309 0.68516016 NA 6.400781202 2 #Michelson 2001
1 4 NA -4.7 -5.8 NA 0.558585877 0.56348913 NA 2.572984648 2 #Pohl 1989
1 3 NA -0.64 -0.88 NA 0.077192103 0.073554247 NA 0.705072866 2 #Pollack 1998
1 9 NA -0.85 -1.04 NA 0.127777778 0.070046772 NA 1.08409517 2 #Carter 1995
1 12 NA -1 -2.1 NA 0.14596009 0.128719181 NA 1.348320715 2 #Schweizer 1993
3 2 NA -13.5 -12.7 NA 1.210692425 1.261431006 NA 12.93972252 2 #Bandelow 2004
2 6 NA -3.32 -3.1 NA 1.289660298 0.978848896 NA 6.942802028 2 #GSK 29060 525
3 2 NA -17.4 -17 NA 0.757802459 0.707223138 NA 8.25991828 2 #Pfizer 2008
1 5 2 -6.8 -9.61 -9.51 0.28102491 0.304979184 0.283719746 4.583858606 3 #Pollack 2007b
1 10 11 -1.2 -1.5 -1.6 0.070243936 0.099215674 0.100175845 0.987761683 3 #Stahl 2003
1 4 12 -0.9 -1.9 -2.3 0.223606798 0.156524758 0.400083325 1.360828412 3 #Taylor 1990
1 13 12 -0.9 -2.4 -1.8 0.298481003 0.254950976 0.265361389 1.312346571 3 #Tesar 1991
1 12 14 -6.1 -7.8 -7.6 0.22501758 0.169841555 0.188888889 1.738676445 3 #Noyes 1996
END

```

Agoraphobia, end of treatment (run in WinBUGS)

```

1 Placebo
2 Paroxetine
3 Desipramine
4 Reboxetine
5 Citalopram
6 Escitalopram
7 Clomipramine
8 Fluvoxamine
9 Ritanserin
10 Imipramine
11 Alprazolam
12 Adinazolam
13 Diazepam
14 Buspirone

# Normal likelihood, identity link: SMD with arm-based means
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]){
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions

```

```

y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
phi[i,k] <- theta[i,k] * Pooled.sd[i] # theta is SMD
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])/var[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]){ # LOOP THROUGH ARMS
# trial-specific RE distributions
delta[i,k] ~ dnorm(md[i,k], taud[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of RE distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]
# cumulative adjustment for multi-arm trials
sw[i,k] <-sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,10) # vague prior for for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# pairwise differences
for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- d[k] - d[c] } }
# rank treatments
for (k in 1:nt) {
rk[k] <- rank(d[],k)
best[k] <- equals(rk[k],1) # Smallest is best (i.e. rank 1)
# prob treat k is h-th best, prob[1,k]=best[k]
for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
}
}
} # *** PROGRAM ENDS
DATA
#nt=no. treatments, ns=no. studies;
list(nt=14,ns=15)
t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] Pooled.sd[] na[] #Study#
1 2 NA 4.8 4.09 NA 0.38523473 0.225498915 NA 3.245320377 2 #Ballenger 1998
1 3 NA 4 2.8 NA 0.56694671 0.529150262 NA 2.901723626 2 #Lydiard 1993
1 2 NA 31 24.2 NA 0.949904626 0.98 NA 18.6045613 2 #Sheehan 2005
1 4 NA 5.2 3.2 NA 0.486664263 0.207142724 NA 2.311832577 2 #Versiani 2002
1 5 6 21.1 17.2 16.1 0.635941766 0.800339772 0.899793754 8.56053517 3 #Stahl 2003
1 7 5 34 27 22.78 0.306186218 0.282842712 0.689015234 9.057498202 3 #Wade 1997
1 8 9 28.84 23.75 31.1 2.473101611 2.569242106 1.996808704 10.1808113 3 #Den Boer 1990

```

```

1 10 11 3.2 2.6 2.6 0.151716521 0.141602086 0.157785846 2.964898818 3 #CNCPS 1992
1 10 11 1.83 1.68 1.47 0.141421356 0.133279156 0.088775453 0.680104716 3 #Schweizer 1993b
1 10 11 4.9 5 3.66 0.670820393 0.626099034 1.138506724 5.494917966 3 #Uhlenhuth 1989
1 12 NA 4.7 4.9 NA 0.200002137 0.200002525 NA 2.010396454 2 #Davidson 1994
1 11 13 5.2 3.6 3.5 0.382529886 0.32836034 0.333333333 3.087825103 3 #Noyes 1996
1 11 NA 5.3 3.9 NA 0.300002381 0.247671167 NA 2.790035842 2 #Pecknold 1994
1 11 14 27.2 16.8 25.5 3.435363756 3.063766745 3.899219543 17.88476183 3 #Sheehan 1993
1 11 NA 14.63 8.89 NA 1.36 1.209712776 NA 5.282290997 2 #Munjack 1989

```

END

Agoraphobia, change in baseline (run in WinBUGS)

```

1=Placebo
2=Venlafaxine
3=Clomipramine
4=Paroxetine
5=Alprazolam
6=Imipramine
7=Adinazolam
# Normal likelihood, identity link: SMD with arm-based means
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]){
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
phi[i,k] <- theta[i,k] * Pooled.sd[i] # theta is SMD
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])/var[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]){ # LOOP THROUGH ARMS
# trial-specific RE distributions
delta[i,k] ~ dnorm(md[i,k], tau[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of RE distributions (with multi-arm trial correction)
tau[i,k] <- tau *2*(k-1)/k
#adjustment, multi-arm RCTs
w[i,k] <- delta[i,k] - d[t[i,k]] + d[t[i,1]]
# cumulative adjustment for multi-arm trials
sw[i,k] <-sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance

```

```

d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,10) # vague prior for for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# pairwise differences
for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- d[k] - d[c] } }
# rank treatments
for (k in 1:nt) {
rk[k] <- rank(d[,k])
best[k] <- equals(rk[k],1) # Smallest is best (i.e. rank 1)
# prob treat k is h-th best, prob[1,k]=best[k]
for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }
}
} # *** PROGRAM ENDS
DATA
#nt=no. treatments, ns=no. studies;
list(nt=7, ns=9)
t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] Pooled.sd[] na[] #Study#
1 2 NA -14.83 -21.06 NA 1.637158543 1.666520327 NA 21.15183355 2 #Bradwejn 2005
1 3 NA -8.2 -30.3 NA 5.939773488 5.990214242 NA 21.8100321 2 #Broocks 1998
1 2 NA -14.99 -21.56 NA 1.70995633 1.709813779 NA 21.15057636 2 #Liebowitz 2009
1 3 4 -1.4 -2.7 -2.8 0.230143654 0.264575131 0.29970746 2.831821872 3 #Lecrubier 1997
1 2 4 -16.38 -25.1 -25.55 0.224179415 1.182285788 0.240373674 15.00388961 3 #Pollack 2007b
1 4 5 -0.9 -1.1 -1.3 0.20010414 0.198680835 0.199585778 1.498866044 3 #GSK 1994/04
1 6 5 -3.2 -4.9 -4.3 0.894427191 1.498165545 0.816496581 4.881262004 3 #Taylor 1990
1 7 NA -2.63 -2.95 NA 0.522222222 0.312589636 NA 4.714796447 2 #Carter 1995
1 5 NA -2.1 -3.7 NA 0.29192018 0.287142787 NA 2.853041141 2 #Schweizer 1993
END

```

References

References to studies included in this review

Amore 1999 {published data only}

studyIdentifiers

Amore M, Magnani K, Cerisoli M, Casagrande C, Ferrari G. Panic disorder. A long-term treatment study: fluoxetine vs imipramine. *Human Psychopharmacology: Clinical and Experimental* 1999;14(6):429-34.

Amore 1999 bis {published data only}

studyIdentifiers

Amore M, Magnani K, Cerisoli M, Ferrari G. Short-term and long-term evaluation of selective serotonin reuptake inhibitors in the treatment of panic disorder: fluoxetine vs citalopram.. *Human Psychopharmacology: Clinical and Experimental* 1999;14(6):435-40.

Asnis 2001 {published data only}

studyIdentifiers

Asnis G M, Hameedi F A, Goddard A W, Potkin S G, Black D, Jameel M et al. Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. *Psychiatry Research* 2001;103:1-14.

Baker 2003 {published data only}

studyIdentifiers

Baker B, Khaykin Y, Devins G, Dorian P, Shapiro C, Newman D. Correlates of therapeutic response in panic disorder presenting with palpitations: heart rate variability, sleep, and placebo effect.. Canadian Journal of Psychiatry/Revue Canadienne de Psychiatrie 2003;48(6):381-7.

Bakish 1993 {published data only}

studyIdentifiers

Bakish D, Saxena BM, Bowen R, D'Souza J. Reversible monoamine oxidase-A inhibitors in panic disorder. Clinical Neuropharmacology 1993;16(Suppl 2):S77-S82.

Ballenger 1998 {published data only}

studyIdentifiers

Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. American Journal of Psychiatry 1998;155:36-42.

Bandelow 2004 {published data only}

studyIdentifiers

Bandelow B, Behnke K, Lenoir S, Hendriks GJ, Alkin T, Goebel C, et al. Sertraline versus paroxetine in the treatment of panic disorder: an acute, double-blind noninferiority comparison. Journal of Clinical Psychiatry 2004;65(3):405-13.

Barlow 2000 {published data only}

studyIdentifiers

Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 2000;283:2529-2536.

Beauclair 1994 {published data only}

studyIdentifiers

Beauclair L, Fontaine R, Annable L, Holobow N, Chouinard G. Clonazepam in the treatment of panic disorder: a double-blind, placebo-controlled trial investigating the correlation between clonazepam concentrations in plasma and clinical response. Journal of Clinical Psychopharmacology 1994;14(2):111-8.

Bergink 2005 {published data only}

studyIdentifiers

Bergink V, Westenberg HGM. Metabotropic glutamate II receptor agonists in panic disorder: a double-blind clinical trial with LY354740. International Clinical Psychopharmacology 2005;20:291-293.

Black 1993 {published data only}

studyIdentifiers

Black DW, Wesner R, Bowers W, Gabel J. A comparison of fluvoxamine, cognitive therapy and placebo in the treatment of panic disorder. Archives of General Psychiatry 1993;50:44-50.

Bradwejn 2005 {published data only}

studyIdentifiers

Bradwejn J, Ahokas A, Stein DJ, Salinas E, Emilien G, Whitaker T. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. British Journal of Psychiatry 2005;187:352-359.

Broocks 1998 {published data only}

studyIdentifiers

Bandelow B, Broocks A, Pekrun G, George A, Meyer T, Pralle L, et al. The use of the panic and agoraphobia scale (P & A) in a controlled clinical trial. Pharmacopsychiatry 2000;33:174-181.

* Broocks A, Bandelow B, Pekrun G, George A, Meyer T, Bartmann U, et al. Comparison of aerobic exercise, clomipramine and placebo in the treatment of panic disorder. American Journal of Psychiatry 1998;155:603-609.

Broocks A, Stevinson C. Exercise may help treat panic disorder. Focus on Alternative and Complementary Therapies 1999;4:84-85.

Bystritsky 1994 {published data only}

studyIdentifiers

Bystritsky A, Rosen RM, Murphy KJ, Bohn P, Keys SA, Vapnik T. Double-blind pilot trial of desipramine versus fluoxetine in panic patients. *Anxiety* 1994;1(6):287-90.

Caillard 1999 {published data only}

studyIdentifiers

Caillard V, Rouillon F, Viel JF, Markabi S, French University Antidepressants Group. Comparative effects of low and highdoses of clomipramine and placebo in panic disorder: a double-blind controlled study. *Acta Psychiatrica Scandinavica* 1999;99:51-58.

Carter 1995 {published data only}

studyIdentifiers

Carter CS, Fawcett J, Hertzman M, Papp LA, Jones W, Patterson WM, et al. Adinazolam-SR in panic disorder with agoraphobia: relationship of daily dose to efficacy. *Journal of Clinical Psychiatry* 1995;56(5):202-10.

CNCPS 1992 {published data only}

studyIdentifiers

Cross National Collaborative Panic Study Second Phase Investigators. Drug treatment of panic disorder: Comparative efficacy of alprazolam, imipramine, and placebo. *British Journal of Psychiatry* 1992;160:191-202.

Davidson 1994 {published data only}

studyIdentifiers

Davidson JR, Beitman B, Greist JH, Maddock RJ, Lewis CP, Sheridan AQ, et al. Adinazolam sustained-release treatment of panic disorder: a double-blind study. *Journal of Clinical Psychopharmacology* 1994;14(4):255-63.

Den Boer 1988 {published data only}

studyIdentifiers

Den Boer JA, Westenberg HGM. Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder; a double-blind comparative study with fluvoxamine and maprotiline. *International Clinical Psychopharmacology* 1988;3(1):59-74.

Den Boer 1990 {published data only}

studyIdentifiers

Den Boer JA, Westenberg HGM. Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin. *Psychopharmacology* 1990;102:85-94.

Gentil 1993 {published data only}

studyIdentifiers

Gentil V, Lotufo-Neto F, Andrade L, Cordás T, Bernik M, Ramos R, et al. Clomipramine, a better reference drug for panic/agoraphobia. Effectiveness comparison with imipramine. *Journal of Psychopharmacology* 1993;7(4):316-24.

GSK 1994/04 {published data only}

studyIdentifiers

GlaxoSmithKline. A double-blind, multicentered, flexible-dose study of paroxetine, alprazolam and placebo in the treatment of panic disorder.. www.gsk-clinicalstudyregister.com/study/29060/223 2008.

GSK 29060 525 {published data only}

studyIdentifiers

GSK. A double blind, multicenter randomized drug-controlled study to assess the efficacy and tolerance of paroxetine compared with clomipramine in treatment of panic disorder. GSK Clinical Studies Register [<http://www.gsk-clinicalstudyregister.com/>].

Hoehn-Saric 1993 {published data only}

studyIdentifiers

Hoehn-Saric R, McLeod DR, Hipsley PA. Effect of fluvoxamine on panic disorder. *Journal of Clinical Psychopharmacology* 1993;13:321-326.

Holland 1999 {published data only}

studyIdentifiers

Holland R, Musch B, Hindmarch I. Specific effects of benzodiazepines and tricyclic antidepressants in panic disorder: comparisons of clomipramine with alprazolam SR and adinazolam SR. *Human Psychopharmacology Clinical Experimental* 1999;14:119-24.

Johnston 1995 {published data only}

studyIdentifiers

Johnston DG, Troyer IE, Whitsett SF, Dalby T. Clomipramine treatment and behaviour therapy with agoraphobic women. *Canadian Journal of Psychiatry* 1995;40(4):192-99.

Klosko 1990 {published data only}

studyIdentifiers

Klosko JS, Barlow DH, Tassinari R, Cerny JA. A comparison of alprazolam and behavior therapy in treatment of panic disorder. *Journal of Consulting and Clinical Psychology* 1990;58(1):77-84.

Koszycki 2011 {published data only}

studyIdentifiers

Koszycki D, Taljaard M, Segal Z, Bradwejn J. A randomized trial of sertraline, self-administered cognitive behavior therapy, and their combination for panic disorder. *Psychological Medicine* 2011;41:373-383.

Krueger 1999 {published data only}

studyIdentifiers

Krueger MB, Dahl AA. The efficacy and safety of moclobemide compared to clomipramine in the treatment of panic disorder. *European Archives of Psychiatry and Clinical Neuroscience* 1999;249(Suppl 1):S19-S24.

Lecrubier 1997 {published data only}

studyIdentifiers

Bakker A, van Dyck R, Spinhoven P, van Balkom AJ. Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder. *Journal of Clinical Psychiatry* 1999;60:831-838.

- * Lecrubier Y, Bakker A, Dunbar G, Judge R and the Collaborative Panic Study Investigators. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatrica Scandinavica* 1997;95:145-52.

Lecrubier Y, Judge R and the Collaborative Paroxetine Panic Study Investigators. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatrica Scandinavica* 1997;95:153-60.

Lepola 1990 {published data only}

studyIdentifiers

Lepola U, Heikkinen H, Rimon R, Riekkinen P. Clinical evaluation of alprazolam in patients with panic disorder; a double-blind comparison with imipramine. *Human Psychopharmacology* 1990;5:159-63.

Liebowitz 2009 {published data only}

studyIdentifiers

Liebowitz MR, Asnis G, Mangano R, Tzanis E. A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder. *Journal of Clinical Psychiatry* 2009;70:550-561.

Londborg 1998 {published data only}

studyIdentifiers

Londborg PD, Wolkow R, Smith WT, DuBoff E, England D, Ferguson J, et al. Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. *British Journal of Psychiatry* 1998;173:54-60.

Lydiard 1992 {published data only}

studyIdentifiers

Lydiard RB, Lesser IM, Ballenger JC, Rubin RT, Laraia M, DuPont R. A fixed-dose study of alprazolam 2 mg, alprazolam 6 mg, and placebo in panic disorder.. *Journal of Clinical Psychopharmacology* 1992;12(2):96-103.

Lydiard 1993 {published data only}

studyIdentifiers

Lydiard RB, Morton WA, Emmanuel NP, Zealberg JJ, Laraia MT, Stuart GW, et al. Preliminary report: placebo-controlled, double-blind study of the clinical and metabolic effects of desipramine in panic disorder. *Psychopharmacology Bulletin* 1993;29(2):183-8.

Michelson 2001 {published data only}

studyIdentifiers

Michelson D, Allgulander C, Dantendorfer K, Knezevic A, Maierhofer D, Micev V, et al. Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder: randomised, placebo-controlled trial. *British Journal of Psychiatry* 2001;179:514-8.

Moroz 1999 {published data only}

studyIdentifiers

Moroz G, Rosenbaum JF. Efficacy, safety, and gradual discontinuation of clonazepam in panic disorder: a placebo-controlled, multicenter study using optimized dosages. *Journal of Clinical Psychiatry* 1999;60(9):604-12.

Munjack 1989 {published data only}

studyIdentifiers

Munjack DJ, Brown RA, McDowell D, Palmer R. Actual medication versus therapist guesses: in a blind study, how blind is blind? *Journal of Clinical Psychopharmacology* 1989;9(2):148-9.

Nair 1996 {published data only}

studyIdentifiers

Nair NP, Bakish D, Saxena B, Amin M, Schwartz G, West TE. Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder. *Anxiety* 1996;2(4):192-8.

Noyes 1996 {published data only}

studyIdentifiers

Noyes R, Burrows GD, Reich JH, Judd FK, Garvey MJ, Norman TR, et al. Diazepam versus alprazolam for the treatment of panic disorder.. *Journal of Clinical Psychiatry* 1996;57(8):349-55.

Pecknold 1994 {published data only}

studyIdentifiers

Pecknold J, Luthe L, Munjack D, Alexander P. A double-blind, placebo-controlled, multicenter study with alprazolam and extended-release alprazolam in the treatment of panic disorder. *Journal of Clinical Psychopharmacology* 1994;14(5):314-21.

Pfizer 2008 {published data only}

studyIdentifiers

Pfizer. A randomized, double-blind, multicenter study of sertraline compared with paroxetine in the treatment of panic disorder. <http://clinicaltrials.gov/show/NCT006773522008>.

Pohl 1989b {published data only}

studyIdentifiers

Pohl R, Balon R, Yeragani VK, Gershon S. Serotonergic anxiolytics in the treatment of panic disorder: a controlled study with buspirone. *Psychopathology* 1989;22(Suppl 1):60-67.

Pollack 1998 {published data only}

studyIdentifiers

Pollack MH, Otto MW, Worthington JJ, Gus Manfro G, Wolkow R. Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. *Archives of General Psychiatry* 1998;55:1010-6.

Pollack 2007a {published data only}

studyIdentifiers

Pollack MH, Mangano R, Entsuah R, Tzanis E, Simon NM. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. *Psychopharmacology* 2007;194:233-42.

Pollack 2007b {published data only}

studyIdentifiers

Pollack MH, Lepola U, Koponen H, Simon NM, Worthington JJ, Emilien G et al. A double-blind study of the efficacy of venlafaxine extended-release, paroxetine and placebo in the treatment of panic disorder. *Depression and Anxiety* 2007;24:1-14.

Ribeiro 2001 {published data only}

studyIdentifiers

Ribeiro L, Busnello JV, Kauer-Sant'Anna M, Madruga M, Quevedo J, Busnello EAD, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. *Brazilian Journal of Medical and Biological Research* 2001;34:1303-7.

Robinson 1989 {published data only}

studyIdentifiers

Robinson D, Shrotriya RC, Alms DR, Messina M, Andary J. Treatment of panic disorder: nonbenzodiazepine anxiolytics, including buspirone. *Psychopharmacology Bulletin* 1989;25(1):21-6.

Rosenbaum 1997 {published data only}

studyIdentifiers

Rosenbaum JF, Moroz G, Bowden CL. Clonazepam in the treatment of panic disorder with or without agoraphobia: a dose-response study of efficacy, safety, and discontinuance. Clonazepam Panic Disorder Dose-Response Study Group.. *Journal of Clinical Psychopharmacology* 1997;17(5):390-400.

Savoldi 1990 {published data only}

studyIdentifiers

Savoldi F, Somenzini G, Ecari U. Etizolam versus placebo in the treatment of panic disorder with agoraphobia: a double-blind study. *Current Medical Research and Opinion* 1990;12(3):185-90.

Schweizer 1992 {published data only}

studyIdentifiers

Schweizer E, Clary C, Dever AI, Mandos LA. The use of low-dose intranasal midazolam to treat panic disorder: a pilot study.. *Journal of Clinical Psychiatry* 1992;53(1):19-22.

Schweizer 1993 {published data only}

studyIdentifiers

Schweizer E, Rickels K, Weiss S, Zavodnick S. Maintenance drug treatment of panic disorder. I. Results of a prospective, placebo-controlled comparison of alprazolam and imipramine. *Archives of General Psychiatry* 1993;50:51-60.

Sharp 1990 {published data only}

studyIdentifiers

Sharp DM, Power KG, Simpson RJ, Swanson V, Moodie E, Anstee JA, et al. Fluvoxamine, placebo and cognitive behaviour therapy used alone and in combination in the treatment of panic disorder and agoraphobia. *Journal of Anxiety Disorders* 1996;10(4):219-42.

Sheehan 1993 {published data only}

studyIdentifiers

Sheehan DV, Raj AB, Harnett Sheehan K, Soto S, Knapp E. The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: a double-blind placebo-controlled study. *Acta Psychiatrica Scandinavica* 1993;88(1):1-11.

Sheehan 2005 {published data only}

studyIdentifiers

Sheehan DV, Burnham DB, Iyengar MK, Perera P. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *Journal of Clinical Psychiatry* 2005;66:34-40.

Sheikh 1999 {published data only}

studyIdentifiers

Sheikh JI, Swales PJ. Treatment of panic disorder in older adults: a pilot study comparison of alprazolam, imipramine, and placebo. *International Journal of Psychiatry in Medicine* 1999;29(1):107-17.

Stahl 2003 {published data only}

studyIdentifiers

Stahl S, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry* 2003;64:1322-7.

Taylor 1990 {published data only}

studyIdentifiers

Taylor CB, Hayward C, King R, Ehlers A, Margraf J, Maddock R, et al. Cardiovascular and symptomatic reduction effects of alprazolam and imipramine in patients with panic disorder: results of a double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology* 1990;10(2):112-8.

Tesar 1991 {published data only}

studyIdentifiers

Tesar GE, Rosenbaum JF, Pollack MH, Otto MW, Sachs GS, Herman JB, et al. Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder. *Journal of Clinical Psychiatry* 1991;52(2):69-76.

Tiller 1999 {published data only}

studyIdentifiers

Tiller JWG, Bouwer C, Behnke K. Moclobemide and fluoxetine for panic disorder. *European Archives of Psychiatry and Clinical Neuroscience* 1999;249((Suppl1)):S7-S10.

Tsutsui 1997 {published data only}

studyIdentifiers

Tsutsui S. Clinical evaluation of paroxetine Hcl, a selective serotonin reuptake inhibitor, in the treatment of panic disorder: late phase II double-blind, parallel group study. *Japanese Pharmacology and Therapeutics* 2000;28:S271-S294.

Tsutsui 2000a {published data only}

studyIdentifiers

Tsutsui S. Clinical evaluation of paroxetine Hcl, a selective serotonin reuptake inhibitor, in the treatment of panic disorder: late phase II double-blind, parallel group study. *Japanese Pharmacology and Therapeutics* 2000;28:S271-94.

Tsutsui 2000b {published data only}

studyIdentifiers

Tsutsui S. Clinical evaluation of paroxetine Hcl, a selective serotonin reuptake inhibitor, in the treatment of panic disorder: phase III double-blind, parallel group study. *Japanese Pharmacology and Therapeutics* 2000;28:S295-314.

Uhlenhuth 1989 {published data only}

studyIdentifiers

Uhlenhuth EH, Matuzas W, Glass RM, Easton C. Response of panic disorder to fixed doses of alprazolam or imipramine. *Journal of Affective Disorders* 1989;17(3):261-70.

Valenca 2000 {published data only}

studyIdentifiers

Valenca AM, Nardi AE, Nascimento I, Mezzasalma MA, Lopes FL, Zin W. Double-blind clonazepam vs placebo in panic disorder treatment. *Arquivos de Neuro-Psiquiatria* 2000;58(4):1025-9.

Van Vliet 1993 {published data only}

studyIdentifiers

Van Vliet I M, Westenberg H G M, Den Boer J A. MAO inhibitors in panic disorder: clinical effects of treatment with brofaromine. *Psychopharmacology* 1993;112:483-9.

Van Vliet 1996 {published data only}

studyIdentifiers

van Vliet IM, den Boer JA, Westenberg HGM, Slaap BR. A double-blind comparative study of brofaromine and fluvoxamine in outpatients with panic disorder. *Journal of Clinical Psychopharmacology* 1996;16(4):299-306.

Versiani 2002 {published data only}

studyIdentifiers

Versiani M, Cassano G, Perugi G, Benedetti A, Mastalli L, Nardi A, et al. Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *Journal of Clinical Psychiatry* 2002;63:31-37.

Wade 1997 {published data only}

studyIdentifiers

Wade AG, Lepola U, Koponen HJ, Pedersen V, Pedersen T. The effect of citalopram in panic disorder. *British Journal of Psychiatry* 1997;170:549-53.

Zhang 2000 {published data only}

studyIdentifiers

Zhang HY, Zhao QP, Ma C. Paroxetine versus clomipramine for the treatment of panic disorders: a double-blind randomised study. *Chinese Mental Health Journal* 2000;14(6):410-3.

References to studies excluded from this review

Ananth 1979 {published data only}

studyIdentifiers

Ananth J, Van den Steen N. Clobazam in the treatment of anxiety neurosis: a double-blind study. *Current Therapeutic Research, Clinical and Experimental* 1979;26(1):119-26.

Bakish 1994 {published data only}

studyIdentifiers

Bakish D. The use of the reversible monoamine oxidase-A inhibitor brofaromine in social phobia complicated by panic disorder with or without agoraphobia. *Journal of Clinical Psychopharmacology* 1994;14(1):74-5.

Baldini Rossi 2000 {published data only}

studyIdentifiers

Baldini Rossi NA, Cassano PA, Dell'Osso LA, Ciapparelli AA, Bandettini di Poggio AA, Russo AA, et al. Depression comorbid with panic disorder or other anxiety disorders: a 16-week multicentre randomised parallel-group trial of moclobemide versus paroxetine. *European Neuropsychopharmacology* 2000;10(Suppl 2):S52-3.

Ballenger 1988 {published data only}

studyIdentifiers

Ballenger JC, Burrows GD, DuPont RL, Lesser IM, Noyes R, Pecknold JC. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I. Efficacy in short-term treatment. *Archives of General Psychiatry* 1988;45(5):413-22.

Balon 1991 {published data only}

studyIdentifiers

Balon R, Pohl R, Yeragani VK, Ramesh C, Glitz DA. The changes of thyroid hormone during pharmacological treatment of panic disorder patients. *Progress in Neuropsychopharmacology and Biological Psychiatry* 1991;15(5):595-600.

Balon 1993 {published data only}

studyIdentifiers

Balon R, Yeragani VK, Pohl R, Merlos B, Sherwood P. Changes in appetite and weight during the pharmacological treatment of patients with panic disorder. *Canadian Journal of Psychiatry* 1993;38(1):19-22.

Barbosa 1980 {published data only}

studyIdentifiers

Barbosa MFS. Treatment of neurotic anxiety with clobazam: double-blind clinical trial against placebo. *Clinica Terapeutica* 1980;9(4):285-8.

Bernardi 1998 {published data only}

studyIdentifiers

Bernardi F, Cairolì S, D'Aurizio C, De Rosa A, Grasso A, Sannino V, et al. Double-blind comparative study of alprazolam (Xanax) and amitriptyline in the treatment of anxiety associated with depression [Studio in doppio cieco di confronto fra alprazolam (Xanax) e amitriptilina nel trattamento dell'ansia associata a depressione]. *Minerva Psichiatrica* 1988;29(4):203-10.

Bueno 1988 {published data only}

studyIdentifiers

Bueno JR, Laks J. Anti anxiety activity of buspirone: comparative trial with placebo and diazepam [Atividade ansiolítica da buspirona: estudo comparativo com placebo e diazepam]. *Jornal Brasileiro de Psiquiatria* 1988;37(2):97-9.

Bystritsky 1990 {published data only}

studyIdentifiers

Bystritsky AA, Pasnau RO. Initial reaction and subsequent response to antidepressants in panic patients. *American Journal of Psychiatry* 1990;147(11):1575.

Charney 1986 {published data only}

studyIdentifiers

Charney DS, Woods SW, Goodman WK, Rifkin B, Kinch M, Aiken B, et al. Drug treatment of panic disorder: the comparative efficacy of imipramine, alprazolam, and trazodone. *Journal of Clinical Psychiatry* 1986;47(12):580-6.

Chen 1997 {published data only}

studyIdentifiers

Chen ZM, Hu XZ, Zhang YL, Zhang JH. Buspirone vs diazepam treatment of anxiety disorders in a double blind study. *Zhongyuan Journal of Psychologic Medicine* 1997;3(3):146-7.

Chen 1998 {published data only}

studyIdentifiers

Chen ZM, Hu XZ, Zhang YL, Zhang JH. Buspirone vs diazepam in treating anxiety disorders in a double-blind study [Chinese Journal of New Drugs and Clinical Remedies]. 1998 17;2:99-100.

Chen 2003 {published data only}

studyIdentifiers

Chen Z, Guo B, Zhang J. Mianserin vs. alprazolam in treating anxiety disorder. *Chinese Journal of New Drugs and Clinical Remedies* 2003;22(7):405-7.

Chouinard 1983 {published data only}

studyIdentifiers

Chouinard G, Annable L, Fontaine R, Solyom L. Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study.. *Psychopharmacology Bulletin* 1983;18(1):115-6.

Chouinard 1982 {published data only}

studyIdentifiers

Chouinard G, Annable L, Fontaine R, Solyom L. Alprazolam in the treatment of generalized anxiety and panic disorders: a double-blind placebo-controlled study. *Psychopharmacology* 1982;77(3):229-33.

Cohn 1984 {published data only}

studyIdentifiers

Cohn JB, Wilcox CS. Long-term comparison of alprazolam, lorazepam and placebo in patients with an anxiety disorder. *Pharmacotherapy* 1984;4(2):93-8.

Cooper 1990 {published data only}

studyIdentifiers

Cooper SJ, Kelly CB, McGilloway S, Gilliland A. Beta 2-adrenoceptor antagonism in anxiety. *European Neuropsychopharmacology* 1990;1(1):75-7.

Cooper 1991 {published data only}

studyIdentifiers

Cooper SJ, Gilliland A, Kelly C, McGilloway S. A comparison of beta-2-adrenoceptor antagonist (ICI 118,551), diazepam and placebo in the treatment of acute anxiety. *Journal of Psychopharmacology* 1991;5(2):155-9.

Csanalosi 1977 {published data only}

studyIdentifiers

Csanalosi I, Pereira Ogan J, Case G, Werblowsky J, Rickels K. Triflubazam (ORF 8063), a new benzodiazepine in anxiety neurosis. *Current Therapeutic Research, Clinical and Experimental* 1977;22(1):166-71.

Cunha 1988 {published data only}

studyIdentifiers

Cunha JM, Swicker AP. Anti-anxiety activity of cannabidiol; double-blind, comparative trial with diazepam and placebo [Efeito ansiolítico do canabidiol; um estudo comparativo duplo-cego com diazepam e placebo. *R. Cent. Ci.c Bioméd. Univ. Fed. Uberlândia* 1988;4(1):27-34.

Dager 1992 {published data only}

studyIdentifiers

Dager SR, Roy-Byrne PP, Hendrickson H, Cowley DS, Avery DH, Hall KC, et al. Long-term outcome of panic states during double-blind treatment and after withdrawal of alprazolam and placebo. *Annals of Clinical Psychiatry* 1992;4(4):251-8.

Dasberg 1974 {published data only}

studyIdentifiers

Dasberg H. The effect of daily oral dosage of diazepam, plasma concentrations and metabolic clearance of diazepam and demethyldiazepam on various constituents of the acute clinical anxiety syndrome. *Psychotherapy and Psychosomatics* 1974;24(2):113-8.

Davis 1981 {published data only}

studyIdentifiers

Davis JM, Nasr S, Spira N, Vogel C. Anxiety: differential diagnosis and treatment from a biologic perspective. *Journal of Clinical Psychiatry* 1981;42(11 pt 2):4-14.

De Candia 2009 {published data only}

studyIdentifiers

De Candia MP, DiSciascio G, Durbano F, Mencacci C, Rubiera M, Aguglia E, et al. Effects of treatment with etizolam 0.5 mg BID on cognitive performance: a 3-week, multicenter, randomized, double-blind, placebo-controlled, two-treatment, three-period, noninferiority crossover study in patients with anxiety disorder. *Clinical Therapeutics* 2009;31(12):2851-9.

de Jonghe 1989 {published data only}

studyIdentifiers

de Jonghe F, Swinkels J, Tuynman-Qua H, Jonkers F. A comparative study of suriclone, lorazepam and placebo in anxiety disorder.. *Pharmacopsychiatry* 1989;22(6):266-71.

Dell'Erba 2006 {published data only}

studyIdentifiers

Dell'Erba GL, Nuzzo E. Effectiveness treatment for panic and agoraphobia in comparison between drug and specialized psychological treatment [Il trattamento efficace nella pratica del disturbo di panico e agorafobia in una valutazione comparativa tra psicofarmacologia e trattamento psicologico specifico]. *Rivista di Psichiatria* 2006;41(6):397-403.

den Boer 1987 {published data only}

studyIdentifiers

den Boer JA, Westenberg HG, Kamerbeek WD, Verhoeven WM, Kahn RS. Effect of serotonin uptake inhibitors in anxiety disorders; a double-blind comparison of clomipramine and fluvoxamine.. *International Clinical Psychopharmacology* 1987;2(1):21-32.

De Rosa 1980 {published data only}

studyIdentifiers

De Rosa E, De Rosa G, Coppi R, Zannella F, Pepe C. Randomized double-blind study of loxapine as compared with diazepam in therapy of patients with anxiety neuroses [Ricerca in doppio cieco randomizzata sulla loxapina in comparazione al diazepam nell'ambito di pazienti affetti da nevrosi d'ansia]. *Clinica Terapeutica* 1980;95(2):127-46.

Downing 1978 {published data only}

studyIdentifiers

Downing RW, Rickels K. Prediction of response to chlordiazepoxide and placebo in anxious outpatients: an attempt at replication. *Pharmakopsychiatr Neuropsychopharmakol* 1978;11(5):207-19.

Downing 1979 {published data only}

studyIdentifiers

Downing RW, Rickels K, Rickels LA, Downing D. Nonspecific factors and side effect complaints. Factors affecting the incidence of drowsiness in drug and placebo treated anxious and depressed outpatients. *Acta Psychiatrica Scandinavica* 1979;60(5):438-48.

Downing 1983 {published data only}

studyIdentifiers

Downing RW, Rickels K. Physician prognosis in relationship to drug and placebo response in anxious and depressed psychiatric outpatients. *Journal of Nervous and Mental Disease* 1983;171(3):182-5.

Dunner 1986 {published data only}

studyIdentifiers

Dunner DL, Ishiki D, Avery DH, Wilson LG, Hyde TS. Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: a controlled study. *Journal of Clinical Psychiatry* 1986;47(9):458-60.

Dyukova 1992 {published data only}

studyIdentifiers

Dyukova GM, Shepeleva IP, Vorob'eva OV. Treatment of negative crises (panic attacks). *Neuroscience and Behavioral Physiology* 1992;22(4):343-5.

Dyukova 1993 {published data only}

studyIdentifiers

Dyukova GM, Shepeleva IP, Vorov'eva OV. Treatment of autonomic attacks (panic attacks). *Journal of Russian and East European Psychiatry* 1993;26(1):22-7.

Evans 1986 {published data only}

studyIdentifiers

Evans L, Kenardy J, Schneider P, Hoey H. Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks. A double-blind comparison of zimeldine, imipramine and placebo.. *Acta Psychiatrica Scandinavica* 1986;73(1):49-53.

Fahy 1992 {published data only}

studyIdentifiers

Fahy TJ, O'Rourke D, Brophy J, Schazmann W, Sciascia S. The Galway Study of Panic Disorder. I: Clomipramine and lofepramine in DSM III-R panic disorder: a placebo controlled trial. *Journal of Affective Disorders* 1992;26(1):63-75.

Fava 1989 {published data only}

studyIdentifiers

Fava M, Rosenbaum JF, MacLaughlin RA, Tesar GE, Pollack MH, Cohen LS, et al. Dehydroepiandrosterone-sulfate/cortisol ratio in panic disorder. *Psychiatry Research* 1989;28:345-350.

Filip 1981 {published data only}

studyIdentifiers

Filip V, Sladka R, Dostalova J, Haskovcova V, Jarosova M, Faltus F, et al. A double-blind, placebo-controlled study with tofizopam in anxiety neurosis. *Agressologie* 1981;22(C):27-30.

Franulic 1989 {published data only}

studyIdentifiers

Franulic AM, Sanchez GV, O'Ryan FG, Gladic DM, Barahona MC, Gloger SK. Clomipramine and diazepam plasma levels in panic disorder and agoraphobia. Preliminary findings [Concentraciones plasmaticas de clomipramina y diazepam en Desorden de Panico y Agoraphobia. Un estudio preliminar]. *Revista Chilena de Neuro-Psiquiatria* 1989;27:101-10.

Furukawa 2009 {published data only}

studyIdentifiers

Furukawa TA, Katherine Shear M, Barlow DH, Gorman JM, Woods SW, Money R, et al. Evidence-based guidelines for interpretation of the Panic Disorder Severity Scale. *Depression and Anxiety* 2009;26(10):922-9.

Greiss 1980 {published data only}

studyIdentifiers

Greiss KC, Fogari R. Double-blind clinical assessment of alprazolam, a new benzodiazepine derivative, in the treatment of moderate to severe anxiety. *Journal of Clinical Pharmacology* 1980;20(11-12):693-9.

Grilo 1988 {published data only}

studyIdentifiers

Grilo CM, Money R, Barlow DH, Goddard AW, Gorman JM, Hofmann SG, et al. Pretreatment patient factors predicting attrition from a multicenter randomized controlled treatment study for panic disorder. *Comprehensive Psychiatry* 1998;39(6):323-32.

Hare 1974 {published data only}

studyIdentifiers

Hare MK. Treatment of anxiety and depression: a comparative trial of amitriptyline (Laroxyl) and diazepam (Valium). *Clinical Trials Journal* 1974;11(1):39-44.

Hofmeijer-Sevink 2017 {published data only}

studyIdentifiers

Hofmeijer-Sevink MK, Duits P, Rijkeboer MM, Hoogendoorn AW, van Megen HJ, Vulink NC, et al. No effects of d-cycloserine enhancement in exposure with response prevention therapy in panic disorder with agoraphobia: a double-blind, randomized controlled trial.. *Journal of Clinical Psychopharmacology* 2017;37(5):531-9.

Hu 2002 {published data only}

studyIdentifiers

Hu H, Meng HQ. A comparative study in psychotherapy and drug in treatment of anxiety disorders. *Chinese Journal of Nervous and Mental Diseases* 2002;28(2):85-7.

Huppert 2004 {published data only}

studyIdentifiers

Huppert JD, Schultz LT, Foa EB, Barlow DH, Davidson JR, Gorman JM, et al. Differential response to placebo among patients with social phobia, panic disorder, and obsessive-compulsive disorder. *American Journal*

Kahn 1986 {published data only}

studyIdentifiers

Kahn RJ, McNair DM, Lipman RS, Covi L, Rickels K, Downing R, et al. Imipramine and chlordiazepoxide in depressive and anxiety disorders. II. Efficacy in anxious outpatients. Archives of General Psychiatry 1986;43(1):79-85.

Kaplan 2000 {published data only}

studyIdentifiers

Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Harmatz JS, Shader RI. Differences in pharmacodynamics but not pharmacokinetics between subjects with panic disorder and healthy subjects after treatment with a single dose of alprazolam. Journal of Clinical Psychopharmacology 2000;20(3):338-46.

Keller 1993 {published data only}

studyIdentifiers

Keller MB, Lavori PW, Goldenberg IM, Baker LA, Pollack MH, Sachs GS, et al. Influence of depression on the treatment of panic disorder with imipramine, alprazolam and placebo. Journal of Affective Disorders 1993;28(1):27-38.

Kerry 1983 {published data only}

studyIdentifiers

Kerry RJ, McDermott CM. Alprazolam in the treatment of neurotic anxiety. Pharmatherapeutica 1983;3(7):451-5.

Klein 1988 {published data only}

studyIdentifiers

Klein DF. Nottingham study of neurotic disorder. Lancet 1988;2(8618):1915.

Klerman 1990 {published data only}

studyIdentifiers

Klerman GL. Depression and panic anxiety: the effect of depressive co-morbidity on response to drug treatment of patients with panic disorder and agoraphobia. Journal of Psychiatric Research 1990;24(Suppl 2):27-41.

Knijnik 1990 {published data only}

studyIdentifiers

Knijnik L, D'Arrigo BE. Comparative study of clonazepam and placebo in anxiety neurosis [Estudo comparativo sobre o emprego do clonazepam e placebo em neurose de ansiedade]. Jornal Brasileiro de Psiquiatria 1990;39(4):209-12.

Laakmann 1980 {published data only}

studyIdentifiers

Laakmann G, Blaschke D, Buttermann M, Hippus H, Schewe S, Uberla K. Double blind study with the benzodiazepine derivative Ka-2547 in outpatients with anxiety neurosis [Doppelblindstudie mit dem Benzodiazepin-Derivat Ka-2547 bei ambulanten Patienten mit Angstneurose]. Arzneimittelforschung 1980;30(8):1233-4.

Lapierre 1975 {published data only}

studyIdentifiers

Lapierre YD. Clinical and physiological assessment of chlorazepate, diazepam and placebo in anxious neurotics. International Journal of Clinical Pharmacology and Biopharmacy 1975;11(4):315-22.

Lepola 1989 {published data only}

studyIdentifiers

Lepola U, Jolkkonen J, Rimón R, Riekkinen P. Long-term effects of alprazolam and imipramine on cerebrospinal fluid monoamine metabolites and neuropeptides in panic disorder. Neuropsychobiology 1989;2(4):182-6.

Lorch 1995 {published data only}

studyIdentifiers

Lorch B, Graf-Morgenstern M, Hain C, Sandmann J, Schlegel S, Hautzinger M, Benkert O. Treatment of panic disorder: pharmacological versus behavioral therapy? *Pharmacopsychiatry* 1995;28:199.

Marks 1993 {published data only}

studyIdentifiers

Marks IM, Swinson RP, Basoglu M, Kuch K, Noshirvani H, O'Sullivan G, et al. Alprazolam and exposure alone and combined in panic disorder with agoraphobia. A controlled study in London and Toronto. *British Journal of Psychiatry* 1993;162:776-87.

Mavissakalian 1982 {published data only}

studyIdentifiers

Mavissakalian M, Michelson L. Agoraphobia: behavioral and pharmacological treatments, preliminary outcome, and process findings. *Psychopharmacology Bulletin* 1982;18(4):91-103.

Mavissakalian 2003 {published data only}

studyIdentifiers

Mavissakalian MR. Imipramine vs. sertraline in panic disorder: 24-week treatment completers. *Annals of Clinical Psychiatry* 2003;15(3):171-80.

McCurdy 1978 {published data only}

studyIdentifiers

McCurdy L, Schatzberg AF. Studies with oral lorazepam in anxiety neurosis associated with depressive symptomatology. *Journal of Clinical Psychiatry* 1978;39(10 Pt 2):30-4.

McEilly 1981 {published data only}

studyIdentifiers

McEilly JP, Etemad B. Double-blind comparison in parallel groups with nightly single doses of halazepam and placebo [Comparacion dobleciega en grupos paralelos con dosis unicas nocturnas de halazepam y placebo]. *Invest Med Int* 1981;8(2):202-8.

McHugh 2007 {published data only}

studyIdentifiers

McHugh RK, Otto MW, Barlow DH, Gorman JM, Shear MK, Woods SW. Cost-efficacy of individual and combined treatments for panic disorder. *Journal of Clinical Psychiatry* 2007;68(7):1038-44.

Mellman 1986 {published data only}

studyIdentifiers

Mellman TA, Uhde TW. Withdrawal syndrome with gradual tapering of alprazolam. *American Journal of Psychiatry* 1986;143(11):1464-6.

Miretzky 1992 {published data only}

studyIdentifiers

Miretzky A, Horn R, Koehler K, Moeller HJ. Combination of alprazolam, antidepressive drugs and cognitive behavior therapy in the treatment of panic disorder. *Clinical Neuropharmacology* 1992;15(1 pt B):536.

Mueller 1986 {published data only}

studyIdentifiers

Mueller AA, Binz U, Wendt G, Stoll KD. Treatment outcomes of diazepam and oxprenolol with anxiety neurosis patients [Therapieerfolge von Diazepam und Oxprenolol bei Patienten mit Angstneurose]. In: *Angst und Psychopharmaka: Methoden und Ergebnisse pharmakopsychologischer, pharmakopsychiatrischer und verhaltenspharmakologischer Forschung*. Kohlhammer, 1986:261-270.

Muncy 1981 {published data only}

studyIdentifiers

Muncy SM. Panic: a comparison of four treatment methods. *Dissertation Abstracts International* 1991;51(12-B Pt 1):6115.

Nair 1982 {published data only}

studyIdentifiers

Nair NP, Singh AN, Lapierre Y, Saxena BM, Nestoros JN, Schwartz G. Ketazolam in the treatment of anxiety: a standard and placebo controlled study. *Current Therapeutic Research, Clinical & Experimental* 1982;31(5):679-91.

Nanivadekar 1973 {published data only}

studyIdentifiers

Nanivadekar AS, Wig NN, Khorana AB, Master RS, Kulkarni SS. A multicenter investigation of lorazepam in anxiety neurosis. *Current Therapeutic Research, Clinical and Experimental* 1973;15(7):500-7.

Nardi 2011 {published data only}

studyIdentifiers

Nardi AE, Valença AM, Freire RC, Mochcovitch MD, Amrein R, Sardinha A, et al. Psychopharmacotherapy of panic disorder: 8-week randomized trial with clonazepam and paroxetine. *Brazilian Journal of Medical and Biological Research* 2011;44(4):366-73.

Ogunremi 1973 {published data only}

studyIdentifiers

Ogunremi OO, Adamson L, Brezinová V, Hunter WM, Maclean AW, Oswald I, et al. Two anti-anxiety drugs: a psychoneuroendocrine study. *British Medical Journal* 1973;2(5860):202-5.

Padron 1974 {published data only}

studyIdentifiers

Padron C. Comparative clinical evaluation of lorazepam [Essai clinique comparatif lorazepamdiazepam]. *Schweizerische Rundschau fur Medizin Praxis* 1974;63(16):494-6.

Pareek 2014 {published data only}

studyIdentifiers

Ipsca Laboratories Ltd. Comparative Evaluation of Efficacy and Safety of Clonazepam-CR and Conventional Clonazepam in Patients with Panic Disorder. <http://www.ctri.nic.in>.

Pasini 1972 {published data only}

studyIdentifiers

Pasini E. Double blind study on the use of medazepam in ambulatory therapy] [Etude en doubleaveugle sur l'emploi du medazepam en therapeutique ambulatoire]. *Cahiers de Médecine (Europa Medica)* 1972;13(6):456-7.

Pfizer 2002 {published data only}

studyIdentifiers

Pfizer. A double-blind, placebo-controlled, parallel-group comparison of venlafaxine extended-release capsules and paroxetine in outpatients with panic disorder. <http://clinicaltrials.gov/show/NCT00044772>.

Pfizer 2005 {published data only}

studyIdentifiers

Pfizer. Pilot study of venlafaxine extended release (XR) in the treatment of panic disorder (PD) in comparison to paroxetine. <http://clinicaltrials.gov/show/NCT001955982005>.

Piedade 1987 {published data only}

studyIdentifiers

Piedade RAM, Sougey EB, de Almeida FJB, Knijnik L, de Barros Camargo I, Del Porto JA, et al. Efficacy of cloxazolam versus placebo in the therapy of anxious status: double-blind controlled study [Estudo da eficacia do cloxazolam versus placebo na terapia de estados ansiosos: estudo duplocego controlado]. *Jornal Brasileiro de Psiquiatria* 1987;36(3):189-97.

Pohl 1989a {published data only}

studyIdentifiers

Pohl R, Rickels K, Charney D. Clinical results on the use of lorazepam to treat panic attacks [Risultati clinici sull'uso del lorazepam nel disturbo da attacchi di panico]. *Rivista di Psichiatri* 1989;24(2):99-100.

Pollack 2002 {published data only}

studyIdentifiers

Pollack MH, Rapaport MH, Fayyad R, Otto MW, Nierenberg AA, Clary CM. Early improvement predicts endpoint remission status in sertraline and placebo treatments of panic disorder. *Journal of Psychiatric Research* 2002;36(4):229-36.

Pollack 2003 {published data only}

studyIdentifiers

Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. *Journal of Psychopharmacology* 2003;17(3):276-82.

Pols 1996 {published data only}

studyIdentifiers

Pols H, Verburg K, Hauzer R, Meijer J, Griez E. Alprazolam premedication and 35% carbon dioxide vulnerability in panic patients. *Biological Psychiatry* 1996;40(9):913-7.

Porta 1974 {published data only}

studyIdentifiers

Porta V, Jann G, Delzanno GB. Comparative double-blind clinical trial of SB 5833 and temazepam [Essai clinique compare, en double aveugle, du SB 5833 et du temazepam]. *Bruxelles Medical* 1974;54(11):655-8.

Predescu 1969 {published data only}

studyIdentifiers

Predescu V, Ciurezu T, Romila A, Piree S, Ionescu G, Roman I, et al. The "double-blind" procedure in study of the anxiolytic effects of the preparation Wy 3498 (Oxazepam). Evaluation of anxiety states with the Hamilton scale (HS) [Procedeu "dubluorb" in studiul efectelor anxiolitice ale preparatului Wy 3498 (Oxazepam). Evaluarea starilor de anxietate la scala Hamilton (SH)]. *Neurologia, Psihiatria, Neurochirurgia* 1969;14(2):153-65.

Pyke 1989 {published data only}

studyIdentifiers

Pyke RE, Greenberg HS. Double-blind comparison of alprazolam and adinazolam for panic and phobic disorders.. *Journal of Clinical Psychopharmacology* 1989;9(1):15-21.

Raffaele 2002 {published data only}

studyIdentifiers

Raffaele R, Vecchio I, Malaguarnera M, Rampello L, Ruggieri M, Nicoletti F. Therapy of panic attacks in the elderly. *Archives of Gerontology and Geriatrics. Supplement* 2002;8:295-301.

Rapaport 2000 {published data only}

studyIdentifiers

Rapaport MH, Gladsjo J, McKinney R, Auerbach M, Hahn T, Rabin A, et al. Alprazolam-XR and neuropsychological function in panic disorder. *International Journal of Neuropsychopharmacology* 2000;3(Suppl 1):272.

Rifkin 1991 {published data only}

studyIdentifiers

Rifkin A. The sequence of improvement of the symptoms encountered in patients with panic disorder. *Comprehensive Psychiatry* 1991;32(6):559-60.

Rizley 1986 {published data only}

studyIdentifiers

Rizley R, Kahn RJ, McNair DM, Frankenthaler LM. A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. *Psychopharmacology Bulletin* 1986;22(1):167-72.

Roll 2004 {published data only}

studyIdentifiers

Roll D, Ray SE, Marcus SM, Passarelli V, Money R, Barlow DH, et al. Independent evaluator knowledge of treatment in a multicenter comparative treatment study of panic disorder. *Neuropsychopharmacology* 2004;29(3):612-8.

Roy-Byrne 2001 {published data only}

studyIdentifiers

Roy-Byrne PP, Katon W, Cowley DS, Russo J. A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care.. *Archives of General Psychiatry* 2001;58(9):869-76.

Rynn 2003 {published data only}

studyIdentifiers

Rynn M, Garcia-Espana F, Greenblatt DJ, Mandos LA, Schweizer E, Rickels K. Imipramine and buspirone in patients with panic disorder who are discontinuing long-term benzodiazepine therapy. *Journal of Clinical Psychopharmacology* 2003;23(5):505-8.

Saiz-Ruiz 1992 {published data only}

studyIdentifiers

Saiz-Ruiz J, Ibanez A. Personality traits and treatment response in panic disorder. *Clinical Neuropharmacology* 1992;15(1 Pt B):533.

Sciegghi 1986 {published data only}

studyIdentifiers

Sciegghi G, Levi-Minzi A, Greco C. The intravenous infusion use of chlordemethyldiazepam in neurotic anxiety [Psicopatologia e psicofarmacologia dell'ansia nevrotica A proposito dell'impiego del clordemetildiazepam per infusione venosa]. *Rivista Sperimentale Freniatria* 1986;3:531-42.

Sheehan 1980 {published data only}

studyIdentifiers

Sheehan DV, Ballenger J, Jacobsen G. Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Archives of General Psychiatry* 1980;37(1):51-9.

Sladka 1979 {published data only}

studyIdentifiers

Sladka R, Dostalova J, Haskovcova V, Jarosova M, Faltus F, Slanska J, et al. A placebo-controlled clinical trial with tofizopam in the treatment of anxiety neurosis. *Therapia Hungarica* 1979;27(4):176-80.

Sonne 1986 {published data only}

studyIdentifiers

Sonne LM, Bruun Hansen J. Alprazolam (Tafil) and bromazepam (Lexotan) in the treatment of anxiety: a randomized, double-blind comparison in psychiatric outpatients [Alprazolam (Tafil) og bromazepam (Lexotan) i angstbehandling. En randomiseret, dobbeltblind sammenligning fra psykiatrisk specialpraksis]. *Ugeskrift for Laeger* 1986;148(23):1392-5.

Surman 1986 {published data only}

studyIdentifiers

Surman OS, Williams J, Sheehan DV, Strom TB, Jones KJ, Coleman J4. Immunological response to stress in agoraphobia and panic attacks. *Biological Psychiatry* 1986;21(8-9):768-74.

Svebak 1990 {published data only}

studyIdentifiers

Svebak S, Cameron A, Levander S. Clonazepam and imipramine in the treatment of panic attacks: a double-blind comparison of efficacy and side effects. *Journal of Clinical Psychiatry* 1990;51(Suppl 5):14-7.

Taylor 1982 {published data only}

studyIdentifiers

Taylor CB, Kenigsberg ML, Robinson JM. A controlled comparison of relaxation and diazepam in panic disorder. *Journal of Clinical Psychiatry* 1982;43(10):423-5.

Telch 1985 {published data only}

studyIdentifiers

Telch MJ, Agras WS, Taylor CB, Roth WT, Gallen CC. Combined pharmacological and behavioral treatment for agoraphobia. *Behaviour Research and Therapy* 1985;23(3):325-35.

Terra 1971 {published data only}

studyIdentifiers

Terra SO, Bueno JR, Pires LL. Evaluation of the anti-anxiety activity of lorazepam in ambulatory patients [Avaliacao da atividade ansiolitica dolorazepam empacientes de ambulatorio]. *Jornal Brasileiro de Psiquiatria* 1971;20(3):237-47.

Tesar 1990 {published data only}

studyIdentifiers

Tesar GE. High-potency benzodiazepines for short-term management of panic disorder: the US experience. *Journal of Clinical Psychiatry* 1990;51(5 Suppl):4-10.

Tyrer 1984 {published data only}

studyIdentifiers

Tyrer P, Owen R. Anxiety in primary care: is short-term drug treatment appropriate? *Journal of Psychiatric Research* 1984;18(1):73-8.

Tyrer 1988 {published data only}

studyIdentifiers

Tyrer P, Seivewright N, Murphy S, Ferguson B, Kingdon D, Barczak P, et al. The Nottingham study of neurotic disorder: comparison of drug and psychological treatments. *Lancet* 1988;2(8605):235-40.

van Apeldoorn 2008 {published data only}

studyIdentifiers

van Apeldoorn FJ, van Hout WJ, Mersch PP, Huisman M, Slaap BR, Hale WW, et al. Is a combined therapy more effective than either CBT or SSRI alone? Results of a multicenter trial on panic disorder with or without agoraphobia. *Acta Psychiatrica* 2008;117(4):260-70.

Van Balkom 1996 {published data only}

studyIdentifiers

Van Balkom AJ, de Beurs E, Koele P, Lange A, van Dyck R. Long-term benzodiazepine use is associated with smaller treatment gain in panic disorder with agoraphobia. *Journal of Nervous and Mental Disease* 1996;184(2):133-5.

Van Boeijen 2007 {published data only}

studyIdentifiers

Van Boeijen C, Van Oppen P, Boeke J, Visser S, Kempe P, Blankenstein N, et al. First-line treatment of anxiety disorders: a randomized controlled trial [Angststoornissen in de eerste lijn vaak goed te behandelen: Een gerandomiseerd gecontroleerd onderzoek]. *Huisarts en Wetenschap* 2007;50(7):315-20.

Versiani 1983 {published data only}

studyIdentifiers

Versiani M, Bueno JR. Evaluation of the use of cloxazolam in patients with moderate anxiety [Avaliacao do emprego do cloxazolam em portadores de ansiedade moderada]. *Jornal Brasileiro de Psiquiatria* 1983;32(1):27-30.

Wiesner 1993 {published data only}

studyIdentifiers

Wiesner J, Grunder G, Wetzel H, Hiemke C. Bretazenil: neuroendocrinological profile of a partial benzodiazepine agonist in patients suffering from panic disorder with agoraphobia. *Pharmacopsychiatry* 1993;26:212.

Woods 1988 {published data only}

studyIdentifiers

Woods WS, Charney SD, Silver MJ, Krystal HJ, Heninger RG. Benzodiazepine receptor antagonist effects in panic disorder. In: 141st Annual Meeting of the American Psychiatric Association. Montreal, Quebec, 7-12th May 1988.

Yang 2005 {published data only}

studyIdentifiers

Yang H, Yu C, Gao H. The control study of mirtazapine in treating patients with panic disorder. Medical Journal of Chinese People Health 2005;17(3):133-5.

Yang 2006 {published data only}

studyIdentifiers

Yang H, Gao H, Yu C. Effect of citalopram in the treatment of panic disorder. Shandong Archives of Psychiatry 2006;19(2):186-7.

Yeragani 1992 {published data only}

studyIdentifiers

Yeragani VK, Pohl R, Balon R, Ramesh C, Weinberg P. Imipramine-induced jitteriness and decreased serum iron levels. Neuropsychobiology 1992;25(1):8-10.

Zajacka 1996 {published data only}

studyIdentifiers

Zajacka JM. The effect of nefazodone on comorbid anxiety symptoms associated with depression: experience in family practice and psychiatric outpatient settings. Journal of Clinical Psychiatry 1996;57(Suppl 2):10-4.

Zmorski 1985 {published data only}

studyIdentifiers

Zmorski T, Fischer Cornelssen KA. [Clinical experiences with the new-generation anxiolytic agent cloxazolam: a double-blind study.] Klinische Erfahrungen mit dem Anxiolytikum der neuen Generation: CloxazolamEine Doppelblindstudie. Schweizerische Rundschau fur Medizin Praxis 1985;74(27):728-34.

Additional references

Allison 2003

Allison C, Pratt JA. Neuroadaptive processes in GABAergic and glutamatergic systems in benzodiazepine dependence. Pharmacology & Therapeutics 2003;98:171-195.

Altman 1996

Altman DG, Bland MJ. Detecting skewness from summary information. BMJ 1996;313(7066):1200.

Anderson 2000

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. Journal of Affective Disorders 2000;58(1):19-36.

Andrews 2018

Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Australian & New Zealand Journal of Psychiatry 2018;52:1109-1172.

Andrisano 2013

Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. International Clinical Psychopharmacology 2013;28:33-45.

APA 1994

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, DC: American Psychiatric Publishing, 1994.

APA 2009

American Psychiatric Association. American Psychiatric Association Practice Guideline for the Treatment of Panic Disorder. Washington, DC: American Psychiatric Publishing, 2009.

APA 2013a

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Publishing, 2013.

APA 2013b

American Psychiatric Association. Highlights of changes from DSM-IV-TR to DSM-5. www.dsm5.org/Documents/changes%20from%20dsm-iv-tr%20to%20dsm-5.pdf (accessed prior to 10 June 2017).

Bakker 2002

Bakker A, van Balkom AJ, Spinhoven P. SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. *Acta Psychiatrica Scandinavica* 2002;106:163-7.

Baldwin 2014

Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2014;28:403-439.

Ballenger 1998

Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Baldwin DS, den Boer JA, et al. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. *Journal of Clinical Psychiatry* 1998;59(Suppl 8):47-54.

BAP 2014

Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *Journal of Psychopharmacology (Oxford, England)* 2014;28(5):403-39.

Batelaan 2007

Batelaan N, Smit F, de Graaf R, van Balkom A, Vollebergh W, Beekman A. Economic costs of full-blown and subthreshold panic disorder. *Journal of Affective Disorders* 2007;104(1-3):127-36.

Bighelli 2016

Bighelli I, Trespici C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, et al. Antidepressants and benzodiazepines for panic disorder in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No: CD011567. [DOI: [10.1002/14651858.CD011567.pub2](https://doi.org/10.1002/14651858.CD011567.pub2)]

Bighelli 2018

Bighelli I, Castellazzi M, Cipriani A, Girlanda F, Guaiana G, Koesters M, et al. Antidepressants versus placebo for panic disorder in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No: CD010676. [DOI: [10.1002/14651858.CD010676.pub2](https://doi.org/10.1002/14651858.CD010676.pub2)]

Bijl 1998

Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology* 1998;33:587-95.

Boissel 1999

Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, et al. The problem of therapeutic efficacy indices. Comparison of the indices and their use. *Therapie* 1999;54:405-11.

Breilmann 2019

Breilmann J, Girlanda F, Guaiana G, Barbui C, Cipriani A, Castellazzi M, et al. Benzodiazepines versus placebo for panic disorder in adults. *Cochrane Database of Systematic Reviews* 2019;28(3):CD010677.

Brettschneider 2019

Brettschneider C, Bleiber F, Hiller TS, Konnopka A, Breitbart J, Margraf J, et al. The allocation of resources in the care for patients with panic disorder in Germany: an excess cost analysis informing policy and science. *Cost Effectiveness and Resource Allocation* 2019;17:9.

Briley 1993

Briley M, Moret C. Neurobiological mechanisms involved in antidepressant therapies. *Clinical Neuropharmacology* 1993;16:387-400.

Bruce 2003

Bruce SE, Vasile RG, Goisman RM, Salzman C, Spencer M, Machan JT, et al. Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? *American Journal of Psychiatry* 2003;160:1432-8.

Caldwell 2005

Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897-900.

Cameron 2007

Cameron OG, Huang GC, Nichols T, Koeppe RA, Minoshima S, Rose D, et al. Reduced gamma-aminobutyric acid(A)-benzodiazepine binding sites in insular cortex of individuals with panic disorder. *Archives of General Psychiatry* 2007;64:793-800.

Chaimani 2012

Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012;3(2):161-76.

Chawla 2022

Chawla N, Anothaisintawee T, Charoenrungrueangchai K, Thaipisuttikul P, McKay GJ, Attia J, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2022;376:e066084. [DOI: doi: 10.1136/bmj-2021-066084]

CINeMA 2017 [Computer program]

CINeMA. Confidence in Network Meta-Analysis. Bern: Institute of Social and Preventive Medicine, University of Bern, 2017.

Cipriani 2013

Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Annals of Internal Medicine* 2013;159(2):130-7.

Cleare 2015

Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, Dickens C, Ferrier IN, Geddes J, Gilbody S, Haddad PM, Katona C, Lewis G, Malizia A, McAllister-Williams RH, Ramchandani P, Scott J, Taylor D, Uher R, Members of the Consensus Meeting. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology* 2015;29:459-525.

Cohen 1992

Cohen J. A power primer. *Psychological Bulletin* 1992;112(1):155-9.

Cristea 2017

Cristea IA, Gentili C, Pietrini P, Cuijpers P. Sponsorship bias in the comparative efficacy of psychotherapy and pharmacotherapy for adult depression: meta-analysis. *British Journal of Psychiatry* 2017;210:16-23.

Davies 2022

Davies SJ, Rudoler D, de Oliveira C, Huang A, Kurdyak P, Iaboni A. Comparative safety of chronic versus intermittent benzodiazepine prescribing in older adults: A population-based cohort study. *Journal of Psychopharmacology* 2022;36:460-469.

Deeks 2000

Deeks J. Issues in the selection for meta-analyses of binary data. In: Proceedings of the 8th International Cochrane Colloquium; Cape Town, South Africa. 2000 Oct 25-28.

Dias 2013a

Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical Decision Making* 2013;33:607-17.

Dias 2013b

Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Medical Decision Making* 2013;33:618-40.

Du 2021

Du Y, Du B, Diao Y, Yin Z, Li J, Shu Y, et al. Comparative efficacy and acceptability of antidepressants and benzodiazepines for the treatment of panic disorder: A systematic review and network meta-analysis. *Asian Journal of Psychiatry* 2021;60:102664. [DOI: doi: 10.1016/j.ajp.2021.102664]

Eaton 1994

Eaton WW, Kessler RC, Wittchen H-U, Magee WJ. Panic and panic disorder in the United States. *American Journal of Psychiatry* 1994;151:413-20.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;31:140-9.

Fava 2019

Fava GA, Cosci F. Understanding and Managing Withdrawal Syndromes After Discontinuation of Antidepressant Drugs. *Journal of Clinical Psychiatry* 2019;80:19com12794.

Fava 2020

Fava GA. May antidepressant drugs worsen the conditions they are supposed to treat? The clinical foundations of the oppositional model of tolerance. *Therapeutic Advances in Psychopharmacology* 2020;10:2045125320970325..

Fluyau 2022

Fluyau D, Mitra P, Jain A, Kailasam VK, Pierre CG. Selective serotonin reuptake inhibitors in the treatment of depression, anxiety, and post-traumatic stress disorder in substance use disorders: a Bayesian meta-analysis. *European Journal of Clinical Pharmacology* 2022;78:931-942.

Furukawa 2002

Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An empirical study of summary effect measures in meta-analyses. *International Journal of Epidemiology* 2002;31:72-6.

Furukawa 2005

Furukawa TA, Cipriani A, Barbui C, Brambilla P, Watanabe N. Imputing response rates from means and standard deviations in meta-analysis. *International Clinical Psychopharmacology* 2005;20:49-52.

Furukawa 2006

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2000;59:7-10.

Furukawa 2007

Furukawa TA, Watanabe N, Churchill R. Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No: CD004364. [DOI: [10.1002/14651858.CD004364.pub2](https://doi.org/10.1002/14651858.CD004364.pub2)]

Furukawa 2021

Furukawa TA, Shinohara K, Sahker E, Karyotaki E, Miguel C, Ciharova M, et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. *World Psychiatry* 2021;20:387-396.

Goisman 1995

Goisman RM, Warshaw MG, Steketee GS, Fierman EJ, Rogers MP, Goldenberg I, et al. DSM-IV and the disappearance of agoraphobia without a history of panic disorder: new data on a controversial diagnosis. *American Journal of Psychiatry* 1995;152:1438-43.

Gorman 2000

Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. *American Journal of Psychiatry* 2000;157:493-505.

Grant 2006

Grant BF, Hasin DS, Stinson FS, Dawson DA, Goldstein RB, Smith S, et al. The epidemiology of DSM-IV panic disorder and agoraphobia in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry* 2006;67:363-74.

Higgins 1996

Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Statistics in Medicine* 1996;15:2733-49.

Higgins 2011

Higgins JPT, Altman D, Gotzsche P, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 6*. The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook.

Hirschtritt 2021

Hirschtritt ME, Olfson M, Kroenke K. Balancing the Risks and Benefits of Benzodiazepines. *JAMA* 2021;325:347-348.

Horowitz 2021

Horowitz MA, Wright JM, Taylor D. Risks and Benefits of Benzodiazepines. *JAMA* 2021;325:2208.

Imai 2014

Imai H, Tajika A, Chen P, Pompoli A, Guaiana G, Castellazzi M, et al. Azapirones versus placebo for panic disorder in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No: CD010828. [DOI: [10.1002/14651858.CD010828.pub2](https://doi.org/10.1002/14651858.CD010828.pub2)]

Katzman 2014

Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, Canadian Anxiety Guidelines Initiative Group on behalf of the Anxiety Disorders Association of Canada/Association Canadienne des troubles anxieux and McGill University. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry* 2014;14 Suppl 1:S1.

Kessler 2006

Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. *Archives of General Psychiatry* 2006;63:415-24.

Kessler 2012

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research* 2012;21:169-84.

King 2008

King M, Nazareth I, Levy G, Walker C, Morris R, Weich S, et al. Prevalence of common mental disorders in general practice attendees across Europe. *British Journal of Psychiatry* 2008;192:362-7.

Klein 1964

Klein DF. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia* 1964;5:397-408.

Lu 2004

Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;23:3105-24.

Lunn 2009

Lunn D J, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future directions. *Statistics in Medicine* 2009;28:3049-67.

Malizia 1998

Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain GABA(A)-benzodiazepine receptor binding in panic disorder: preliminary results from a quantitative PET study. *Archives of General Psychiatry* 1998;55:715-20.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *PLoS Medicine* 2009;6(6):e1000097.

Nash 2008

Nash JR, Sargent PA, Rabiner EA, Hood SD, Argyropoulos SV, Potokar JP, et al. Serotonin 5-HT_{1A} receptor binding in people with panic disorder: positron emission tomography study. *British Journal of Psychiatry* 2008;193:229-34.

NICE 2011

National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults [CG113]. London: National Institute for Health and Care Excellence, 2011.

Nikolakopoulou 2019

Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. Assessing confidence in the results of network meta-analysis (CINeMA). Available at www.biorxiv.org/content/10.1101/597047v1.

Otto 2001

Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *American Journal of Psychiatry* 2000;158:1989-92.

Papola 2022

Papola D, Ostuzzi G, Tedeschi F, Gastaldon C, Purgato M, Del Giovane C, et al. Comparative efficacy and acceptability of psychotherapies for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. *British Journal of Psychiatry* 2022;221:507-519.

Pfizer 2008

Pfizer. A Study Of Sertraline Compared With Paroxetine In The Treatment Of Panic Disorder. [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00677352). [CLINICALTRIALS.GOV: NCT00677352]

Phillippo 2018

Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ. Sensitivity of treatment recommendations to bias in network meta-analysis. *Journal of the Royal Statistical Society. Series A, (Statistics in Society)* 2018;181(3):843-67.

Phillippo 2019

Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE. Threshold Analysis as an Alternative to GRADE for Assessing Confidence in Guideline Recommendations Based on Network Meta-analyses. *Annals of Internal Medicine* 2019;170(8):538-46.

Preti 2016

Preti A, Vrublevska J, Veroniki AA, Huedo-Medina TB, Fountoulakis KN. Prevalence, impact and treatment of generalised anxiety disorder in bipolar disorder: a systematic review and meta-analysis. *Evidence-Based Mental Health* 2016;19:73-81.

Puhan 2014

Puhan MA, Schunemann, Murad MH, Li T, Brignardello-Peterson R, Singh JA, Kessels AG, Guyatt GH. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.

Review Manager 2014 [Computer program]

Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network or multiple-treatments meta-analysis: many names, many benefits. *Research Synthesis Methods* 2012;3(2):80-97.

Silberman 2021

Silberman E, Balon R, Starcevic V, Shader R, Cosci F, Fava GA, et al. Benzodiazepines: it's time to return to the evidence. *British Journal of Psychiatry* 2021;218:125-127.

Starcevic 2009

Starcevic V. *Anxiety Disorders in Adults: A Clinical Guide*. Oxford: Oxford University Press, 2009.

Stein 2010

Stein M, Steckler T, Lightfoot JD, Hay E, Goddard AW. Pharmacologic treatment of panic disorder. *Current Topics in Behavioral Neurosciences* 2010;2:469-85.

van Valkenhoef 2016

van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Research Synthesis and Methods* 2016;7:80-93.

Wade 1999

Wade AG. Antidepressants in panic disorder. *International Clinical Psychopharmacology* 1999;14(Suppl 2):13-7.

Watanabe 2009

Watanabe N, Churchill R, Furukawa TA. Combined psychotherapy plus benzodiazepines for panic disorder. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No: CD005335. [DOI: [10.1002/14651858.CD005335.pub2](https://doi.org/10.1002/14651858.CD005335.pub2)]

Wilkinson 1991

Wilkinson G, Balestrieri M, Ruggeri M, Bellantuono C. Meta-analysis of double-blind placebo-controlled trials of antidepressants and benzodiazepines for patients with panic disorders. *Psychological Medicine* 1991;21:991-8.

Wilkinson 2016

Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. *Cochrane Database of Systematic Reviews* 2016, Issue 9: CD006727. Art. No: CD006727. [DOI: [10.1002/14651858.CD006727.pub3](https://doi.org/10.1002/14651858.CD006727.pub3)]

Winbugs 2012 [Computer program]

Winbugs. MRC Medical Biostatistics Unit Cambridge, 2012. www.mrc-bsu.cam.ac.uk/bugs/.

References to other published versions of this review

Guaiana 2020

Guaiana G, Barbui C, Meader N, Davies SJC, Furukawa TA, Imai H, et al. Pharmacological treatments in panic disorder in adults: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No: CD012729. [DOI: [10.1002/14651858.CD012729.pub2](https://doi.org/10.1002/14651858.CD012729.pub2)]

Additional tables

Table 1

Model selection for non-response outcome

--	--	--

Model	Deviance Information Criterion	Total residual deviance
Individual-effects model	669.12	mean=123.7, datapoints=107
Class-effects model	678.58	mean= 136.0, datapoints=107
Individual effects model adjusting for small-study effects (variance)	664.55	mean=108.6, datapoints=107
Individual-effects model adjusting for baseline risk	673.2	mean=112.4, datapoints=107
Individual-effects model adjusting for risk of bias in attrition and selective reporting	679.317	mean=120.7, datapoints=107
Individual-effects model adjusting for publication date	689.96	mean=126.3, datapoints=107
Individual-effects model adjusting for use of validated measures	679.91	mean=124.0, datapoints=107

Table 2

Meta-regression analyses for response outcome

Model	Covariates	median covariate estimate (95% CrI)	Between-study SD ¹ (95% CrI)
Small-study effects	variance in individual study (continuous)	-1.20 (-2.59 to 0.46)	0.28 (0.05 to 0.50)
Baseline risk	baseline risk (continuous)	-0.79 (-1.02 to -0.40)	0.52 (0.32 to 0.75)
Risk of bias	attrition bias (low risk of bias vs unclear or high risk of bias)	-0.01 (-0.57 to 0.48)	0.54 (0.29 to 0.85)
	outcome reporting bias (low risk of bias vs unclear or high risk of bias)	0.02 (-0.47 to 0.57)	
Publication date	publication date (continuous)	-0.03 (-0.06 to 0.04)	0.45 (0.23 to 0.74)
Validated outcome	validated measure of response (yes vs no)	-0.36 (-0.84 to 0.14)	0.46 (0.24 to 0.75)

1. Between-study SD in individual-effects model without covariates=0.50 (95% CrI 0.28 to 0.79)

Table 3

Summary results comparing interventions with placebo for non-response (sorted by mean rank, equivalence range and invariant range)

Intervention	RR (95% CrI): small study effects	OR (95% CrI): small study effects	Mean rank (95% CrI): small study effects	RR (95% CrI): baseline risk	Mean rank (95% CrI): baseline risk	No. trials	Sample size
95% CrI does not cross equivalence range or invariant range							
diazepam	0.65 (0.28 to 0.96)	0.33 (0.14 to 0.82)	3 (1 to 15)	0.67 (0.24 to 0.99)	7 (1 to 17)	1	160
alprazolam	0.68 (0.39 to 0.92)	0.37 (0.23 to 0.61)	4 (1 to 11)	0.60 (0.31 to 0.89)	5 (2 to 11)	7	895
clonazepam	0.71 (0.41 to 0.94)	0.40 (0.24 to 0.71)	5 (1 to 14)	0.63 (0.30 to 0.91)	6 (2 to 13)	5	938
paroxetine	0.85 (0.64 to 0.97)	0.60 (0.45 to 0.82)	11 (6 to 16)	0.75 (0.46 to 0.95)	10 (4 to 16)	8	1635
venlafaxine	0.84 (0.60 to 0.97)	0.58 (0.41 to 0.84)	11 (4 to 17)	0.71 (0.34 to 0.97)	8 (2 to 17)	4	1693
clomipramine	0.85 (0.57 to 0.99)	0.60 (0.37 to 0.96)	11 (4 to 17)	0.72 (0.40 to 0.94)	9 (3 to 15)	4	468
fluoxetine	0.78 (0.42 to 1.00)	0.50 (0.24 to 0.99)	8 (2 to 17)	0.57 (0.14 to 0.97)	4 (1 to 16)	1	180
adinazolam	0.82 (0.50 to 1.00)	0.54 (0.29 to 0.99)	9 (2 to 17)	0.72 (0.33 to 0.98)	9 (2 to 17)	2	517
95% CrI crosses equivalence range but not invariant range							
escitalopram	0.78 (0.40 to 1.03)	0.48 (0.21 to 1.11)	8 (1 to 18)	0.93 (0.41 to 1.32)	16 (3 to 19)	1	254
imipramine	0.82 (0.40 to 1.09)	0.54 (0.20 to 1.38)	9 (2 to 18)	0.83 (0.41 to 1.07)	13 (3 to 18)	2	147
fluvoxamine	0.86	0.62	12 (3 to 18)	0.71	10	5	450

	(0.53 to 1.05)	(0.32 to 1.20)		(0.34 to 0.97)	(3 to 16)		
citalopram	0.87 (0.57 to 1.02)	0.62 (0.37 to 1.09)	12 (3 to 18)	0.89 (0.54 to 1.07)	15 (7 to 18)	2	628
sertraline	0.89 (0.67 to 1.02)	0.67 (0.43 to 1.07)	13 (6 to 18)	0.84 (0.58 to 0.99)	13 (6 to 17)	3	470
95% CrI crosses equivalence range in both directions but not invariant range							
desipramine	0.94 (0.43 to 1.37)	0.82 (0.22 to 3.01)	15 (2 to 20)	0.69 (0.22 to 1.05)	7 (1 to 18)	1	56
buspirone	1.14 (0.48 to 2.06)	2.40 (0.32 to 14.3)	19 (2 to 20)	1.13 (0.76 to 1.88)	19 (12 to 20)	1	67
ritanserin	1.19 (0.01 to 2.70)	10.43 (0.04 to 2807)	20 (1 to 20)	1.18 (0.46 to 2.23)	20 (3 to 20)	1	39
95% CrI crosses equivalence and/or invariant ranges							
etizolam	0.58 (0.03 to 1.43)	0.29 (0.01 to 5.69)	2 (1 to 20)	0.37 (0.05 to 0.92)	1 (1 to 15)	1	30
reboxetine*	0.77 (0.24 to 1.19)	0.46 (0.10 to 1.86)	7 (1 to 19)	0.85 (0.32 to 1.20)	13 (2 to 19)	1	82

RR=risk ratio, CrI=credible interval *does not cross invariant range in baseline risk model

Table 4

Model selection for dropout outcome

Model	DIC	Total residual deviance	SD (95% CrI)
Individual-effects model	844.64	mean=172.2, datapoints=146	0.24 (0.04 to 0.46)
Class-effects model	840.91	mean=169.6, datapoints=146	0.27 (0.06 to 0.48)
Adjustment for small studies	831.46	mean=149.1, datapoints=146	0.18 (0.01 to 0.37)

Table 5

Summary results comparing interventions with placebo for drop out (sorted by mean rank, equivalence range and invariant range)

Intervention	RR (95% CrI)	OR (95% CrI)	Mean rank (95% CrI)	No. trials	Sample size: participants
95% CrI does not cross equivalence range or invariant interval					
Alprazolam	0.46 (0.33 to 0.66)	0.37 (0.28 to 0.50)	3 (1 to 6)	14	1979
Diazepam	0.50 (0.23 to 0.91)	0.39 (0.17 to 0.87)	4 (1 to 9)	1	160
Venlafaxine	0.99 (0.80 to 1.21)	0.98 (0.73 to 1.33)	12 (7 to 18)	4	1693
Sertraline	1.01 (0.81 to 1.31)	1.01 (0.71 to 1.44)	13 (7 to 19)	4	647
Paroxetine	1.07 (0.92 to 1.07)	1.11 (0.89 to 1.39)	15 (10 to 19)	8	2524
Buspirone	1.83 (1.17 to 3.34)	3.36 (1.25 to 9.10)	21 (18 to 21)	3	170
95% CrI crosses equivalence range but not invariant interval					
Reboxetine	0.40 (0.13 to 1.17)	0.40 (0.13 to 1.17)	4 (1 to 15)	1	82
Escitalopram	0.68 (0.38 to 1.08)	0.59 (0.30 to 1.12)	6 (2 to 15)	1	254
Imipramine	0.85 (0.63 to 1.12)	0.78 (0.55 to 1.18)	8 (5 to 16)	9	1207
Citalopram	0.88 (0.62 to 1.20)	0.83 (0.53 to 1.31)	9 (5 to 17)	2	628
Clonazepam	0.94 (0.74 to 1.13)	0.88 (0.55 to 1.36)	10 (5 to 18)	5	959
Clomipramine	0.97 (0.74 to 1.24)	0.94 (0.67 to 1.38)	11 (6 to 17)	7	720
Fluvoxamine	1.17 (0.85 to 1.66)	1.28 (0.75 to 2.10)	17 (8 to 20)	4	467
Adinazolam	1.19 (0.87 to 1.69)	1.35 (0.82 to 2.20)	17 (9 to 20)	2	517
95 % CrI crosses equivalence range in both directions but not invariant interval					
Desipramine	0.63 (0.14 to 1.70)	0.54 (0.11 to 2.61)	5 (1 to 20)	1	56
Fluoxetine	1.13 (0.60 to 1.90)	1.24 (0.51 to 2.87)	16 (5 to 20)	1	180
95% CrI crosses equivalence range in both directions and invariant interval					
Etizolam	0.37 (0.01 to 2.49)	0.28 (0.01 to 8.29)	2 (1 to 21)	1	30

Table 6

Model selection for remission outcome

Model	Deviance Information Criterion	Total residual deviance
Individual effects model	560.47	mean=95.00, from 88 datapoints

Class effects model	554.86	mean=96.34, from 88 datapoints
Individual effects model-outliers removed	472.19	mean=72.53, from 71 datapoints

Table 7

Summary results comparing interventions with placebo for remission (sorted by mean rank and equivalence range)

Comparator	RR (95% CrI)	OR (95% CrI)	Mean rank (95% CrI)	No. of trials	No. of participants
95% CrI does not cross the equivalence range					
Desipramine	0.66 (0.29 to 0.97)	0.31 (0.11 to 0.89)	2 (1 to 13)	1	52
Alprazolam	0.65 (0.44 to 0.84)	0.31 (0.23 to 0.40)	2 (1 to 5)	9	1732
Fluoxetine	0.76 (0.46 to 0.96)	0.43 (0.22 to 0.84)	5 (1 to 13)	1	180
Clonazepam	0.76 (0.53 to 0.92)	0.43 (0.28 to 0.64)	5 (1 to 11)	4	940
Diazepam	0.74 (0.43 to 0.96)	0.41 (0.20 to 0.82)	5 (1 to 13)	1	160
Fluvoxamine	0.77 (0.50 to 0.95)	0.44 (0.25 to 0.77)	6 (1 to 12)	3	311
Imipramine	0.79 (0.57 to 0.94)	0.48 (0.31 to 0.71)	7 (2 to 12)	3	904
Venlafaxine	0.87 (0.70 to 0.96)	0.61 (0.45 to 0.83)	10 (5 to 13)	4	1693
Paroxetine	0.88 (0.71 to 0.97)	0.62 (0.47 to 0.82)	10 (6 to 13)	5	2065
95% CrI crosses equivalence range					
Sertraline	0.86 (0.68 to 1.01)	0.58 (0.33 to 1.02)	9 (3 to 15)	2	353
Escitalopram	0.92 (0.65 to 1.09)	0.73 (0.36 to 1.45)	12 (3 to 16)	1	254
95% CrI crosses equivalence range in both directions					
Citalopram	0.97 (0.73 to 1.15)	0.89 (0.44 to 1.79)	13 (6 to 16)	1	251
Buspirone	0.99 (0.65 to 1.24)	0.95 (0.35 to 2.64)	14 (3 to 16)	1	67
Clomipramine	1.01 (0.83 to 1.16)	1.02 (0.58 to 1.81)	15 (9 to 16)	1	244

RR=risk ratio, CrI=credible interval

Table 8

Model selection for panic scales outcome

Model	Deviance Information Criterion	Total Residual Deviance
Endpoint		
Individual-effects	22.17	mean=40.54, from 41 datapoints
Class-effects	22.31	mean=42.16, from 41 datapoints
Change from baseline		
Individual-effects	49.27	mean=37.89, from 37 datapoints
Class-effects	51.37	mean=41.11, from 37 datapoints

Table 9

Summary results comparing interventions with placebo for mean score on panic scales

Comparator	Endpoint		Change from Baseline		No. trials	No. participants
	SMD (95% CrI)	Mean Rank (95% CrI)	SMD (95% CrI)	Mean Rank (95% CrI)		
Brofaromine	-3.78 (-5.02 to -2.55)	1 (1 to 2)	-	-	1	29
Clonazepam	-2.36 (-3.27 to -1.45)	2 (1 to 3)	-1.23 (-2.63 to 0.17)	3 (1 to 13)	3	101
Reboxetine	-1.03 (-2.13 to 0.08)	3 (2 to 10)	-	-	1	82
Clomipramine	-0.68 (-1.38 to 0.03)	5 (3 to 9)	-1.96 (-3.27 to -0.81)	1 (1 to 6)	2	210
Alprazolam	-0.48 (-1.19 to 0.24)	6 (3 to 11)	-0.86 (-1.62 to -0.11)	6 (2 to 11)	7	1255
Imipramine	-0.28 (-1.03 to 0.47)	7 (3 to 12)	-0.57 (-1.60 to 0.46)	8 (2 to 14)	5	1032
Paroxetine	-0.22 (-0.69 to 0.25)	8 (5 to 11)	-0.94 (-1.97 to -0.01)	5 (2 to 12)	5	1968

Fluvoxamine	-0.17 (-0.79 to 0.45)	8 (4 to 12)	-	-	3	338
Venlafaxine	0.30 (-0.39 to 0.99)	12 (7 to 12)	-0.59 (-1.60 to 0.40)	8 (2 to 14)	4	1693
Adinazolam	-0.18 (-1.00 to 0.63)	8 (4 to 12)	-0.17 (-1.66 to 1.30)	11 (2 to 14)	2	517
Diazepam	-	-	-0.80 (-2.15 to 0.53)	6 (1 to 14)	1	160
Fluoxetine	-	-	-0.61 (-2.08 to 0.87)	8 (1 to 14)	1	180
Escitalopram	-	-	-0.40 (-1.87 to 1.08)	10 (2 to 14)	1	254
Citalopram	-	-	-0.30 (-1.77 to 1.17)	11 (2 to 14)	1	251
Sertraline	-	-	-0.78 (-1.90 to 0.27)	7 (2 to 13)	1	176
Desipramine	-	-	-0.63 (-2.18 to 0.92)	8 (1 to 14)	1	56

Table 10

Model selection for frequency of panic attacks

Model	Deviance Information Criterion	Total Residual Deviance
Individual-effects	212.73	mean=90.08, from 93 datapoints
Class-effects	211.56	mean=90.76, from 93 datapoints
Individual-effects, removed midazolam	204.98	mean=88.04, from 90 datapoints

Table 11

Summary results comparing interventions with placebo for frequency of panic attacks

Comparator	MD (95% CrI)	Mean Rank (95% CrI)	No. trials	No. participants
Clonazepam	-3.75 (-7.64 to -0.01)	3 (1 to 12)	3	532
Reboxetine	-3.54 (-8.57 to 1.50)	4 (1 to 14)	1	82
Alprazolam	-2.58 (-4.79 to -0.43)	6 (2 to 12)	10	958
Paroxetine	-1.97 (-4.22 to 0.27)	7 (2 to 13)	6	1496
Sertraline	-1.68 (-4.81 to 1.42)	8 (2 to 15)	3	522
Venlafaxine	-1.28 (-3.93 to 1.37)	9 (3 to 15)	4	1693
Clomipramine	-0.96 (-4.06 to 2.15)	10 (3 to 15)	2	424
Fluoxetine	-0.70 (-6.29 to 4.89)	10 (1 to 16)	1	180
Adinazolam	-0.33 (-3.75 to 3.08)	11 (3 to 16)	2	517
Imipramine	-0.71 (-6.43 to 5.03)	11 (1 to 16)	6	319
Desipramine	-4.60 (-10.55 to 1.33)	2 (1 to 14)	1	56
Diazepam	-0.66 (-7.67 to 6.35)	11 (1 to 16)	1	160
Fluvoxamine	0.06 (-3.46 to 3.55)	12 (4 to 15)	3	338

MD=mean difference, CrI=credible interval

Table 12

Model selection for agoraphobia symptoms

Model	Deviance Information Criterion	Total Residual Deviance
individual-effects, outliers removed (endpoint)	92.93	mean=37.34, from 38 datapoints
class-effects, outliers removed (endpoint)	91.01	mean=37.1, from 38 datapoints
individual-effects (change from baseline)	50.56	mean=18.36, from 18 datapoints

Table 13

Summary results comparing interventions with placebo for mean score on agoraphobia symptoms scales

Comparator	Endpoint		Change from baseline		No. trials	No. participants
	SMD (95% CrI)	Mean Rank (95% CrI)	SMD (95% CrI)	Mean Rank (95% CrI)		
Citalopram	-0.87 (-1.32 to -0.40)	2 (1 to 10)	-	-	2	628
Reboxetine	-0.86 (-1.62 to -0.11)	2 (1 to 10)	-	-	1	82
Escitalopram	-0.78 (-1.40 to -0.16)	3 (1 to 10)	-	-	1	254
Clomipramine	-0.60 (-1.18 to -0.01)	5 (1 to 11)	-0.54 (-0.95 to -0.17)	2 (1 to 5)	3	468
Diazepam	-0.52 (-1.14 to 0.08)	6 (1 to 12)	-	-	1	160
Fluvoxamine	-0.50 (-1.42 to 0.41)	6 (1 to 13)	-	-	1	39
Alprazolam	-0.46 (-0.75 to -0.20)	6 (3 to 10)	-0.44 (-0.74 to -0.11)	3 (1 to 6)	10	1951
Desipramine	-0.41 (-1.22 to 0.39)	7 (1 to 14)	-	-	1	56
Paroxetine	-0.30 (-0.76 to 0.16)	8 (3 to 13)	-0.48 (-0.71 to -0.19)	3 (1 to 5)	5	1891
Imipramine	-0.22 (-0.59 to 0.16)	9 (5 to 13)	-0.46 (-1.22 to 0.29)	3 (1 to 7)	4	944
Buspirone	-0.03 (-0.77 to 0.70)	11 (3 to 14)	-	-	1	67
Adinazolam	0.10 (-0.57 to 0.76)	13 (8 to 16)	-0.07 (-0.56 to 0.43)	6 (2 to 7)	2	517
Ritanserin	0.22 (-0.63 to 1.08)	13 (5 to 14)	-	-	1	39

SMD=standardized mean difference, CrI=credible interval

Table 14

Model selection for pooled interventions classes (response)

Model	Total Residual Deviance	DIC
pooled classes	mean=117.7, from 100 datapoints	624.4
pooled classes (small study effects)	mean=100.1, from 100 datapoints	612.2
pooled classes (baseline risk)	mean=107.7, from 100 datapoints	619.9

Table 15

Pooled intervention classes versus placebo and other pooled intervention classes for response (adjusted for small study effects)

Intervention	RR (95% CrI)	OR (95% CrI)	Mean rank (95% CrI)	No. studies	Sample size
SSRIs versus placebo	0.82 (0.61 to 0.96)	0.54 (0.43 to 0.68)	SSRIs: 5 (3 to 6)	20	4,306
SNRIs versus placebo	0.86 (0.67 to 0.97)	0.61 (0.46 to 0.83)	SNRIs: 6 (3 to 6)	4	1,693
TCAs versus placebo	0.74 (0.47 to 0.94)	0.43 (0.29 to 0.64)	TCAs: 2 (1 to 6)	9	957
MAOIs versus placebo	0.76 (0.49 to 0.95)	0.45 (0.31 to 0.68)	MAOIs: 3 (1 to 6)	-	-
BDZs versus placebo	0.76 (0.51 to 0.94)	0.46 (0.33 to 0.64)	BDZs: 3 (1 to 6)	15	2,471
SNRIs versus SSRIs	1.04 (0.93 to 1.27)	1.13 (0.83 to 1.55)	-	2	991
TCAs versus SSRIs	0.92 (0.70 to 1.06)	0.79 (0.54 to 1.15)	-	4	572
MAOIs versus SSRIs	0.93 (0.72 to 1.09)	0.83 (0.57 to 1.23)	-	1	366
BDZs versus SSRIs	0.94 (0.74 to 1.08)	0.84 (0.59 to 1.19)	-	1	154
TCAs versus SNRIs	0.87 (0.61 to 1.03)	0.70 (0.44 to 1.10)	-	-	-
MAOIs versus SNRIs	0.89 (0.64 to 1.06)	0.73 (0.47 to 1.17)	-	-	-
BDZs versus SNRIs	0.90 (0.66 to 1.04)	0.74 (0.49 to 1.13)	-	-	-
MAOIs versus TCAs	1.02 (0.80 to 1.33)	1.05 (0.66 to 1.70)	-	1	135
BDZs versus TCAs	1.02 (0.81 to 1.34)	1.06 (0.67 to 1.70)	-	1	61
BDZs versus MAOIs	1.01 (0.78 to 1.30)	1.02 (0.62 to 1.62)	-	-	-

Table 16

Model selection pooled intervention classes (dropout)

Model	Total Residual Deviance	DIC
pooled classes	mean=137.2, from 128 datapoints	756.0
pooled classes (small study effects)	mean=129, from 128 datapoints	752.5
pooled classes (baseline risk)	mean=135.2, from 128 datapoints	750.4

DIC=deviation information criterion

Table 17

Pooled intervention classes versus placebo and other pooled intervention classes for dropout (adjusted for small study effects)

Intervention	RR (95% CrI)	OR (95% CrI)	Mean rank (95% CrI)	No. studies	Sample size
SSRIs versus placebo	1.01 (0.85 to 1.22)	1.02 (0.79 to 1.33)	SSRIs: 5 (2 to 7)	24	7,260
SNRIs versus placebo	0.97 (0.73 to 1.33)	0.96 (0.62 to 1.48)	SNRIs: 4 (2 to 7)	4	2,020
TCAs versus placebo	0.89 (0.67 to 1.14)	0.83 (0.58 to 1.22)	TCAs: 3 (2 to 6)	13	2,642
MAOIs versus placebo	1.06 (0.58 to 1.80)	1.11 (0.49 to 2.65)	MAOIs: 6 (1 to 7)	-	-
BDZs versus placebo	0.63 (0.45 to 0.83)	0.52 (0.37 to 0.72)	BDZs: 1 (1 to 2)	19	4,085
SNRIs versus SSRIs	0.96 (0.71 to 1.33)	0.94 (0.59 to 1.48)	-	2	1,316
TCAs versus SSRIs	0.88 (0.66 to 1.12)	0.82 (0.58 to 1.18)	-	3	133
MAOIs versus SSRIs	1.05	1.08	-	1	30

	(0.58 to 1.76)	(0.48 to 2.57)			
BDZs versus SSRIs	0.62 (0.44 to 0.83)	0.51 (0.35 to 0.73)	-	2	452
TCAs versus SNRIs	0.91 (0.61 to 1.31)	0.87 (0.52 to 1.51)	-	-	-
MAOIs versus SNRIs	1.10 (0.56 to 1.93)	1.16 (0.47 to 3.01)	-	-	-
BDZs versus SNRIs	0.65 (0.40 to 0.95)	0.55 (0.32 to 0.92)	-	-	-
MAOIs versus TCAs	1.20 (0.69 to 1.97)	1.33 (0.62 to 2.89)	-	2	228
BDZs versus TCAs	0.72 (0.50 to 0.94)	0.63 (0.41 to 0.92)	-	5	1,749
BDZs versus MAOIs	0.60 (0.32 to 1.07)	0.47 (0.19 to 1.08)	-	-	-

Figure 1

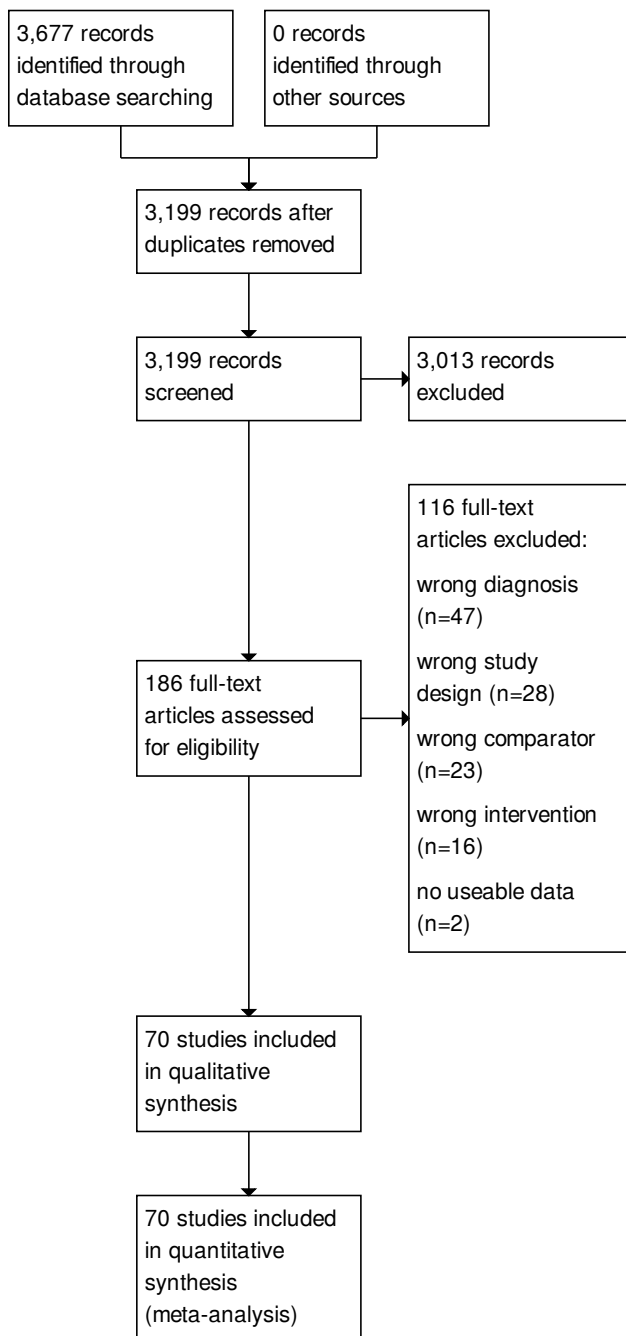


Figure 2

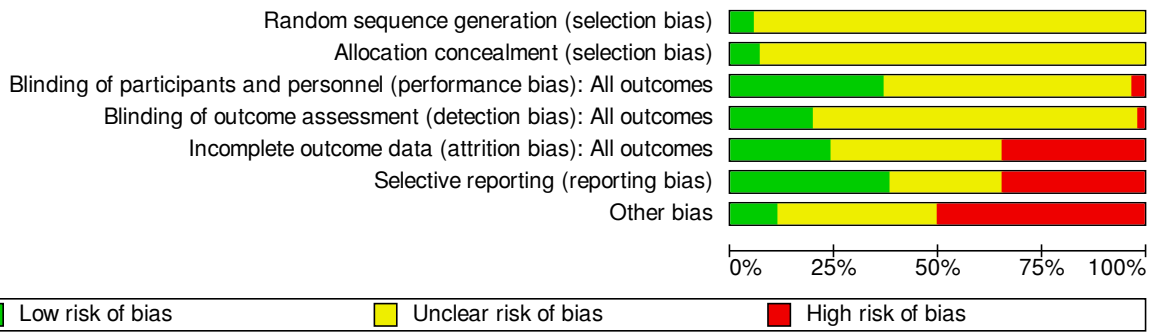
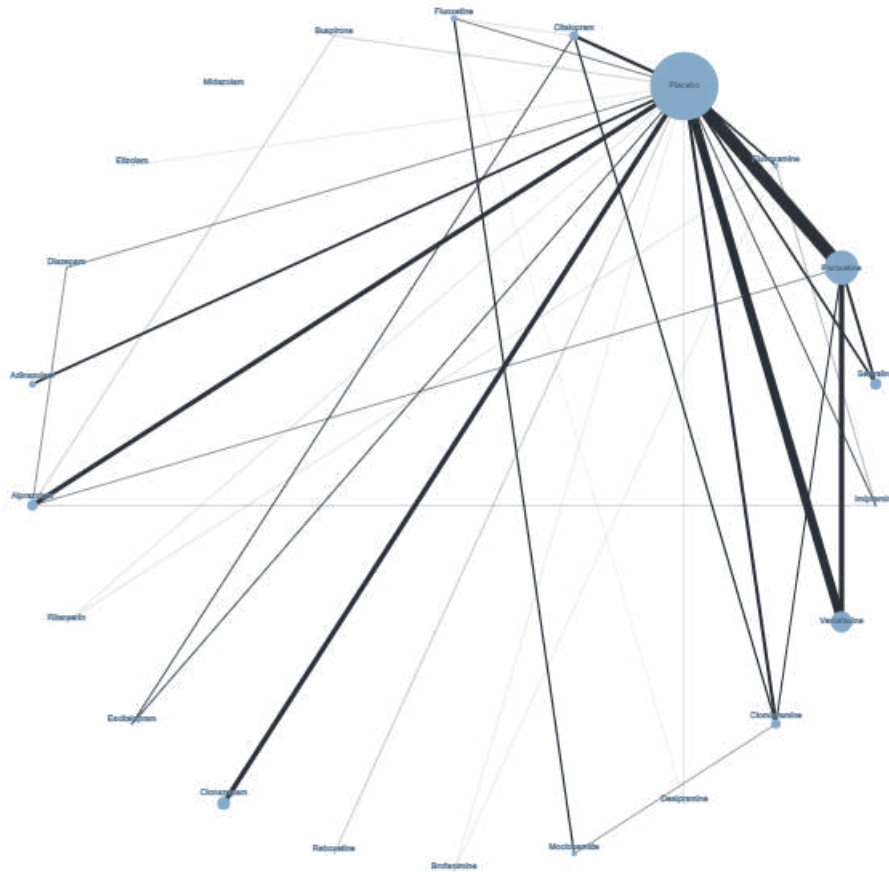


Figure 3

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Amore 1999	?	?	?	?	?	-	?
Amore 1999 bis	?	?	?	?	?	-	?
Asnis 2001	?	?	+	?	?	-	-
Baker 2003	?	?	?	?	?	?	+
Bakish 1993	?	?	?	?	?	-	?
Ballenger 1998	?	?	?	?	+	+	?
Bandelow 2004	?	?	?	?	+	+	-
Barlow 2000	?	?	?	?	?	+	?
Beauchair 1994	?	?	+	+	-	+	?
Bergink 2005	?	?	?	?	+	+	?
Black 1993	?	?	?	?	-	-	-
Bradweijn 2005	?	?	?	?	-	+	-
Broocks 1998	?	?	?	?	?	+	+
Bystritsky 1994	?	?	+	+	?	+	?
Caillard 1999	?	?	?	?	-	?	-
Carter 1995	?	?	+	?	?	-	?
CNCPS 1992	?	?	?	?	?	-	-
Davidson 1994	?	?	?	?	+	-	?
Den Boer 1988	?	?	?	?	-	-	?
Den Boer 1990	?	?	?	?	?	-	?
Gentil 1993	?	?	+	+	?	-	+
GSK 1994/04	?	?	?	?	?	?	+
GSK 29060 525	?	?	?	?	?	+	-
Hoehn-Saric 1993	?	?	?	?	-	-	-
Holland 1999	?	?	?	?	-	?	?
Johnston 1995	?	?	+	+	-	?	-
Klosko 1990	?	?	+	+	-	-	?
Koszycki 2011	+	+	+	+	?	?	-
Krueger 1999	?	?	?	?	+	+	-
Lecrubier 1997	?	?	?	?	+	+	-
Lepola 1990	?	?	?	?	?	+	?
Liebowitz 2009	?	?	?	?	+	+	-

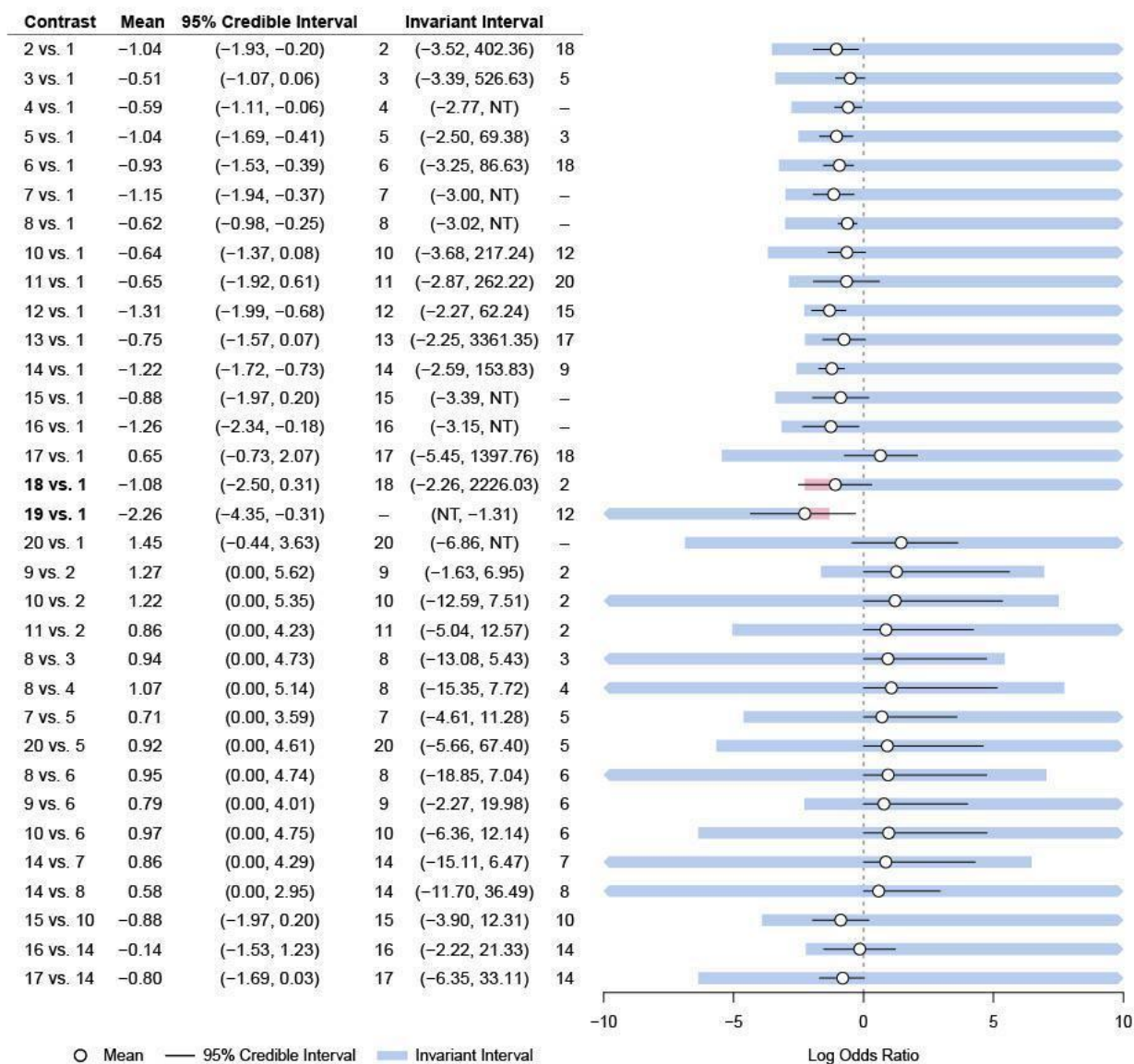
Londborg 1998	?	?	?	?	?	+	-
Lydiard 1992	?	?	+	?	-	-	+
Lydiard 1993	?	?	?	?	?	+	?
Michelson 2001	?	?	?	?	+	+	-
Moroz 1999	?	?	+	?	-	-	-
Munjack 1989	?	?	-	?	-	-	+
Nair 1996	?	?	+	+	+	+	-
Noyes 1996	?	?	?	?	+	+	-
Pecknold 1994	?	?	?	?	-	-	-
Pfizer 2008	?	?	+	+	?	+	-
Pohl 1989b	?	?	+	?	-	-	?
Pollack 1998	+	?	?	?	+	+	-
Pollack 2007a	?	?	+	+	+	?	-
Pollack 2007b	?	?	+	+	?	+	-
Ribeiro 2001	+	+	?	?	?	+	?
Robinson 1989	?	?	+	?	-	?	-
Rosenbaum 1997	+	?	+	?	?	-	-
Savoldi 1990	?	?	?	?	-	?	+
Schweizer 1992	?	?	?	?	+	?	?
Schweizer 1993	?	?	+	+	+	+	-
Sharp 1990	?	?	+	+	?	?	-
Sheehan 1993	?	?	+	?	-	-	?
Sheehan 2005	?	?	?	?	+	+	-
Sheikh 1999	?	?	+	?	-	?	?
Stahl 2003	?	?	?	?	?	+	-
Taylor 1990	?	?	-	-	-	-	?
Tesar 1991	?	?	+	?	-	+	-
Tiller 1999	?	?	?	?	-	?	-
Tsutsui 1997	?	+	+	+	-	?	?
Tsutsui 2000a	?	+	+	?	-	?	-
Tsutsui 2000b	?	+	+	?	?	?	-
Uhlenhuth 1989	?	?	+	+	+	+	-
Valenca 2000	?	?	?	?	?	-	?
Van Vliet 1993	?	?	?	?	-	-	+
Van Vliet 1996	?	?	?	?	?	-	?
Versiani 2002	?	?	?	?	?	?	?
Wade 1997	?	?	?	?	+	?	?
Zhang 2000	?	?	?	?	?	?	-

Figure 4



Network plot for response outcome (node size and edge width weighted by sample size)

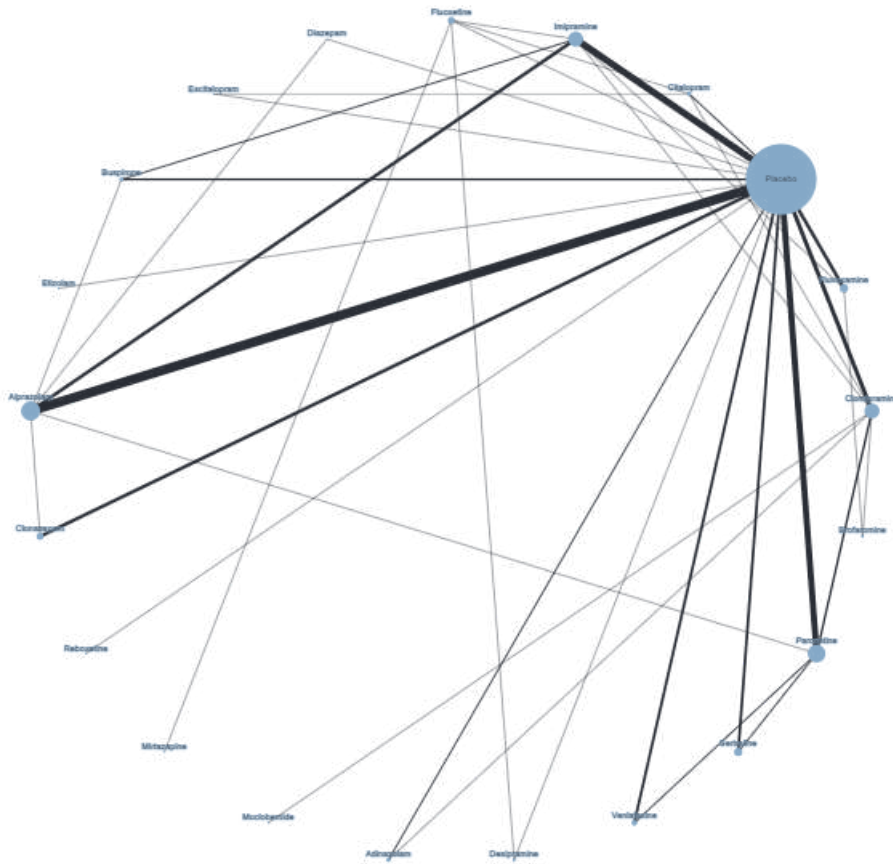
Figure 5



Forest plot for threshold analysis on response

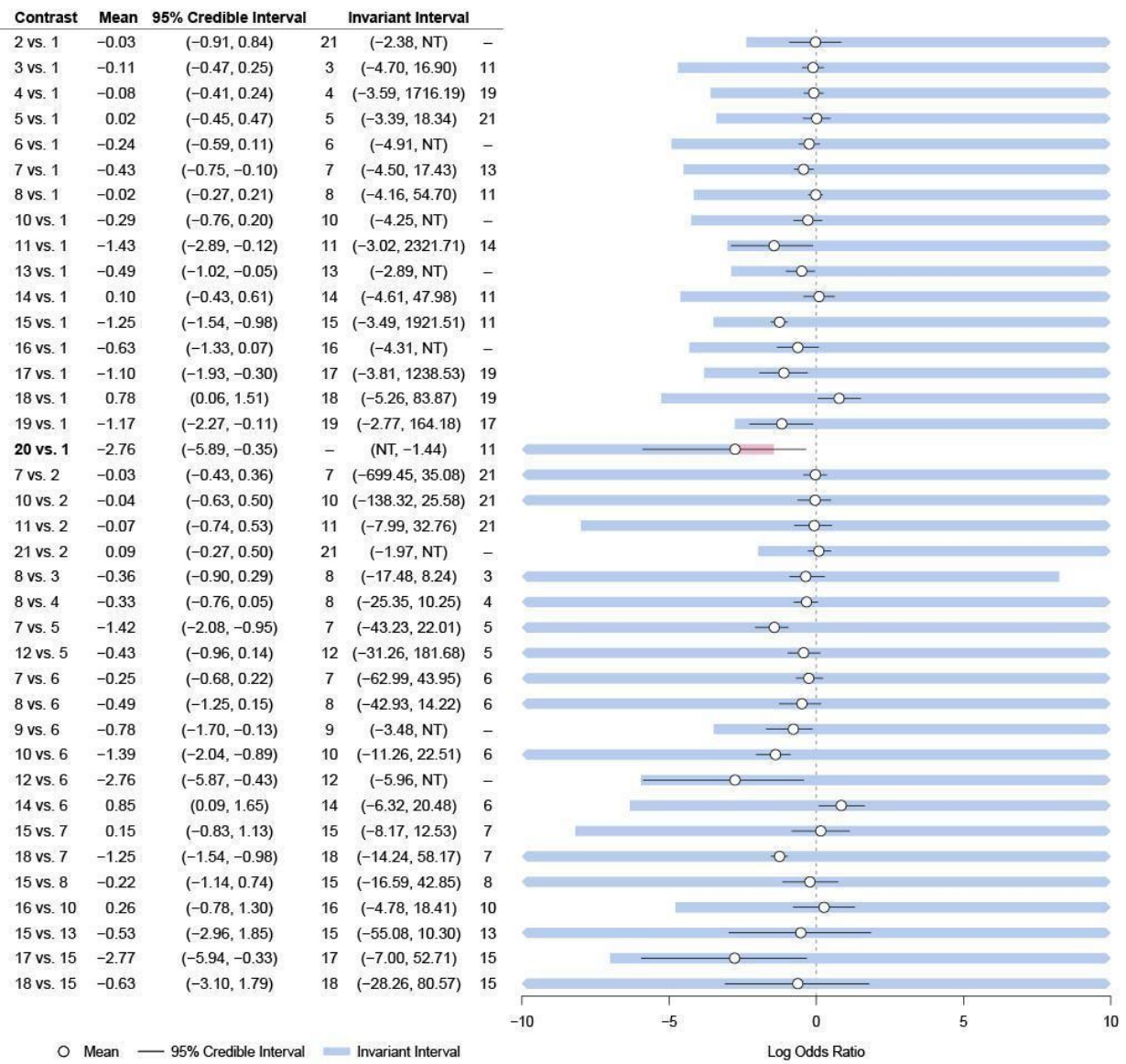
Medications: 1=placebo, 2=fluoxetine, 3=sertraline, 4=venlafaxine, 5=fluvoxamine, 6=clomipramine, 7=imipramine, 8=paroxetine, 9=moclobemide, 10=citalopram, 11=desipramine, 12=clonazepam, 13=adinazolam, 14=alprazolam, 15=escitalopram, 16=diazepam, 17=bupropion, 18=reboxetine, 19=etizolam, 20=ritanserin

Figure 6



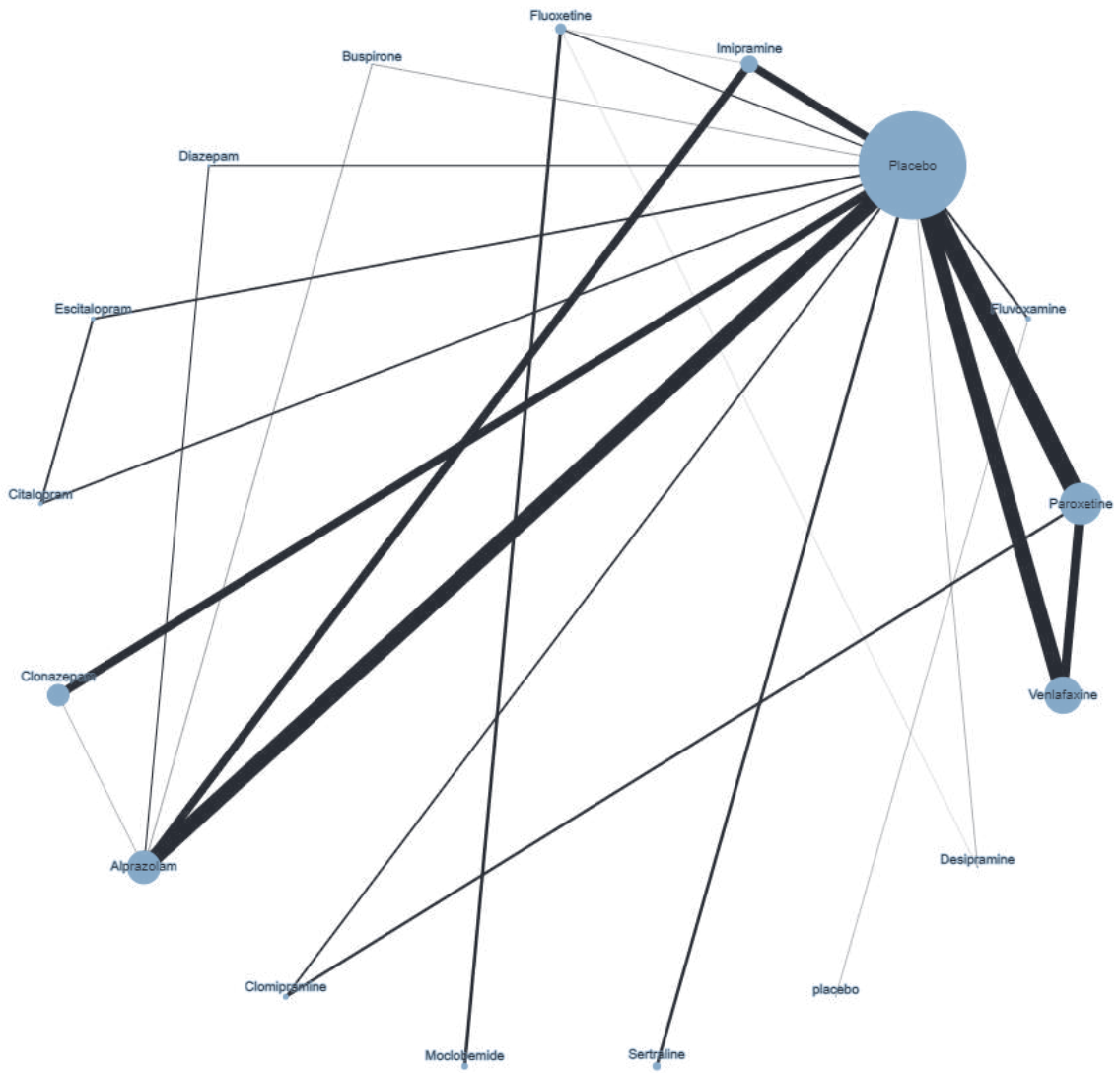
Network plot for drop out (node size and edge width weighted by number of studies)

Figure 7



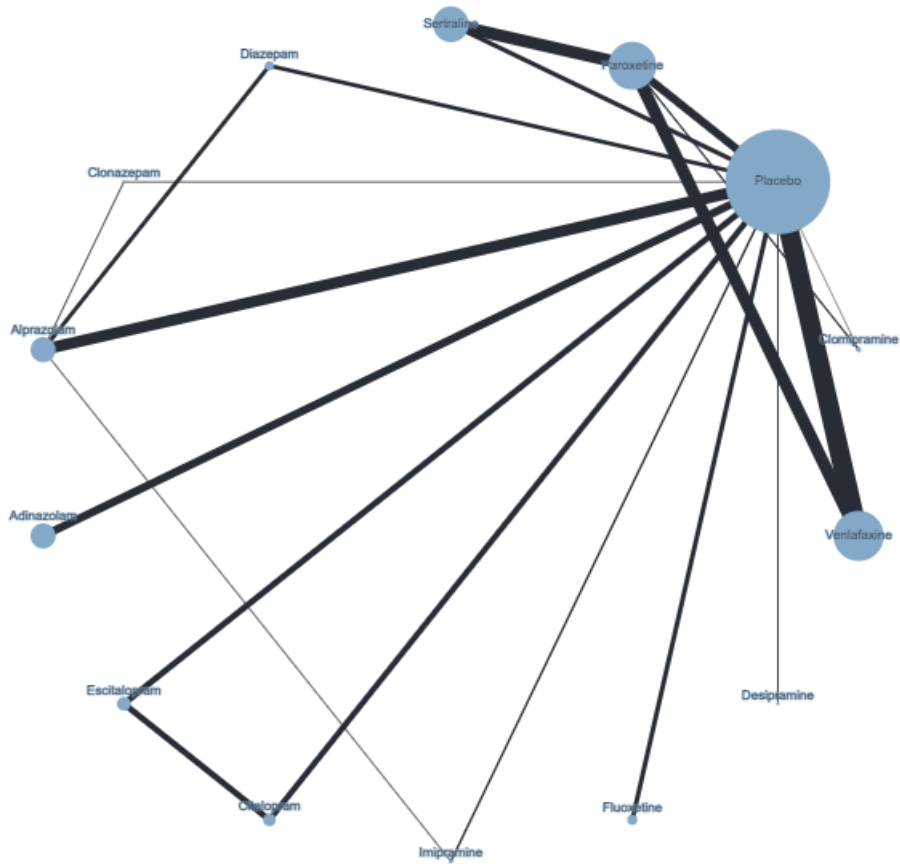
Forest plot of dropout threshold analysis

Figure 8



Network plot remission (node size and edge width weighted by sample size)

Figure 9



Network plot intervention combinations for panic scales (change from baseline)

Figure 10

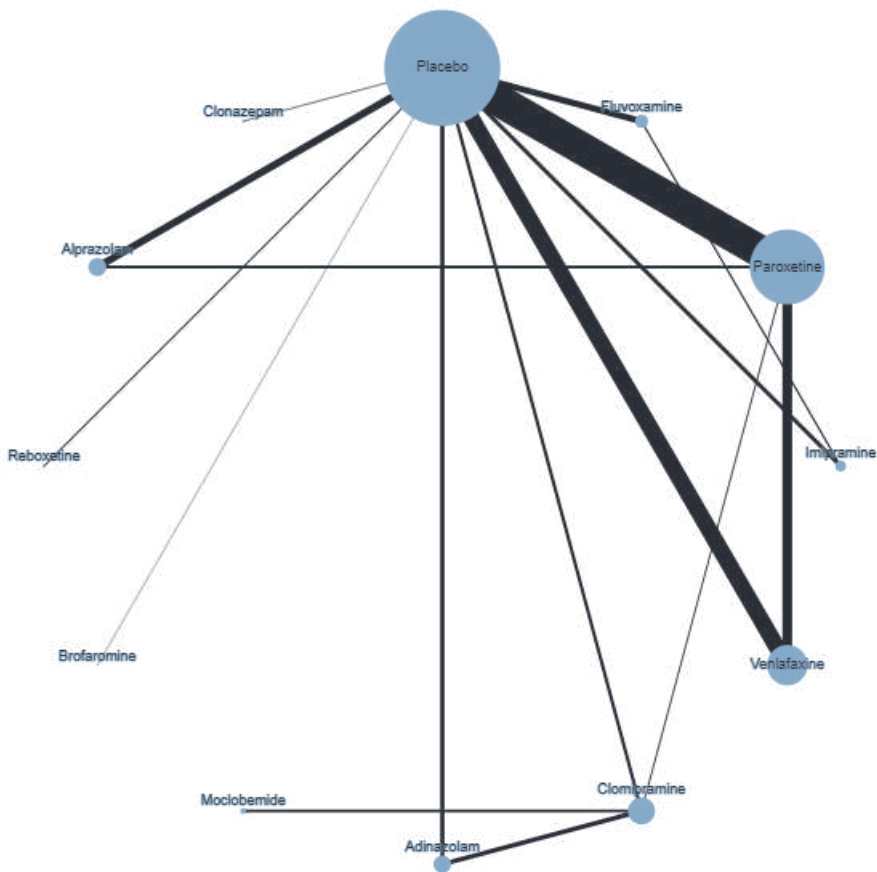
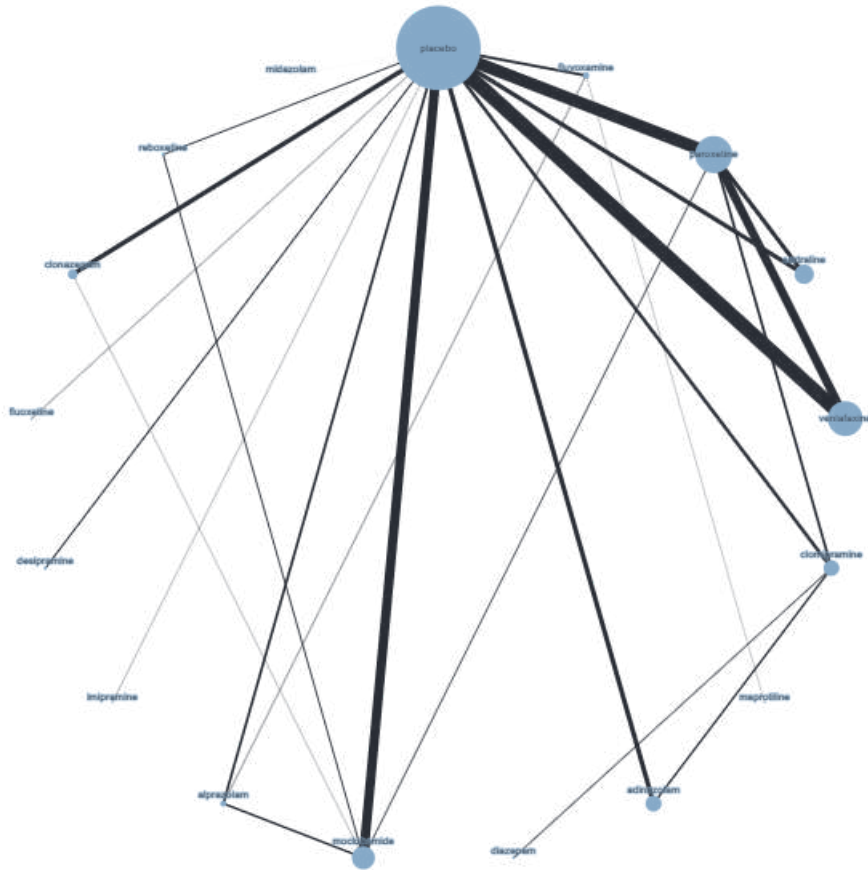
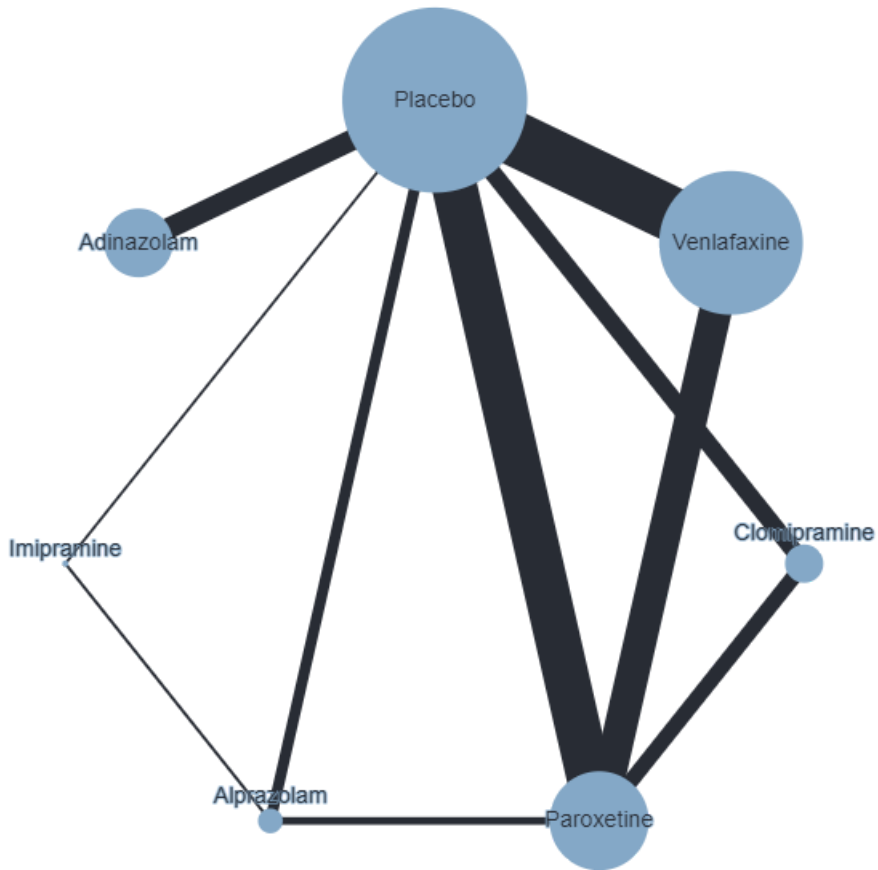


Figure 11



Network plot frequency of panic attacks (node size and edge width weighted by sample size)

Figure 12

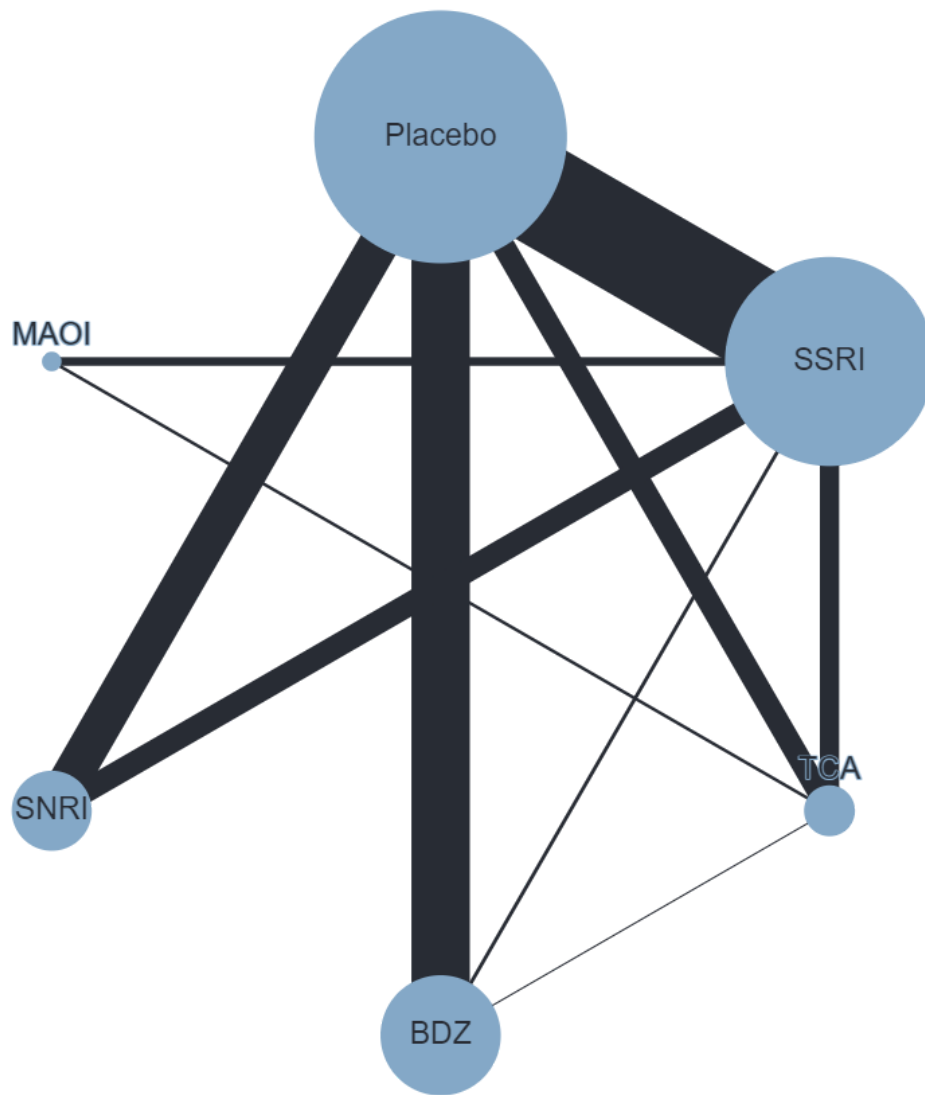


Network plot intervention combinations for agoraphobia (change from baseline)

Figure 13

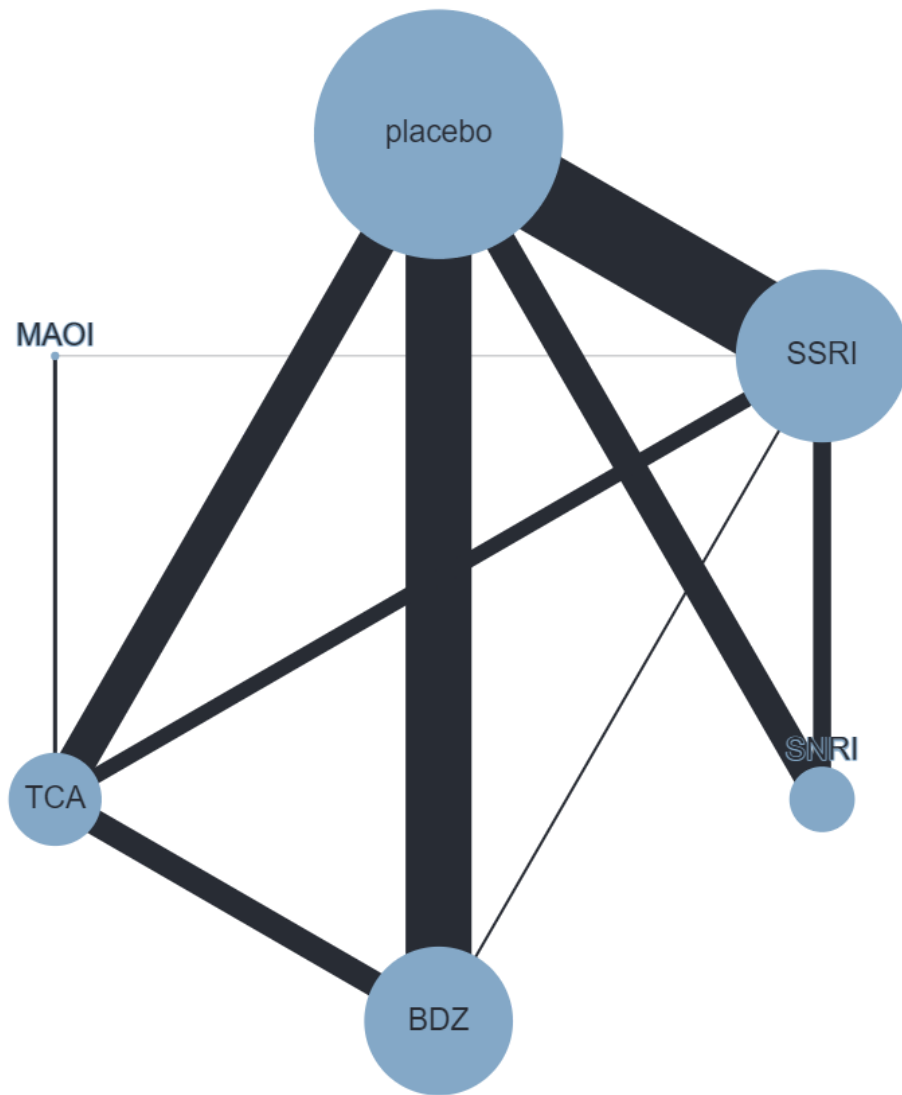


Figure 14



Network plot comparing medications classes for response (node size and edge width weighted by sample size).

Figure 15



Network diagram comparing medication classes with placebo and one another for drop out (node size and edge width weighted by sample size)