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

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| **Corresponding Author:** | Giuseppe Guaiana, M.D., Ph.D.<br>Western University Schulich School of Medicine & Dentistry<br>St Thomas, CANADA |
| **Order of Authors:** | Giuseppe Guaiana, M.D., Ph.D. |
| | Nicholas Meader |
| | Corrado Barbui |
| | Simon JC Davies |
| | Toshi Furukawa |
| | Hissei Imai |
| | Sofia Dias |
| | Deborah M Caldwell |
| | Markus Koesters |
| | Aran Tajika |
| | Irene Bighelli |
| | Alessandro Pompoli |
| | Andrea Cipriani |
| | Sarah Dawson |
| | Lindsay Robertson |

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

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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

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# 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<br>**Settings:** Inpatient, outpatient and primary care<br>**Intervention:** antidepressants (such as sertraline) or benzodiazepines (such as diazepam)<br>**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 RTCs; 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 |

[1]Direct estimates but not indirect estimates crossed equivalence range [2]Indirect estimates but not direct estimates crossed equivalence range [3]95% 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 5H1A serotonin receptor (Nash 2008), which has an inhibitory function, so the increased serotonin throughput may in part serve to overcome this deficit of inhibition. Noradrenergic antidepressants can similarly increase transmission of the catecholamine noradrenaline. Some antidepressants, such as the serotonin-norepinephrine reuptake inhibitor (SNRI) drugs (e.g. venlafaxine, duloxetine) and TCAs, can enhance both serotonin and noradrenaline transmission by inhibiting both transporters.

BDZs moderate the gamma-Aminobutyric acid (GABA) neurotransmitter system, which is the brain's main inhibitory neurotransmitter. They activate the GABA-A BDZ receptor. This receptor complex contains a chloride channel, opened by agonists, which ultimately reduce anxiety and create sedation. The BDZ binding site communicates only indirectly with the channel, meaning that BDZs are safer than their predecessors, the barbiturates. It is known through imaging studies that the inhibitory GABA system is deficient in panic disorder (Malizia 1998; Cameron 2007); thus BDZs' ability to activate the GABA-A BDZ receptor can counteract this. It is likely that both monoamine-based systems and GABA-based systems converge, allowing both antidepressants and BDZs to have efficacy in panic disorder despite their differing actions on neurotransmitter systems. One possibility is via serotonergic 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 $CO_2$ inhalations or lactate infusions);
- Studies administering psychosocial therapies targeted at panic disorder concurrently;
- Studies comparing psychosocial interventions; and
- Quasi-randomised trials.

### Types of participants

The fundamental assumption underpinning a network meta-analysis is that of consistency/transitivity (Caldwell 2005; Cipriani 2013). We 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

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

### Benzodiazepines (BDZs)

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

### Placebo

Placebo can be active (i.e. mimicking side effects) or inactive (completely inert). We 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% CrIs) 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 intracluster correlation coefficient and then following the guidance given in chapter 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

### Cross-over trials

Cross-over trials are trials in which all participants receive both the control and intervention treatment but in a different order. The major problem is a carry-over effect from the first phase to the second phase of the study, especially if the condition of interest is unstable (Elbourne 2002). As this is the case with panic disorder, we 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, $Tau^2$, estimated from the model and the 95% prediction interval for the relative treatment effects.

Inconsistency can be considered an additional layer of heterogeneity which can occur in networks of evidence. It can occur when there is a discrepancy between a direct and indirect estimate of treatment effect. We 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 enroled only outpatients, three trials enroled only inpatients, and both inpatients and outpatients were enroled 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 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-fivestudies 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 severl 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 0.0.65 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 deviaton= 0.63, 95% CrI 0.33 to 1.30) and endpoint data (between study standard deviaton= 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 to 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 interventions 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 enroled 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.

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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]

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# 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.

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- DC: no conflicts of interest.

- MK: no conflicts of interest.

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- SDn: is a Cochrane Editor. She was not involved in the editorial process of the manuscript.

- LR: no conflict of interest

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# 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 | **Diagnosis:** DSM-IV Panic disorder with or without agoraphobia<br>**Method of diagnosis:** not stated<br>**Age, mean (SD) years:** fluoxetine 37.0 (7.1); imipramine 37.2 (8.2)<br>**Sex:** for fluoxetine, 57.89% women, 42.11% men; for imipramine 36.84% women, 63.16% men<br>**Location:** Italy; setting unclear.<br>**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<br>**Rescue medication:** oxazepam (up to a maximum daily dose of 30 mg) permitted during first four weeks of double-blind treatment |
| Interventions | Participants were randomly assigned to either:<br>(1) fluoxetine arm (n = 19)<br>**Duration:** 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders<br>**Treatment protocol:** flexible dosage; range = 10-50 mg, mean 20 mg/day (SD 10) (responder group)<br>(2) imipramine arm (n=19)<br>**Duration:** 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders<br>**Treatment protocol:** flexible dosage; range = 2-250 mg, mean 150 mg/day (SD 25) (responder group) |
| Outcomes | **Time points for assessment:** baseline and weekly for 16 weeks, every two weeks between week 17 and 24, later monthly<br>**Outcomes:**<br>1. Panic-Associated Symptoms Scale (PASS)<br>2. Hamilton Rating Scale for Anxiety (HAMA)<br>3. Hamilton Rating Scale for Depression (HRSD)<br>4. Clinical Global Impression (CGI) |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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: "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 | **Diagnosis:** DSM-IV Panic Disorder with or without agoraphobia<br>**Method of diagnosis:** Not stated<br>**Age:** for fluoxetine, M = 37.2 (SD = 7.0); for citalopram, M = 36.7 (SD = 7.4)<br>**Sex:** for fluoxetine, 57.1% women, 42.9% men; for imipramine 61.9% women, 38.1% men<br>**Location:** Italy; setting unclear<br>**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<br>**Rescue medication:** Oxazepam (up to a maximum daily dose of 30 mg) permitted |
| Interventions | Participants were randomly assigned to either:<br>(1) fluoxetine arm (n = 21)<br>**Duration:** 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders<br>**Treatment Protocol:** flexible dosage; range = 10 - 50 mg, M = 20 mg/day (SD = 10)<br>(2) citalopram arm (n = 21)<br>**Duration:** 24 weeks of active treatment (acute and continuation phase), 6 months maintenance phase for responders<br>**Treatment Protocol:** flexible dosage; range = 20 - 60 mg, M = 40 mg/day (SD = 10) |
| Outcomes | **Time points for assessment:** baseline and weekly for 16 weeks, every two weeks between week 17 and 24, later monthly<br>**Outcomes:**<br>1. Panic-Associated Symptoms Scale (PASS)<br>2. Hamilton Rating Scale for Anxiety (HAMA)<br>3. Clinical Global Impression (CGI)<br>4. Dosage Records and Treatment-Emergent Symptoms Scale (DOTES) |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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: "they were randomly assigned". No further details. |
| Allocation concealment (selection bias) | Unclear risk | No information provided. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis:** not specified<br>**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)<br>**Sex:** 64 men, 115 women<br>**Location:** outpatients, 4 centres throughout the USA<br>**Co-morbidities:** excluded<br>**Rescue medication:** discouraged, but allowed for night time sedation (lorazepam 1-2 mg or chloral hydrate 1-2 mg) |
| Interventions | Participants were randomly assigned to either: |

| | |
|---|---|
| | 1. fluvoxamine arm (randomised n = 93)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 100-300 mg/day, mean 4.2 cps/day (SD = 1.4)<br>2. placebo arm (randomised n = 95)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, mean 5.1 cps/day (SD = 1.2) |
| Outcomes | **Timepoints for assessment:** at baseline and weekly until week 8<br>**Outcomes**<br>1. DPAI<br>2. CAS<br>3. estimate of Panic Attack frequency and severity (item 7 of the CAS)<br>4. SDS<br>5. MADRS<br>6. CGI-S<br>7. CGI-I |
| Notes | **Date of study:** not specified<br>**Funding source:** unclear<br>**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 "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 | **Diagnosis**: DSM-IV panic disorder<br>**Method of diagnosis**: Structured Clinical Interview for DSM-IV (modified version)<br>**Age**: clonazepam: mean = 47.3 (SE = 2.76); Placebo: mean = 44.4 (SE = 1.87)<br>**Sex**: Clonazepam: female 30%; placebo: female 56%<br>**Location**: Canada (Toronto Western Hospital)<br>**Comorbidities**: not stated<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Clonazepam (n = 10)<br>**Duration**: 4 weeks<br>**Treatment protocol**: not stated<br>(2) Placebo (n = 17) |

| | |
|---|---|
| | **Duration**: 4 weeks<br>**Treatment protocol**: not stated |
| Outcomes | **Time points for assessment**: baseline, end of trial<br>**Primary outcomes**:<br>(1) Anxiety: HAMA, weekly<br>(2) Daily diaries<br>(3) General psychiatric symptomatology: SCL-90-R<br>(4) Somatosensory Amplification Scale<br>(5) Illness Intrusiveness Scale<br>(6) Depression: HAMD |
| Notes | **Date of study**: not stated<br>**Funding source**: supported by a grant from the Heart and Stroke Foundation of Ontario<br>**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)<br>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)<br>All outcomes | Unclear risk | Double-blind; no further information |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** Not stated<br>**Age:** Not stated<br>**Sex:** Not stated<br>**Location:** Canada; setting: outpatients<br>**Co-morbidities:** Not stated<br>**Rescue medication:** Chloral hydrate, up to 1 g at night |
| Interventions | Participants were randomly assigned to either:<br>(1) brofaromine arm (n = 47)<br>**Duration:** 8 weeks<br>**Treatment Protocol:** flexible dosage; range = 50 - 150 mg, M and SD not provided<br>(2) clomipramine arm (n = 46)<br>**Duration:** 8 weeks<br>**Treatment Protocol:** flexible dosage; range = 25 - 75 mg, M and SD not provided |
| Outcomes | **Time points for assessment:** baseline, every two weeks<br>**Outcomes:**<br>1. Number of panic attacks per week<br>2. Hamilton Rating Scale for Anxiety (HAMA)<br>3. Hamilton Rating Scales for Depression (HAM-D)<br>4. Clinician Rated Impairment and Disability Scale (CRIDS)<br>5. Clinician Rated Global Change Scale (CRGCS)<br>6. Patient Rating Impairment Disability Scale (PRIDS)<br>7. Patient Rated Anxiety Scale (PRAS)<br>8. Marks Matthews Phobia Scale<br>9. Patient Rated Global Change Scale (PRGCS) |

| | |
|---|---|
| | 10. Daily Panic Inventory (DPI) |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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)<br>All outcomes | Unclear risk | Quote: "double blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** not specified<br>**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)<br>**Sex:** 95 men, 183 women<br>**Location:** outpatients<br>**Co-morbidities:** excluded<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. paroxetine 10 mg arm (randomised n = 67)<br>**Duration:** 10 weeks<br>**Treatment protocol:** fixed dosage 10 mg/day<br>2. paroxetine 20 mg arm (randomised n = 70)<br>**Duration:** 10 weeks<br>**Treatment protocol:** fixed dosage 20 mg/day<br>3. paroxetine 40 mg arm (randomised n = 72)<br>**Duration:** 10 weeks<br>**Treatment protocol:** fixed dosage 40 mg/day<br>4. placebo arm (randomised n = 69)<br>**Duration:** 10 weeks<br>**Treatment protocol:** fixed dosage |
| Outcomes | **Timepoints for assessment:** at baseline, week 4 and week 10<br>**Outcomes:**<br>1. percentage of subject free of panic attacks at endpoint<br>2. mean change from baseline in number of full panic attacks<br>3. percentage of subjects with a 50% reduction from baseline in number of full panic attacks<br>4. CGI-S<br>5. mean number and intensity of panic attacks<br>6. number of unexpected and situational panic attacks<br>7. severity of anticipatory anxiety<br>8. CGI-I<br>9. Marks-Sheehan Phobia Scale |

| | |
|---|---|
| | 10. HAMA<br>11. MADRS<br>12. SDS<br>13. Social Adjustment Self-Report Questionnaire |
| Notes | **Date of study:** not specified<br>**Funding source:** sponsored by the drug company marketing the drug<br>**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.<br>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<br>**Method of diagnosis:** Not stated<br>**Age:** for sertraline, M = 39.6 (SD = 11.7); for paroxetine, M = 38.1 (SD = 11.7)<br>**Sex:** for sertraline, 60% women, 40% men; for paroxetine 66% women, 34% men<br>**Location:** 5 centres in Denmark, 22 centres in Germany, 2 centres in the Netherlands, 2 centres in Switzerland, 2 centres in Turkey; setting: outpatients<br>**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<br>**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:<br>(1) sertraline arm (n = 112)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; range = 25 - 150 mg, M = 84.5, SD = 39.1<br>(2) paroxetine arm (n = 113)<br>**Duration:** 12 weeks<br>**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<br>**Outcomes:**<br>**1.** Panic and Agoraphobia Scale (PAS)<br>**2.** agoraphobia/avoidance behaviour<br>**3.** anticipatory anxiety<br>**4.** disability<br>**5.** health worries |

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

***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)<br>All outcomes | Unclear risk | Quote: "double blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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 | **Study design:** 12 weeks and then 6 months, multicentre, randomised, double-blind, placebo-controlled clinical trial, parallel groups, cluster randomisation |
| Participants | **Diagnosis:** panic disorder with or without mild agoraphobia<br>**Method of diagnosis:** ADIS-R (Anxiety Disorder Interview Schedule-Revised, diagnosis confirmed 2 weeks prior to first treatment visit)<br>**Age (years):** mean 36.1 (SD = 10.7)<br>**Sex:** 62.5% women<br>**Location:** not specified<br>**Co-morbidities:** patients with depression were not excluded, unless suicidal<br>**Rescue medication:** allowed up to 20 doses of benzodiazepines (or 10 alprazolam equivalent) |
| Interventions | Participants were randomly assigned to either:<br>1. imipramine arm (randomised n = 83)<br>**Duration:** 12 weeks<br>**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"<br>2. CBT alone arm (randomised n = 77)<br>**Duration:**12 weeks<br>**Treatment protocol:** unclear<br>3. CBT plus imipramine arm (randomised n = 65)<br>**Duration:**12 weeks<br>**Treatment protocol:** flexible dosage; range = 10-60 mg/day<br>4. CBT plus placebo arm (randomised n = 63)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage<br>5. placebo arm (randomised n = 24)<br>**Duration:** 12 weeks |

| | |
|---|---|
| | **Treatment protocol:** flexible dosage |
| Outcomes | **Timepoints for assessment:** at baseline, at week 12 and then at month 4, 5, and 6<br>**Outcomes:**<br>1. PDSS<br>2. Responders based on CGI |
| Notes | **Date of study:** May 1991-April 1998<br>**Funding source**: the study was mostly funded by public financial support. Sponsorship bias is unlikely to have occurred.<br>**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)<br>All outcomes | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Trained independent evaluators were employed (see "Assessment" paragraph) |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis**: semistructured interview<br>**Age**: range: 21 to 49 years (median: 34)<br>**Sex**: M = 12; F = 17<br>**Location**: Canada; setting: outpatients<br>**Comorbidities**: none<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Clonazepam (n = 13)<br>**Duration**: 4 weeks<br>**Treatment protocol**: flexible dosage; range = 1 to 5 mg (the actual maximum daily dose was 3.5 mg)<br>(2) Placebo (n = 16)<br>**Duration**: 4 weeks<br>**Treatment protocol**: flexible |
| Outcomes | **Time points for assessment**: days 0, 7, 14, 21, 28<br>**Primary outcomes**:<br>(1) Anxiety: modified version of HAMA<br>(2) Overall improvement: CGI of severity of panic disorder; at study entry and termination, Global Assessment Scale<br>(3) Type/frequency/intensity/length: panic attacks: Panic Attack Index; 10-point scale<br>(4) Depression: at study entry and termination, Hamilton Rating Scale for Depression (21-item HAMD)<br>(5) Impairment: Social Readjustment Rating Scale<br>**Secondary outcome**:<br>(1) Adverse events: at each visit, general inquiry |
| Notes | **Date of study**: June 1987 to June 1988<br>**Funding source**: not stated<br>**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 | **Diagnosis:** panic disorder with and without agoraphobia according to the DSM IV criteria<br>**Method of diagnosis:** PDSS, CGI and number of panic attacks per week<br>**Age (years):** the mean age was 41 for the metabotropic glutamate (LY354740), 44 for paroxetine and 45 for placebo<br>**Sex:** 18 men and 27 women<br>**Location:** University Medical Centre (UMC) in Utrecht, the Netherlands<br>**Co-morbidities:** excluded<br>**Rescue medication:** not permitted |
| Interventions | Participants were randomly assigned to either:<br>1. LY354740 arm (randomised n = 18)<br>**Duration:** 9 weeks<br>**Treatment protocol:** flexible dosage; range = 100-200 mg/day<br>2. paroxetine arm (randomised n = 9)<br>**Duration:** 9 weeks<br>**Treatment protocol:** flexible dosage; range = 10-60 mg/day<br>3. placebo arm (randomised n = 0)<br>**Duration:** 9 weeks<br>**Treatment protocol:** flexible dosage |
| Outcomes | **Timepoints for assessment:** at baseline and then at week 3, 6, 9<br>**Outcomes:**<br>1. responders (participants that hadn't had a full panic attack during their final 3-week active drug period):<br>2. number of panic attacks<br>3. MADRS<br>4. HAMA<br>5. PGI-P<br>6. PDSS<br>7. CGI-S |
| Notes | **Date of study:** not specified<br>**Funding source:** unclear<br>**Declarations of interest among the primary researchers:** unclear |
| *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.<br>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 | **Diagnosis:** DSM-III-R criteria for panic disorder with or without agoraphobia<br>**Method of diagnosis:** SCID<br>**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)<br>**Sex:** 22 men, 53 women<br>**Location:** outpatient setting, multicentre, USA<br>**Co-morbidities:** patients with a diagnosis of major depression were also included, medical comorbidities were excluded<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. fluvoxamine arm (randomised n = 25)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = up to 300 mg per day, mean 230 mg (4.6 cps)/day<br>2. CBT arm (randomised n = 25)<br>**Duration:** 8 weeks<br>**Treatment protocol:** psychotherapy sessions<br>3. placebo arm (randomised n = 25)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, 5.5 cps/day |
| Outcomes | **Timepoints for assessment:** at baseline and then at week 4 and 8<br>**Outcomes:**<br>1. number and severity of attacks<br>2. CAS<br>3. CGI<br>4. SDS<br>5. MADRS |
| Notes | **Date of study:** not specified<br>**Funding source:** financed by a drug company<br>**Declarations of interest among the primary researchers:** unclear |

*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)<br>All outcomes | | |
| Blinding of outcome assessment (detection bias)<br>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)<br>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<br>**Method of diagnosis:** DSM-IV and modified Mini International Neuropsychiatric Interview<br>**Age (years):** 38.9 (SD = 12.4) for the venlafaxine ER arm and 38.8 (SD = 12.1) for the placebo arm<br>**Sex:** venlafaxine arm, 61 men and 99 women; placebo arm, 69 men, 99 women<br>**Location:** outpatient setting, 50 sites in Canada, Europe and South Africa<br>**Co-morbidities:** excluded<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. venlafaxine ER arm (randomised n = 181)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 75-225 mg/day, mean = 162.9 mg/day (SD = 60.6) at week 10<br>2. placebo arm (randomised n = 180)<br>**Duration:** 10 weeks<br>**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<br>**Outcomes:**<br>1. PAAS<br>2. CGI-S<br>3. CGI-I<br>4. Phobia Scale (Fear and Avoidance)<br>5. Covi Anxiety scale<br>6. Q-LES-Q<br>7. SDS<br>8. report of adverse effects<br>9. physical examinations |
| Notes | **Date of study:** not specified<br>**Funding source:** the study was funded by the company marketing the drug<br>**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)<br>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)<br>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)<br>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. |

**Broocks 1998**

| ***Study characteristics*** | |
|---|---|
| Methods | **Study design:** 10 weeks, placebo-controlled study, parallel groups, individual randomisation |
| Participants | **Diagnosis:** DSM-III-R and ICD-10 criteria diagnosis of panic disorder and agoraphobia<br>**Method of diagnosis:** SCID for DSM-III-R<br>**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)<br>**Sex:** 23 men, 23 women<br>**Location:** outpatient setting, Germany<br>**Co-morbidities:** excluded<br>**Rescue medication:** prometazine 25-50 mg |
| Interventions | Participants were randomly assigned to either:<br>1. clomipramine arm (randomised n = 15)<br>**Duration:** 10 weeks<br>**Treatment protocol:** fixed dosage; range = 37.5-112.5 mg/day<br>2. aerobic exercise-running arm (randomised n = 16)<br>**Duration:** 10 weeks<br>**Treatment protocol:** running schedule<br>3. placebo arm (randomised n = 15)<br>**Duration:** 10 weeks<br>**Treatment protocol:** fixed dosage |
| Outcomes | **Timepoints for assessment:** at baseline and then at 10 weeks<br>**Outcomes:**<br>1. HAMA<br>2. Panic & Agoraphobia Scale<br>3. CGI<br>4. FQ<br>5. Beck Anxiety Inventory<br>6. BDI<br>7. MADRS |
| Notes | **Date of study:** unclear<br>**Funding source:** grant from a car factory<br>**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 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)<br>All outcomes | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>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 | **Diagnosis:** DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis:** Not stated<br>**Age:** average age of 37 years, no between-group differences<br>**Sex:** 12 males and 9 females, no between-group differences<br>**Location:** USA; setting unclear<br>**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<br>**Rescue medication:** Not stated. |
| Interventions | Participants were randomly assigned to either:<br>(1) desipramine arm (n = 11)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 10 - 300 mg, M = 110, SD = 49<br>(2) fluoxetine arm (n = 11)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 2.5 - 60 mg, M = 19, SD = 10 |
| Outcomes | **Time points for assessment:** weekly<br>**Outcomes:**<br>**1.** Hamilton Rating Scale for Anxiety (HAMA)<br>**2.** Hamilton Rating Scales for Depression (HAM-D)<br>**3.** Four Dimensional Anxiety Scale<br>**4.** Clinical Global Impression-Severity of Illness (CGI-S)<br>**5.** Clinical Global Impression-Improvement (CGI-I) |
| Notes | **Date of study:** Not stated<br>**Funding source:** this research has been supported in part by NIMH grant MH 45342-02 and by an NPI Opportunity Grant<br>**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: "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 | **Diagnosis:** DSM-III-R criteria for panic disorder with or without agoraphobia<br>**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<br>**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)<br>**Sex:** 64 men, 94 women<br>**Location:** outpatient setting, multicentre (15 sites in France)<br>**Co-morbidities:** excluded<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. clomipramine low-dose arm (randomised n = 61)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage; 60 mg/day<br>2. clomipramine high-dose arm (randomised n = 62)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage; 150 mg/day<br>3. Placebo arm (randomised n = 57)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage |
| Outcomes | **Timepoints for assessment:** at baseline and weekly<br>**Outcomes:**<br>1. HAMA<br>2. CGI<br>3. HDRS |
| Notes | **Date of study:** not specified<br>**Funding source:** the sponsor is the drug company marketing clomipramine<br>**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, 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)<br>All outcomes | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No information provided. |
| Incomplete outcome data (attrition bias)<br>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.<br>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 |

| | |
|---|---|
| | **Method of diagnosis**: Structured Clinical Interview for DSM-III-R, Upjohn version (SCID-UP-R); medical questionnaire; physical examination; laboratory test<br>**Age**: not stated<br>**Sex**: not stated<br>**Location**: USA (10 study sites)<br>**Comorbidities**: none<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Adinazolam SR 30 mg (n = 79)<br>**Duration**: 4 weeks<br>**Treatment protocol**: fixed dose: 30 mg<br>(2) Adinazolam SR 60 mg (n = 81)<br>**Duration**: 4 weeks<br>**Treatment protocol**: fixed dose: 60 mg<br>(3) Adinazolam SR 90 mg (n = 72)<br>**Duration**: 4 weeks<br>**Treatment protocol**: fixed dose: 90 mg<br>(4) Placebo (n = 83)<br>**Duration**: 4 weeks |
| Outcomes | **Time points for assessment**: baseline, weeks 1, 2, 4<br>**Primary outcomes**:<br>(1) Number of panic attacks: Panic Anxiety Attack Scale<br>(2) Global improvement: CGI-I, CGI-S<br>(3) Agoraphobia: SCL-90-R<br>(4) Overall phobic avoidance: Patient-rated Phobia Scale (a modification of the Fear Questionnaire)<br>**Secondary outcome**:<br>(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 |
| Notes | **Date of study**: not stated<br>**Funding source**: supported by grants from the Upjohn Company<br>**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 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 | **Diagnosis:** DSM-III-R panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia)<br>**Method of diagnosis:** "patients were evaluated by Structured Clinical Interview for DSM-III Diagnosis, Upjohn (SCID-UP)<br>**Age:** M = 34, SD not provided<br>**Sex:** 62 % female, 38 % male<br>**Location:** 12 centres in USA, Spain, Denmark, Germany, England, Italy, Brazil, Mexico, France, Colombia, Austria, Sweden, Canada, Belgium; setting: inpatients and outpatients |

| | |
|---|---|
| | **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.<br>**Rescue medication:** Quote "patients taking CNS drugs, including benzodiazepines, were excluded from the study. During the washout period, blood was drawn for benzodiazepines screening". |
| Interventions | **Participants were randomly assigned to either:**<br>(1) imipramine arm (n = 391)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 25 - 250 mg, M = 155, SD not provided<br>(2) alprazolam arm (n = 386)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 1 - 10 mg, M = 5.7, SD not provided<br>(3) placebo arm (n = 391)<br>**Duration:** 8 weeks |
| Outcomes | **Time points for assessment:** baseline, weekly, endpoint<br>**Outcomes:**<br>**1.** Physician's and patient's global improvement scales<br>**2.** Panic Attack Scale, patient's diary<br>**3.** Overall Phobia Scale (Marks & Matthews), Phobic Anxiety Factor of the Symptom Check List (SCL-90)<br>**4.** anticipatory anxiety<br>**5.** Hamilton Rating Scale for Anxiety (HAMA)<br>**6.** social functioning, five-point scale<br>**7.** Hamilton Rating Scale for Depression (HRSD)<br>**8.** Hopkins SCL-90 patient self-rating scale for presence and intensity of symptoms |
| Notes | **Date of study:** Data collection: 1984 - 1987<br>**Funding source:** sponsored by Upjohn Company, Kalamazoo, Michigan<br>**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 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 | **Diagnosis**: DSM-III-R panic disorder with agoraphobia<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III-R, Upjohn version (SCID-UP-R)<br>**Age**: Adinazolam: mean = 36.1 (SD = 10.8); Placebo: mean = 35.5 (SD = 8.9)<br>**Sex**: Adinazolam: M = 34%, F = 66%; Placebo: M = 33%, F = 67% |

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|---|---|
| | **Location**: USA (at 4 centres: University of California, Duke University Medical Center, University of Missouri-Columbia, University of Wisconsin)<br>**Comorbidities**: controlled physical illness<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Adinazolam SR (n = 99)<br>**Duration**: 4 weeks<br>**Treatment protocol**: flexible dosage; mean = 84.1 (SD = 28.6); range = 3.5 to 7.5 capsules<br>(2) Placebo (n = 103)<br>**Duration**: 4 weeks<br>**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<br>**Primary outcomes**:<br>(1) Overall improvement: CGI<br>(2) Frequency/duration/intensity of panic attacks: Sheehan Panic and Anxiety Attack Scale<br>(3) Agoraphobia: Phobia Severity Scale; SCL-90, phobic cluster<br>**Secondary outcomes**:<br>(1) Anxiety: HAMA; Sheehan Clinician Rated Anxiety Scale<br>(2) Impairment: Sheehan Disability Scale<br>(3) The main phobia of the Phobia Severity Scale |
| Notes | **Date of study**: not stated<br>**Funding source**: not stated<br>**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)<br>All outcomes | Unclear risk | Quote: "This was a parallel, double-blind, flexible dose, 4 week efficacy and safety study".<br>“Medication was packed in individual bottles”. No information on blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Double-blind; no further information. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There were dropouts in each group (Drug 1 = 12 out of 99, Placebo = 15 out of 103), but there was no imbalance between the 2 groups. Quote: "No statistical difference was found in the dropouts rates between the two treatment groups". |
| Selective reporting (reporting bias) | High risk | Side effects only reported if group difference was statistically significant, SDs only reported as P value. |
| Other bias | Unclear risk | Bristol-Myers Squibb Pharmaceutical Research Institute was involved in this study.<br>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<br>**Method of diagnosis:** Not stated<br>**Age:** for maprotiline, M = 35.0 (SD = 7.4); for fluvoxamine, M = 37.3 (SD = 10.6)<br>**Sex:** for maprotiline, 4 males and 20 females; for fluvoxamine 5 males and 15 females<br>**Location:** the Netherlands; setting: outpatients<br>**Co-morbidities:** patients with major affective disorders, schizophrenia, other psychotic disorder or significant medical problems were excluded<br>**Rescue medication:** Not stated |
| Interventions | **Participants were randomly assigned to either:**<br>(1) maprotiline arm ("24 patients were included in the maprotiline group") |

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|---|---|
| | **Duration:** 6 weeks<br>**Treatment protocol:** flexible dosage; range = 50 - 150 mg, M and SD not provided<br>(2) fluvoxamine arm ("20 patients were included in the fluvoxamine group")<br>**Duration:** 6 weeks<br>**Treatment protocol:** flexible dosage; range = 50 - 150 mg, M and SD not provided |
| Outcomes | **Time points for assessment:** baseline and weekly<br>**Outcomes:**<br>**1.** SCL-90<br>**2.** State Anxiety Inventory (A-STATE)<br>**3.** Self Rating Depression Scale (SDS)<br>**4.** Hamilton Anxiety Scale (HAS)<br>**5.** Hamilton Depression Scale (HDS)<br>**6.** panic attack inventory<br>**7.** side-effects scale |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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: "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 | **Diagnosis:** DSM-III-R<br>**Method of diagnosis:** not stated<br>**Age:** for fluvoxamine M = 37, for ritanserin M = 35, for placebo M = 37<br>**Sex:** the female to male ratio was almost 3 to 1 in all groups<br>**Location:** the Netherlands; setting: outpatients<br>**Co-morbidities:** patients with a primary diagnosis other than panic disorder were excluded<br>**Rescue medication:** none |
| Interventions | **Participants were randomly assigned to either:**<br>(1) fluvoxamine arm<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage = 150 mg<br>(2) ritanserin arm<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage = 20 mg<br>(3) placebo arm<br>**Duration:** 8 weeks<br>Total number of randomised patients = 60. The number of patients randomised for each arm is not provided. |
| Outcomes | **Time points for assessment:** baseline, weekly<br>**Outcomes:** |

| | |
|---|---|
| | **1.** SCL-90<br>**2.** Hamilton Rating Scale for Anxiety (HAMA)<br>**3.** State-Trait Anxiety Inventory (STAI)<br>**4.** Fear Questionnaire (FQ)<br>**5.** panic inventory |
| Notes | **Date of study:** not stated<br>**Funding source:** not stated<br>**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 furher information provided. |
| Allocation concealment (selection bias) | Unclear risk | No information provided. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis:** semi-structured interview<br>**Age:** for imipramine, M = 36.35 (SEM = 2.12); for clomipramine, M = 34.1 (SEM = 1.89)<br>**Sex:** for imipramine, 70% women, 30% men; for clomipramine 50% women, 50% men<br>**Location:** Brazil; setting: outpatients<br>**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<br>**Rescue medication:** Not stated |
| Interventions | **Participants were randomly assigned to either:**<br>(1) imipramine arm (n = 20)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 25 - 200 mg, M = 113.8, SD = 9.5<br>(2) clomipramine arm (n = 20)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 10 - 80 mg, M = 50, SD = 4.2<br>(3) placebo arm (propantheline) (n = 20)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; M = 85.5, SD = 5.7 |
| Outcomes | **Time points for assessment: baseline, week 2, 4, 6 and 8**<br>**Outcomes:**<br>**1.** Clinical Global Impression Scale (CGI)<br>**2.** Sheehan Anxiety Scales<br>**3.** Hamilton Rating Scale for Depression (HRSD)<br>**4.** Beck Depression Inventory (BDI) |
| Notes | **Date of study:** Not stated<br>**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<br>**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: "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 propanteline (placebo) and filled up with lactose. The dose range of propanteline 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 propanteline (placebo) and filled up with lactose. The dose range of propanteline 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 HAMD 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 | **Diagnosis**: DSM-III-R panic disorder<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III-R<br>**Age**: Paroxetine: mean = 39.1 (SD = 11.1); Alprazolam: mean = 39.5 (SD = 12.5); Placebo: mean = 39.0 (SD = 11.8)<br>**Sex**: Paroxetine: M = 28; Alprazolam: M = 29; Placebo: M = 23<br>**Location**: 16 centres in the USA<br>**Comorbidities**: major depression (if secondary)<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Paroxetine (n = 77)<br>**Duration**: 10 weeks<br>**Treatment protocol**: flexible dosage; range: 10 to 60 mg/day<br>(2) Alprazolam (n = 77)<br>**Duration**: 10 weeks<br>**Treatment protocol**: flexible dosage; range: 1 to 6 mg/day<br>(3) Placebo (n = 72)<br>**Duration**: 10 weeks<br>**Treatment protocol**: flexible |
| Outcomes | **Time points for assessment**: not stated<br>**Primary outcomes**:<br>(1) Percentage of participants having zero full panic attacks during the last 2 weeks of treatment phase<br>(2) Mean change from baseline in the number of full panic attacks during the last 2 weeks of treatment phase<br>(3) Percentage of participants with a >= 50% reduction from baseline in the number of full panic attacks during the last 2 weeks of treatment phase<br>(4) Overall improvement: CGI severity of Illness score<br>**Secondary outcomes**:<br>(1) Mean number of full and limited symptoms (all) panic attacks, and full situational and full unexpected panic attacks, per 2-week period<br>(2) Mean intensity of all and full panic attacks per 2-week period<br>(3) Per cent of time engaged in, and intensity of, anticipatory anxiety per 2 weeks<br>(4) Agoraphobia: Marks Sheehan Phobia Scale, Fear and Avoidance Scores<br>(5) Overall improvement: CGI Global improvement score<br>(6) Anxiety: HAMA<br>(7) Depression: MADRS<br>(8) Disability: Sheehan Disability Scale, Social Adjustment Self-Report Scale |
| Notes | **Date of study**: November 1992 to April 1994<br>**Funding source**: GlaxoSmithKline<br>**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)<br>All outcomes | Unclear risk | Double-blind; no further information. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Double-blind; no further information. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** Panic disorder; no further details provided<br>**Method of diagnosis:** Not stated<br>**Age:** for paroxetine, M = 37.12 (SD = 9.92); for clomipramine, M = 40.13 (SD = 11.34)<br>**Sex:** for paroxetine, 14 women, 23 men, 1 unknown; for clomipramine 17 women, 14 men<br>**Location:** China; setting unclear<br>**Co-morbidities:** patients with current major depression were excluded. No other co-morbidities mentioned<br>**Rescue medication:** Not stated |
| Interventions | **Participants were randomly assigned to either:**<br>(1) paroxetine arm (n = 38)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 10 - 50 mg, M and SD not provided<br>(2) clomipramine arm (n = 35)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 50 - 100 mg, M and SD not provided |
| Outcomes | **Time points for assessment:** baseline, endpoint (10 weeks)<br>**Outcomes:**<br>**1.** mean change from baseline in the number of full panic attacks<br>**2.** Hamilton Rating Scale for Anxiety (HAMA)<br>**3.** Panic Associated Symptoms Scale<br>**4.** Clinical Global Impression Severity of Illness Score (CGI-S)<br>**5.** Patient Global Evaluation (PGE) |
| Notes | **Date of study:** September 1998 to September 1999<br>**Funding source:** GSK<br>**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)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** SCID<br>**Age (years):** mean age 38.0 (SD = 9.6)<br>**Sex:** 16 men, 20 women<br>**Location:** outpatient department at Johns Hopkins Hospital (Baltimore, Maryland, USA)<br>**Co-morbidities:** excluded<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. fluvoxamine arm (randomised n = 25)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 100-300 mg/day, mean 206.8 mg/day<br>2. placebo arm (randomised n = 25)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, mean = 5.6 cps/day |
| Outcomes | **Timepoints for assessment:** at baseline and then weekly until week 8<br>**Outcomes:**<br>1. CAS<br>2. MADRS<br>3. SDS<br>4. severity and the number of panic attacks/week |
| Notes | **Date of study:** not stated<br>**Funding source:** cps of fluvoxamine or placebo were provided by the drug company marketing the drug<br>**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<br>**Method of diagnosis:** Not stated<br>**Age:** for adinazolam, M = 36.5; for clomipramine, M = 35.8; SD not provided |

| | |
|---|---|
| | **Sex:** for adinazolam, 36% male; for clomipramine 38% male<br>**Location:** UK; setting unclear<br>**Co-morbidities:** patients with psychiatric co-morbidities were excluded<br>**Rescue medication:** Not stated |
| Interventions | **Participants were randomly assigned to either:**<br>(1) adinazolam arm (n = 166)<br>**Duration:** 24 weeks<br>**Treatment protocol:** flexible dosage; range = 30 - 90 mg, M and SD not provided<br>(2) clomipramine arm (n = 149)<br>**Duration:** 24 weeks<br>**Treatment protocol:** flexible dosage; range = 50 - 150 mg, M and SD not provided |
| Outcomes | **Time points for assessment:** weeks 1, 2, 4, 8, 12, 16, 20 and 24<br>**Outcomes:**<br>**1.** total number of panic attacks (Panic Attack and Anticipatory Anxiety scale)<br>**2.** Clinical Global Impression Improvement Score (CGI-I)<br>**3.** SCL - 90, Phobic Anxiety Dimension<br>**4.** Sheehan Disability Scale |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM-III agoraphobia<br>**Method of diagnosis:** unclear<br>**Age (years):** 18-70 (mean = 37, SD = 10)<br>**Sex:** women<br>**Location:** unclear<br>**Co-morbidities:** excluded<br>**Rescue medication:** unclear |
| Interventions | Participants were randomly assigned to either:<br>1. clomipramine arm (randomised n = 16)<br>**Duration:** 28 weeks<br>**Treatment protocol:** flexible/fixed dosage; range = 25-300 mg/day, mean = 68.3 mg/day (SD = 39.7)<br>2. clomipramine + CBT arm (randomised n = 17)<br>**Duration:** 28 weeks<br>**Treatment protocol:** flexible dosage; range = 25-300 mg/day, mean = 133.3 mg/day (SD = 58.7)<br>3. placebo arm (randomised n = 16)<br>**Duration:** 28 weeks<br>**Treatment protocol:** flexible/fixed dosage; range = 25-300 mg/day, mean = 154.41 mg/day (SD = 51.7)<br>4. placebo + CBT (randomised n = 15)<br>**Duration:** 28 weeks<br>**Treatment protocol:** flexible/fixed dosage; range = 25-300 mg/day, mean = 139.3 mg/day (SD = 73.7) |

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

***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 | **Diagnosis**: DSM-III -R panic disorder with agoraphobia<br>**Method of diagnosis**: Anxiety Disorder Interview Schedule-Revised<br>**Age**: mean = 37 (SD = 11.04)<br>**Sex**: M = 26% F = 74%<br>**Location**: not stated (USA)<br>**Comorbidities**: major depression (if secondary)<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam (n = 17)<br>**Duration**: 15 weeks<br>**Treatment protocol**: flexible dosage; mean = 4.60 (SD = 1.82)<br>(2) Panic control treatment (PCT) (behaviour therapy treatment group) (n = 18)<br>**Duration**: 15 weeks<br>**Treatment protocol**: 15 individual sessions of an integrated CBT in weekly meetings<br>(3) Waiting list (n = 16)<br>**Duration**: 15 weeks<br>**Treatment protocol**: no treatment<br>(4) Placebo arm (n = 18)<br>**Duration**: 15 weeks<br>**Treatment protocol**: flexible dosage; mean = 5.08 (SD = 2.65) |

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|---|---|
| Outcomes | **Time points for assessment**: clinical assessment before and after treatment; self monitoring measures throughout treatment<br>**Primary outcomes**:<br>(1) Anxiety episodes and panic attacks: diary<br>(2) Anxiety: HAMA<br>(3) Depression: HAMD<br>(4) Global clinical severity ratings |
| Notes | **Date of study**: not stated<br>**Funding source**: This research was supported in part by a grant from the National Institute of Mental Health (MH-36800) and the Upjohn Company.<br>**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)<br>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)<br>All outcomes | Low risk | Quote: "the ADIS-r administrators were blind to group assignment." |
| Incomplete outcome data (attrition bias)<br>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 where 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 | **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. |
| Participants | **Diagnosis:** DSM-IV criteria for panic disorder with or without agoraphobia<br>**Method of diagnosis:** psychiatric interview and a Structured Clinical Interview for DSM-IV (SCID)<br>**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)<br>**Sex:** 90 men, 161 women<br>**Location:** outpatient, 15 academic health centres in Canada<br>**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"<br>**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) |
| Interventions | Participants were randomly assigned to either:<br>1. sertraline arm (randomised n = 63)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; range = 25-200 mg/day, mean = 116.1 mg/day (SD = 59.6) |

| | |
|---|---|
| | 2. sertraline + SCBT arm (randomised n = 61)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; range = 25-200 mg/day, mean = 95.8 mg/day (SD = 57.6)<br>3. placebo + SCBT arm (randomised n = 65)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; mean = 138.3 mg/day (SD=59.5)<br>4. placebo arm (randomised n = 62)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage, mean = 138.3 mg/day (SD = 59.5) |
| Outcomes | **Timepoints for assessment:** at baseline at week 1, 2, 3, 4, 6, 8, 10 and 12<br>**Outcomes:**<br>1. frequency of panic attacks and anticipatory anxiety<br>2. Mobility Inventory for Agoraphobia (MI-AAL)<br>3. Body Sensations Questionnaire (BSQ) and Agoraphobic Cognitions Questionnaire (ACQ)<br>4. SDS<br>5. CGI-S<br>6. CGI-I |
| Notes | **Date of study:** not specified<br>**Funding source:** the study was supported by the drug company marketing sertraline<br>**Declarations of interest among the primary researchers:** one of the primary researchers declared a conflict of interest with several drug companies. |

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

| | |
|---|---|
| | **Duration:** 8 weeks<br>**Treatment protocol:** fixed-flexible dosage, range = 300 - 600 mg, M and SD not provided<br>(2) clomipramine arm (n = 68)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed-flexible dosage, range = 100 - 200 mg, M and SD not provided |
| Outcomes | **Time points for assessment:** week 1, 2, 4, and 8<br>**Outcomes:**<br>**1.** number of panic attacks<br>**2.** Patients' Clinical Global Impression of Change (P-CGI-C)<br>**3.** Investigators' rating of Clinical Global Impression of the Severity of the patients' panic disorder (I-CGI-S)<br>**4.** Patients' rating of Clinical Global Impression of Severity (P-CGI-S)<br>**6.** Sheehan Disability Scale (SDS)<br>**7.** Hamilton Rating Scale for Anxiety (HAMA)<br>**8.** Montgomery–Åsberg Depression Rating Scale (MADRS) |
| Notes | **Date of study:** Not stated<br>**Funding source:** Hoffmann - La Roche<br>**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)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis:** not stated<br>**Age:** for paroxetine, M = 34.7 (SD = 9.3); for clomipramine, M = 35.1 (SD = 9.2)<br>**Sex:** for paroxetine, 53 males, 70 females; for clomipramine 46 males, 75 females<br>**Location:** 39 centres in Belgium, Denmark, France, Hungary, Ireland, Israel, Italy, the Netherlands, Norway, Spain, Switzerland, UK, Yugoslavia; setting: outpatients<br>**Co-morbidities:** none<br>**Rescue medication:** chloral hydrate for night time sedation allowed |
| Interventions | **Participants were randomly assigned to either:**<br>(1) paroxetine arm (n = 123)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage, range = 10 - 60 mg, M and SD not provided<br>(2) clomipramine arm (n = 122)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage, range = 10 - 150 mg, M and SD not provided<br>(3) placebo arm (n = 123)<br>**Duration:** 12 weeks |
| Outcomes | **Time points for assessment:** weeks 3, 6, 9, 12 |

| | |
|---|---|
| | **Outcomes:**<br>**1.** change in number of panic attacks<br>**2.** proportion of subjects with zero panic attacks<br>**3.** proportion of subjects with a > 50% reduction in the number of panic attacks<br>**4.** change in intensity of panic attacks<br>**5.** Hamilton Rating Scale for Anxiety (HAMA)<br>**6.** Clinical Global Impression Scale (CGI)<br>**7.** Montgomery–Åsberg Depression Rating Scale (MADRS)<br>**8.** Mark Sheehan Phobia Scale<br>**9.** Patient Global Evaluation (PGE)<br>**10.** Sheehan Disability Scale |
| Notes | **Date of study:** October 1991 - November 1993<br>**Funding source:** Sponsored by GSK<br>**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)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details. |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** Not stated<br>**Age:** M = 37.4, SD not provided<br>**Sex:** not stated<br>**Location:** Finland; setting: inpatients<br>**Co-morbidities:** patients with psychiatric co-morbidities were excluded; medical co-morbidities are not mentioned; six patients suspected cases of epilepsy<br>**Rescue medication:** "the patients did not receive any other treatment during the trial period" |
| Interventions | **Participants were randomly assigned to either:**<br>(1) alprazolam arm (n = 27)<br>**Duration:** 9 weeks<br>**Treatment Protocol:** flexible dosage, range = 1.5 - 8 mg, M = 4.9, SD not provided<br>(2) imipramine arm (n = 28)<br>**Duration:** 9 weeks<br>**Treatment Protocol:** flexible dosage, range = 30 - 225 mg, M = 130, SD not provided |
| Outcomes | **Time points for assessment:** baseline, 3 weeks, 9 weeks<br>**Outcomes:**<br>**1.** panic attack frequency<br>**2.** Hamilton Rating Scale for Anxiety (HAMA) |

| | |
|---|---|
| | **3.** Montgomery–Åsberg Depression Rating Scale (MADRS)<br>**4.** seven-point evaluation scale of the clinical state (not better specified) |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double-blind". No further details |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** not specified<br>**Age (years):** venlafaxine ER arm mean age 36 (SD = 12.4) and placebo arm mean age 36.7 (SD = 12.0)<br>**Sex:** 107 men, 203 women<br>**Location:** outpatient setting, in 56 sites (7 in Canada and 49 in USA)<br>**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<br>**Rescue medication:** unclear |
| Interventions | Participants were randomly assigned to either:<br>1. venlafaxine ER arm (randomised n = 175)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 37.5 to 225 mg/day<br>2. placebo arm (randomised n = 168)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage |
| Outcomes | **Timepoints for assessment:** at baseline and then at week 1, 2, 3, 4, 6, 8 and 10<br>**Outcomes:**<br>1. percentage of participants free of panic attacks, measured with the PAAS<br>2. PDSS<br>3. CGI-I<br>4. PAAS<br>5. HAMA<br>6. Phobia Scale<br>7. Q-LES-Q<br>8. SDS |
| Notes | **Date of study:** the study was conducted from April 2001-December 2002<br>**Funding source:** drug company marketing the drug is likely to have sponsored the study<br>**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.<br>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 | **Diagnosis:** DSM-III-R diagnosis of panic disorder with or without agoraphobia<br>**Method of diagnosis:** SCID (Structured Clinical interview for DSM-III-R)<br>**Age (years):** 18.9-74.5 (the average age of participants was 38.8 years)<br>**Sex:** 53% men, 47% women<br>**Location:** outpatient setting, 7 sites in USA (6 western USA and 1 in West Virginia)<br>**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<br>**Rescue medication:** choral hydrate for sleep |
| Interventions | Participants were randomly assigned to either:<br>1. sertraline 50 mg arm (randomised n = 43)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage 50 mg/day<br>2. sertraline 100 mg arm (randomised n = 44)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage 100 mg/day<br>3. sertraline 200 mg arm (randomised n = 45)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage 200 mg/day<br>3. placebo arm (randomised n = 45)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage, number of tablets not specified |
| Outcomes | **Timepoints for assessment:** at the end of weeks 1, 2, 3, 4, 6, 8, 10 and 12<br>**Outcomes:**<br>1. PAAS<br>2. HAMA<br>3. CGI-S<br>4. CGI-I |
| Notes | **Date of study:** not specified<br>**Funding source:** drug company marketing sertraline<br>**Declarations of interest among the primary researchers:** RW is a Senior Associate Medical Director at the drug company marketing sertraline |

| ***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%)"<br>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 | **Diagnosis**: DSM-III panic disorder or agoraphobia with panic attacks<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III, Upjohn version<br>**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)<br>**Sex**: unclear<br>**Location**: USA<br>**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<br>**Rescue medication**: none | |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam 2 mg (n = 30)<br>**Duration**: 6 weeks<br>**Treatment protocol**: fixed = 2 mg<br>(2) Alprazolam 6 mg (n = 31)<br>**Duration**: 6 weeks<br>**Treatment protocol**: fixed = 6 mg<br>(2) Placebo arm (n = 33)<br>**Duration**: 6 weeks<br>**Treatment protocol**: fixed | |
| Outcomes | **Time points for assessment**: baseline, week 1, 2, 3, 4, 6<br>**Primary outcomes**:<br>(1) Frequency of panic attacks: participant's diary<br>(2) Overall severity of phobia: 11-point scale derived from Marks and Mathews<br>(3) Phobia: 11-point scale<br>(4) Avoidance: 4-point scale<br>(5) Anxiety: HAMA<br>(6) Disability: 5-point Work and Social Disability Scale<br>(7) Global improvement: 11-point scale<br>**Secondary outcome**:<br>(1) Adverse events | |
| Notes | **Date of study**: not stated<br>**Funding source**: not stated<br>**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 | 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 alprazoalm 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:<br>1. desipramine arm (randomised n = 28)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; range = 50-200 mg/day, mean = 177 mg (SD = 81)<br>2. placebo arm (randomised n = 28)<br>**Duration:** 12 weeks<br>**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<br>**Outcomes:**<br>1. HAMA<br>2. Phobia Scale<br>3. CGI-I |
| Notes | **Date of study:** not specified<br>**Funding source:** unclear<br>**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 | **Diagnosis:** DSM-IV criteria for panic disorder with or without agoraphobia<br>**Method of diagnosis:** SCID<br>**Age (years):** mean age in fluoxetine arm 36.5 (SD = 10.3), mean age in placebo arm 34.8 (SD = 9.8)<br>**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)<br>**Location:** outpatients, psychiatric clinics, 9 sites in Europe<br>**Co-morbidities:** excluded<br>**Rescue medication:** unclear |
| Interventions | Participants were randomly assigned to either:<br>1. fluoxetine arm (randomised n = 90)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; range = 20-60 mg/day, mean = 29.8 mg/day (SD is not specified)<br>2. placebo arm (randomised n = 90)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage (the number of tablets is not specified) |
| Outcomes | **Time points for assessment:** at baseline, 6, 12 weeks (endpoint)<br>**Outcomes:**<br>1. PDSS<br>2. number of full panic attacks per week<br>3. CGI-S<br>4. HAMA<br>5. State Anxiety Inventory<br>6. HDRS<br>7. SDS |
| Notes | **Date of study:** not reported in the primary publication<br>**Funding source:** unclear<br>**Declarations of interest among the primary researchers:** some authors are employees of the company marketing the drug, others are paid consultants |

| *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 | 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..."<br>Despite the dropouts the groups still seem comparable.<br>Data imputation was performed (ITT analysis). |
| 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 | **Diagnosis**: DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III-R and a psychiatric interview<br>**Age**: Clonazepam: mean = 36.7 (SD = 11.3); Placebo: mean = 36.8 (SD = 11.4)<br>**Sex**: Clonazepam: F = 141, M = 81; Placebo: F = 140, M = 76<br>**Location**: not stated (USA); setting: outpatients<br>**Comorbidities**: psychiatric (major depression, social phobia, obsessive-compulsive disorder, generalised anxiety disorder) were excluded.<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Clonazepam (n = 230)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; mean = 2.3 mg/day; range = 0.5 to 4 mg (daily dose)<br>(2) Placebo (n = 225)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; mean = 3.0 mg/day |
| Outcomes | **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<br>**Primary outcomes**:<br>(1) Change from baseline in the number of panic attacks: diary<br>(2) Severity of panic disorder: CGI-S<br>(3) Change from baseline: CGI-C<br>(4) PGI-C<br>(5) Estimate of mean duration of anticipatory anxiety: % of time a participant spent experiencing anticipatory anxiety during the preceding week<br>(6) Severity of fear associated with the main phobia: 11-point scale<br>(7) Change in the avoidance (related to the main phobia): 5-point scale<br>(8) Social and Work Impairment: WSDS<br>(9) Anxiety: HAMA<br>**Secondary outcome**:<br>(1) Adverse events: monitoring of the adverse events |
| Notes | **Date of study**: not stated<br>**Funding source**: sponsored by Hoffmann-La Roche Inc., Nutley, NJ<br>**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)<br>All outcomes | Low risk | Double-blind. Quote: "The study medications were clonazepam and identical-looking placebo tablets". |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Double-blind; no further information. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis**: DSM-III panic disorder or agoraphobia with panic attacks<br>**Method of diagnosis**: not stated<br>**Age**: mean = 31 (range = 18 to 62) |

| | |
|---|---|
| | **Sex**: M = 17; F = 38<br>**Location**: California, USA (psychiatric outpatients clinic)<br>**Comorbidities**: not stated<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam (n = 20)<br>**Duration**: 5 weeks<br>**Treatment protocol**: flexible dosage; range = 1.5 to 6 mg, mean = 3.62 (7.24 capsules, SD = 4.09)<br>(2) Placebo (n = 21)<br>**Duration**: 5 weeks<br>**Treatment protocol**: flexible; mean = 9.90 capsules, SD = 3.74 |
| Outcomes | **Time points for assessment**: weekly<br>**Primary outcomes**:<br>(1) Panic: Panic and Anxiety Attack Scales (Sheehan)<br>(2) Avoidance: Phobia Scale (Marks-Sheehan)<br>(3) Anxiety: HAMA<br>(4) Depression: HAMD<br>**Secondary outcome**:<br>(1) Adverse events: Side Effects Checklist |
| Notes | **Date of study**: not stated<br>**Funding source**: not stated<br>**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)<br>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)<br>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)<br>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 | **Diagnosis:** DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis:** not stated<br>**Age:** for fluvoxamine, M = 34.5; for imipramine, M = 34.5, SD not provided<br>**Sex:** for fluvoxamine 56% females 44% males; for imipramine 50% females 50% males<br>**Location:** Canada; setting: outpatients<br>**Co-morbidities:** patients with a history of bipolar disorder, organic brain syndrome, schizophrenia or other psychotic disorders were excluded<br>**Rescue medication:** oxazepam up to 60 mg daily or chloral hydrate up to 2000 mg daily were permitted during first four weeks of treatment |
| Interventions | **Participants were randomly assigned to either:**<br>(1) fluvoxamine arm (n = 50)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, range = 50 - 300 mg, M = 171.4, SD not provided<br>(2) imipramine arm (n = 48)<br>**Duration:** 8 weeks |

| | |
|---|---|
| | **Treatment protocol:** flexible dosage, range = 50 - 300 mg, M = 164.7, SD not provided<br>(3) placebo arm (n = 50)<br>**Duration:** 8 weeks |
| Outcomes | **Time points for assessment:** weekly<br>**Outcomes:**<br>**1.** Sheehan Panic and Anticipatory Anxiety Scale<br>**2.** Clinical Global Impression Scale (CGI)<br>**3.** Montgomery–Åsberg Depression Rating Scale (MADRS)<br>**4.** Sheehan Disability Scale (SDS)<br>**5.** Sheehan Panic Attack Diary (intensity and number of panic attacks)<br>**6.** Sheehan Phobia Scale<br>**7.** Hopkins Symptom Checklist |
| Notes | **Date of study:** Not stated<br>**Funding source:** Orto McNeil Ltd.<br>**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)<br>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)<br>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)<br>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<br>**Method of diagnosis:** Structured Clinical Interview for DSM-III, Upjohn Version<br>**Age:** M = 36.6; SD = 10.5<br>**Sex:** women = 157, men = 84<br>**Location:** USA, Australia; setting: outpatients<br>**Co-morbidities:** patients with major psychiatric co-morbidities, head trauma or seizures were excluded<br>**Rescue medication:** none |
| Interventions | **Participants were randomly assigned to either:**<br>(1) diazepam arm (n = 81)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, range = 10 - 100 mg, M = 43, SD not provided<br>(2) alprazolam arm (n = 78)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, range = 1 - 10 mg, M = 4.9, SD not provided<br>(3) placebo arm (n = 79)<br>**Duration:** 8 weeks |
| Outcomes | **Time points for assessment:** baseline, 4 weeks, 8 weeks<br>**Outcomes:**<br>**1.** frequency of panic attacks |

| | |
|---|---|
| | **2.** Sheehan Self Rated Scale for Anxiety<br>**3.** Hamilton Rating Scale for Anxiety (HAMA)<br>**4.** Marks and Mathews Agoraphobia Scale<br>**5.** Profile of Mood States<br>**6.** Hamilton Rating Scale for Depression (HRSD)<br>**7.** Work and Social Disability Scale<br>**8.** Systematic Assessment for Treatment-Emergent Events |
| Notes | **Date of study:** not stated<br>**Funding source:** supported by a grant from the Upjohn Company<br>**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 | 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 | **Diagnosis**: DSM-III-R panic disorder and extensive phobic avoidance (agoraphobia with panic attacks) or limited phobic avoidance<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III-R<br>**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)<br>**Sex**: for alprazolam CT, 59% female; for alprazolam XR, 63% female; for placebo, 58% female<br>**Location**: USA (2 sites: Rhode Island and Los Angeles) and Canada (1 site: Montreal)<br>**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)<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam CT (n = 69*)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; range = 2 to 7(?) mg; mean = 3.95 (SD = 1.86)<br>(2) Alprazolam XR (n = 70*)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; range = 2 to 7(?) mg; mean = 4.35 (SD = 2.30)<br>(2) Placebo (n = 70*)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; range = 2 to 7(?) mg; mean = 5.46 (SD = 2.26)<br>*The number of participants in the different arms is inconsistently reported. We used the number of participants of the LOCF analyses. |
| Outcomes | **Time points for assessment**: at baseline and weekly thereafter for 6 weeks<br>**Primary outcomes**:<br>(1) Overall improvement (CGI): 7-point global scale<br>(2) Number/duration/intensity of spontaneous and situational panic attacks: participants' diaries<br>(3) Fear/avoidance: Marks-Mathews Phobia Scale<br>(4) Overall phobia: not stated |

| | |
|---|---|
| | (5) Anxiety: HAMA (at baseline and week 3 and 5); Sheehan Patient Rated Anxiety Scale<br>(6) Disability: WSDS<br>(7) Depression: HAMD (at baseline and at the end of weeks 3 and 6)<br>**Secondary outcome**:<br>(1) Adverse effects: (SAFTEE-UP) |
| Notes | **Date of study**: not stated<br>**Funding source**: The study was supported by the Upjohn Company.<br>**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<br>**Method of diagnosis:** no information provided<br>**Age: range =** 18 - 64 years, mean and SD not provided<br>**Sex: sertraline:** female = 113, male = 44; paroxetine: female = 109, male = 53<br>**Location:** Japan; setting unclear<br>**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"<br>**Rescue medication:** none |
| Interventions | **Participants were randomly assigned to either:**<br>(1) sertraline arm (n = 157)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage, range = 25 - 100 mg<br>(2) paroxetine arm (n = 164)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage, range = 10 - 30 mg |
| Outcomes | **Time points for assessment:**<br>**Outcomes:**<br>**1.** Panic and Agoraphobia Scale<br>**2.** Clinical Global Impression Improvement Score (CGI-I)<br>**3.** frequency of panic attacks<br>**4.** Hamilton Rating Scale for Anxiety (HAMA) |

| | |
|---|---|
| Notes | **Date of study:** May 2008 - February 2010<br>**Funding source:** Pfizer<br>**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)<br>All outcomes | Low risk | Quote: "Masking: double-blind (subject, investigator)". |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Masking: double-blind (subject, investigator)". |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "Last Obsevation 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<br>**Method of diagnosis:** not stated<br>**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)<br>**Sex:** for buspirone, 44% women, 56% men; for placebo 50% women, 50% men<br>**Location:** outpatients, USA<br>**Co-morbidities:** excluded<br>**Rescue medication:** none |
| Interventions | Participants were randomly assigned to either:<br>1. buspirone arm (randomised n = 18)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 10-60 mg, mean = 29.5 (SD = 4.0)<br>2. imipramine arm (randomised n = 20)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 50-300 mg, mean = 140 (SD = 17.5)<br>3. placebo arm ( randomised n = 22)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible |
| Outcomes | **Timepoints for assessment:** weekly for the first 4 weeks, and biweekly for the last 4 weeks<br>**Outcomes:**<br>1. 7-point scale for the degree of global psychopathology<br>2. CGI-I<br>3. Global phobic disability<br>4. Symptom Check List (SCL-90)<br>5. HAMA |
| Notes | **Date of study:** not stated<br>**Funding source:** not stated<br>**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)<br>All outcomes | Low risk | Identical capsules were used. |

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>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)<br>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<br>**Method of diagnosis:** SCID<br>**Age (years):** mean age in sertraline arm 37.8 (SD = 11.6), mean age in placebo arm 34.9 (SD = 9.6)<br>**Sex:** 115 women, 63 men<br>**Location:** outpatient setting, 10 sites, USA and Brazil<br>**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"<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. sertraline arm (randomised n = 88)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dose, range 25-200 mg/day, mean 118.1 mg/day (SD = 62.9)<br>2. placebo arm (randomised n = 88)<br>**Duration:** 10 weeks<br>**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<br>**Outcomes:**<br>1. Sheehan PAAS<br>2. CGI-S<br>3. CGI-I<br>4. PGE<br>5. PDSS<br>6. HAMA<br>7. Hamilton Rating Scales for Depression (HAM-D)<br>8. Q-LES-Q |
| Notes | **Date of study:** not specified<br>**Funding source:** supported by the company marketing the drug<br>**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)<br>All outcomes | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No information provided. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM-IV panic disorder with or without agoraphobia<br>**Method of diagnosis:** Mini-International Neuropsychiatric Interview<br>**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<br>**Sex:** for venlafaxine 75 mg, females = 65%, males = 35%; for venlafaxine 225 mg, females = 68%, males = 33%; for paroxetine females = 68%, males = 32%<br>**Location:** Argentina, Mexico, Chile, Costa Rica; setting: outpatients<br>**Co-morbidities:** patients with other predominant Axis I or II disorders and important medical conditions were excluded<br>**Rescue medication:** zaleplon or zolpidem permitted up to 3 times per week for the first 2 weeks of randomised treatment |
| Interventions | **Participants were randomly assigned to either:**<br>(1) venlafaxine 75 mg arm (n = 163)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage = 75 mg/day<br>(2) venlafaxine 225 mg arm (n = 167)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage = 225 mg/day<br>(3) paroxetine arm (n = 161)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage = 40 mg/day<br>(4) placebo arm (n = 162)<br>**Duration:** 12 weeks |
| Outcomes | **Time points for assessment:** baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12<br>**Outcomes:**<br>**1.** patients free of panic attacks at endpoint<br>**2.** Panic Disorder Severity Scale (PDSS)<br>**3.** panic attacks frequency<br>**4.** Clinical Global Impression Improvement Score (CGI-I) |
| Notes | **Date of study:** not stated<br>**Funding source:** Wyeth Research, Collegeville, Pennsylvania<br>**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 |

***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 | **Diagnosis:** DSM-IV panic disorder with or without agoraphobia<br>**Method of diagnosis:** Mini-International Neuropsychiatric Interview<br>**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<br>**Sex:** for venlafaxine 75 mg, females = 66%, males = 34%; for venlafaxine 150 mg, females = 70%, males = 30%; for paroxetine females = 64%, males = 36%<br>**Location:** Europe; setting: outpatients<br>**Co-morbidities:** patients with other predominant Axis I or II disorders and important medical conditions were excluded<br>**Rescue medication:** zaleplon or zolpidem permitted up to 3 times per week for the first 2 weeks of randomised treatment |
| Interventions | **Participants were randomly assigned to either:**<br>(1) venlafaxine 75 mg arm (n = 166)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage = 75 mg/day<br>(2) venlafaxine 150 mg arm (n = 168)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage = 150 mg/day<br>(3) paroxetine arm (n = 166)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage = 40 mg/day<br>(4) placebo arm (n = 163)<br>**Duration:** 12 weeks |
| Outcomes | **Time points for assessment:** baseline, weeks 1, 2, 3, 4, 6, 8, 10, 12<br>**Outcomes:**<br>**1.** frequency of panic attacks from the Panic and Anticipatory Anxiety Scale<br>**2.** patients free of panic attacks at endpoint<br>**3.** Panic Disorder Severity Scale (PDSS)<br>**4.** PDSS: anticipatory anxiety<br>**5.** Phobia Scale<br>**6.** Hamilton Rating Scale for Anxiety (HAMA)<br>**7.** Sheehan Disability Scale (SDS)<br>**8.** Quality of Life Enjoyment and Satisfaction Questionnaire<br>**9.** Clinical Global Impression Improvement Score (CGI-I) |
| Notes | **Date of study:** not stated<br>**Funding source:** sponsored by Wyeth Research<br>**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. |

***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)<br>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)<br>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)<br>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<br>**Method of diagnosis:** not stated<br>**Age:** for mirtazapine, M = 36.1, SD = 10.9; for fluoxetine, M = 36.4, SD = 10.1<br>**Sex:** for mirtazapine, 86.7% females, for fluoxetine 66.7% females<br>**Location:** Brasil; setting: outpatients<br>**Co-morbidities:** patients with psychiatric and physical disorders were excluded<br>**Rescue medication:** none |
| Interventions | **Participants were randomly assigned to either:**<br>(1) mirtazapine arm (n = 15)<br>**Duration:** 8 weeks<br>**Treatment Protocol:** flexible dosage, range = 15 - 30 mg, M = 17.9, SD = 4.3<br>(2) fluoxetine arm (n = 15)<br>**Duration:** 8 weeks<br>**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<br>**Outcomes:**<br>**1.** Panic Diary<br>**2.** Clinical Global Impression Severity of Illness Score (CGI-S)<br>**3.** Clinical Global Impression Improvement Score (CGI-I)<br>**4.** Hamilton Rating Scale for Anxiety (HAMA)<br>**5.** Sheehan Phobic Scale |
| Notes | **Date of study:** November 1998 - March 1999<br>**Funding source:** research supported by FIPE-HCPA (FUNDO DE INCENTIVO À PESQUISA E EVENTOS)<br>**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<br>**Method of Diagnosis:** Not stated<br>**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)<br>**Sex:** for buspirone, 64% women, 36% men; for placebo 62% women, 38% men; imipramine 75% women, 25% men<br>**Location:** United States of America<br>**Co-morbidities:** unclear<br>**Rescue medication:** none |
| Interventions | Participants were randomly assigned to either: |

| | |
|---|---|
| | (1) Buspirone arm (n = 34)<br>**Duration:** 8 weeks<br>**Treatment Protocol:** flexible dosage; range = not stated, M = 43 (SD = 3)<br>(2) Placebo arm (n = 29)<br>**Duration:** 8 weeks<br>**Treatment Protocol:** Flexible<br>(3) Imipramine arm (n = 28)<br>**Duration:** 8 weeks<br>**Treatment Protocol:** flexible dosage; range = not stated, M = 221 (SD = 18) |
| Outcomes | **Timepoints for assessment:** at 0, 2, 4, 6, 7, 8 weeks<br>**Outcomes:**<br>1. Hamilton Anxiety rating scale<br>2. Number of panic attacks<br>3. Global ratings of social disability |
| Notes | **Date of study:** Not stated<br>**Funding source:** Not stated<br>**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. |

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

| | |
|---|---|
| | **Treatment protocol**: fixed dose = 3.0 mg<br>(5) Clonazepam 4.0 mg (n = 72)<br>**Duration**: 9 weeks (+ discontinuance phase: 7 weeks)<br>**Treatment protocol**: fixed dose = 4.0 mg<br>(6) Placebo arm (n = 69)<br>**Duration**: 9 weeks (+ discontinuance phase: 7 weeks)<br>**Treatment protocol**: fixed |
| Outcomes | **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)<br>**Primary outcomes**:<br>(1) Number of panic attacks: participant's diary, interview<br>(2) Overall improvement: CGI-S<br>(3) Mean duration of anticipatory anxiety<br>(4) Frequency of avoidance associated with the main phobia (agoraphobia): 5-point scale<br>(5) Severity of fear associated with the main phobia: 11-point scale<br>**Secondary outcomes**:<br>(1) CGI-C; Patient's Global Impression of Change (CGI-P)<br>(2) Overall impairment in work and social activities: 5-point scale<br>(3) Adverse events |
| Notes | **Date of study**: October 1992 to June 1995<br>**Funding source**: This clinical trial was supported by Hoffmann-La Roche.<br>**Declarations of interest among the primary researchers**: not stated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization to treatment groups was done by means of computer-generated codes for each centre, using the fixed-block method with a block size of six". |
| Allocation concealment (selection bias) | Unclear risk | No information 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 | **Diagnosis**: DSM-III panic disorder with agoraphobia<br>**Method of diagnosis**: not stated<br>**Age**: mean = 37.7 (SD = 7.97)<br>**Sex**: M = 12; F = 18<br>**Location**: not stated<br>**Comorbidities**: none<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Etizolam (n = 15)<br>**Duration**: 4 weeks<br>**Treatment protocol**: fixed dosage = 0.50 mg<br>(2) Placebo arm (n = 15)<br>**Duration**: 4 weeks<br>**Treatment protocol**: fixed |
| Outcomes | **Time points for assessment**: baseline, week 2, 4<br>**Primary outcomes**:<br>(1) Anxiety: HAMA, Covi Anxiety Scale |

| | |
|---|---|
| | (2) Agoraphobia: HAMA, item 2<br>(3) Frequency of panic attacks: not stated<br>(4) Depression: HAMD<br>**Secondary outcome**:<br>(1) Tolerability: 4-point scale, semi-structured interview |
| Notes | **Date of study**: not stated<br>**Funding source**: not stated<br>**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 etizoalm 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<br>**Method of diagnosis**: not stated<br>**Age**: mean = 35<br>**Sex**: 3 males, 2 females<br>**Location**: not stated<br>**Comorbidities**: social phobia (n = 1)<br>**Rescue medication**: none (besides midazolam when necessary) |
| Interventions | Participants were randomly assigned to either:<br>(1) Midazolam (n = 3 + 2)<br>**Duration**: 3 + 3 weeks<br>**Treatment protocol**: flexible dosage; range = 0.25 to 1 mg; mean number of doses (week 3) = 6.1 (0.44 mg/day)<br>(2) Placebo (n = 2 + 3)<br>**Duration**: 3 + 3 weeks<br>**Treatment protocol**: flexible |
| Outcomes | **Time points for assessment**: baseline, week 1, 2, 3, 4, 5, 6<br>**Primary outcomes**:<br>(1) Number of panic attacks: participants' diaries<br>(2) Global phobia: 11-point Global Phobia Scale<br>(3) Anxiety: HAMA; Sheehan Patient Rated Anxiety Scale<br>(4) Overall improvement: 7-point CGI-I |
| Notes | **Date of study**: not stated<br>**Funding source**: not stated<br>**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:**<br>(1) alprazolam arm (n = 37)<br>**Duration:** 8 weeks short term, 32 weeks long term<br>**Treatment protocol:** flexible dosage, range = 2 - 10 mg, M = 5.4, SD = 2.1<br>(2) imipramine arm (n = 34)<br>**Duration:** 8 weeks short term, 32 weeks long term<br>**Treatment protocol:** flexible dosage, range = 50 - 250 mg, M = 152, SD = 65<br>(3) placebo arm (n = 35)<br>**Duration:** 8 weeks short term, 32 weeks long term |
| Outcomes | **Time points for assessment:** weekly until week 6, week 8, monthly for 6 months<br>**Outcomes:**<br>**1.** panic attack frequency and severity<br>**2.** Hamilton Rating Scale for Anxiety (HAMA)<br>**3.** phobias<br>**4.** disability resulting from the phobic anxiety<br>**5.** global assessment of improvement<br>**6.** safety questionnaire (SAFTEE)<br>**7.** benzodiazepines plasma levels |
| Notes | **Date of study:** not stated<br>**Funding source:** sponsored by Upjohn Co.<br>**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 | **Diagnosis:** DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis:** not specified<br>**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<br>**Sex:** 115 women, 32 men<br>**Location:** general practice/primary care, Scotland, UK<br>**Co-morbidities:** excluded<br>**Rescue medication:** not allowed | |
| Interventions | Participants were randomly assigned to either:<br>1) fluvoxamine arm (randomised n = 36)<br>**Treatment protocol:** fixed dose, range 50-150 mg/day, mean = 150 mg/day<br>**Duration:** 12 weeks<br>2. placebo arm (randomised n = 37)<br>**Treatment protocol:** fixed dose; range not stated<br>**Duration:** 12 weeks<br>3. fluvoxamine + CBT ( randomised n = 38)<br>**Treatment protocol:** fixed dose; 150 mg/day<br>**Duration:** 12 weeks<br>4. placebo + CBT arm (randomised n = 36)<br>**Treatment protocol:** fixed dose; range not stated<br>**Duration:** 12 weeks<br>(5) CBT arm (randomised n = 43)<br>**Treatment protocol:** 30-60-min sessions<br>**Duration:** 12 weeks | |
| Outcomes | **Timepoints for assessment:** at baseline and at weeks 1, 2, 4, 6, 8, 10 and 12<br>**Outcomes:**<br>1. Clinical Global Impression-Severity of Illness (CGI-S)<br>2. HAMA<br>3. Kellner and Sheffield Symptom Rating Test (SRT)<br>4. MADRS<br>5. FQ<br>6. frequency of panic attacks<br>7. SDS | |
| Notes | **Date of study:** not specified<br>**Funding source:** funded by the company marketing the drug<br>**Declarations of interest among the primary researchers:** not specified | |
| *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)<br>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)<br>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 | **Diagnosis**: DSM-III-R panic disorder with extensive phobic avoidance, panic disorder with limited phobic avoidance<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III (SCID-UP)<br>**Age**: Alprazolam: mean = 36.4 (SD = 8.8); Buspirone: mean = 36.6 (SD = 9.4); Placebo: mean = 37.2 (SD = 10.9)<br>**Sex**: Alprazolam: F = 76%, Buspirone: F = 67; Placebo: F = 77<br>**Location**: USA<br>**Comorbidities**: major depressive disorder (if secondary to panic disorder)<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam (n = 34)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible dosage; range = 1.5 to 10 mg, mean = 5.2 (SD = 2.6)<br>(1) Buspirone (n = 34)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible dosage; range = 15 to 100 mg, mean = 61 (SD = 26.5)<br>(2) Placebo (n = 33)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible dosage; range = 3 to 20 capsules, mean = 16.5 capsules (SD = 5) |
| Outcomes | **Time points for assessment**: baseline, weekly for 8 visits<br>**Primary outcomes**:<br>(1) Panic symptoms: Panic and Anticipatory Anxiety Scale, participant's diary<br>(2) Anxiety: Sheehan Clinician Rated Anxiety Scale, Sheehan Patient Rated Anxiety Scale, HAMA<br>(3) Depression: 31-item Beck Depression Inventory, HAMD, MADRS<br>(4) Agoraphobia: Phobia Scale<br>(5) Overall impairment: Disability Scale, SCL-90-R<br>(6) Overall improvement: Clinician Rated Global Improvement (CGI-21)<br>**Secondary outcome**:<br>(1) Adverse events: 42-item symptoms and side effects inventory |
| Notes | **Date of study**: not stated<br>**Funding source**: This study was supported in part by grant 4447 from the Upjohn Company.<br>**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: "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<br>**Method of diagnosis:** DSM-IV<br>**Age (years):** 18-65, mean 37.6 (SD = 10.22) in paroxetine CR group, 37.8 (SD = 10.61) in placebo group<br>**Sex:** 356 men, 543 women<br>**Location:** USA and Canada, outpatient setting<br>**Co-morbidities:** inclusion of people with secondary Axis I disorders<br>**Rescue medication:** not allowed |
| Interventions | Participants were randomly assigned to either:<br>1. paroxetine CR arm (randomised n = 444)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage; range = 12.5-75 mg/day, mean = 50 mg/day (SD = not specified)<br>2. Placebo arm (randomised n = 445)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage |
| Outcomes | **Timepoints for assessment:** at baseline and at weekly and bi-weekly intervals<br>**Outcomes:**<br>1. percentage of participants free of panic attacks<br>2. number of full panic attacks for 2 weeks<br>3. CGI-S<br>4. HAMA<br>5. Marks Sheehan Phobia Scale<br>6. CGI-I |
| Notes | **Date of study:** November 1996-September 1997<br>**Funding source:** the studies were sponsored by the company marketing paroxetine CR<br>**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)<br>All outcomes | Unclear risk | The studies are described as "double blind", no other information is provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No information provided. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The number of dropouts and the reasons of withdrawals are clearly reported.<br>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* |
|---|

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|---|---|
| Methods | **Study design**: Randomised controlled trial |
| Participants | **Diagnosis**: DSM-III-R panic disorder with or without agoraphobia<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III-R - Patient version (SCID-P)<br>**Age**: mean = 61.24 (SD = 5.27), range = 55 to 73<br>**Sex**: M = 2; F = 32<br>**Location**: USA<br>**Comorbidities**: none<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam (n = 8)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible dosage; range = 1 to 6 mg, mean = 2.87 (SD = 1.66)<br>(2) Imipramine (n = 10)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible dosage; range = 10 to 200 mg, mean = 77.5 (SD = 59.4)<br>(3) Placebo arm (n = 7)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible |
| Outcomes | **Time points for assessment**: baseline, at each subsequent medication visit<br>**Primary outcomes**:<br>(1) Number/intensity of panic attacks: participant's diary<br>(2) Anxiety: HAMA<br>(3) Depression: HAMD<br>(4) Overall improvement: CGI; PGI |
| Notes | **Date of study**: 2-year period (1988-90)<br>**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.<br>**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)<br>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)<br>All outcomes | Unclear risk | Double-blind; no further information |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** not stated<br>**Age:** for escitalopram, M = 37.5, for citalopram M = 37.1<br>**Sex:** for escitalopram 57.6 % female, for citalopram 61.6% female<br>**Location:** USA; setting: outpatients<br>**Co-morbidities:** patients with bipolar disorder, schizophrenia, obsessive-compulsive disorder or other psychotic disorder, |

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|---|---|
| | psychoactive substance use disorder, clinically significant abnormalities in laboratory evaluations or electrocardiographic readings were excluded<br>**Rescue medication:** zolpidem |
| Interventions | **Participants were randomly assigned to either:**<br>(1) escitalopram arm (n = 129)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage, range = 5 - 20 mg, M = 10.8 SD not provided<br>(2) citalopram arm (n = 126)<br>**Duration:** 10 weeks<br>**Treatment protocol:** flexible dosage, range = 10 - 40 mg, M = 21.3, SD not provided<br>(3) placebo arm (n = 125)<br>**Duration:** 10 weeks |
| Outcomes | **Time points for assessment:** baseline, weeks 1, 2, 4, 6, 8 and 10<br>**Outcomes:**<br>**1.** Panic and Anticipatory Anxiety Scale (PAAS)<br>**2.** panic attack frequency<br>**3.** Panic & Agoraphobia Scale<br>**4.** Clinical Global Impression Improvement Score (CGI-I)<br>**5.** Clinical Global Impression Severity of Illness Score (CGI-S)<br>**6.** Hamilton Rating Scale for Anxiety (HAMA)<br>**7.** Patient Global Evaluation (PGE)<br>**8.** Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)<br>**9.** Hamilton Rating Scale for Depression (HAM-D) |
| Notes | **Date of study:** 1999 - 2001<br>**Funding source:** sponsored by Forest Laboratories<br>**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".<br>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<br>**Method of diagnosis**: Structured Clinical Interview for Diagnoses-Upjohn version (SCID-UP)<br>**Age**: Alprazolam: mean = 35.0; Imipramine: mean = 34.1; Placebo: mean = 34.9<br>**Sex**: Alprazolam: Male = 19%, Imipramine: 30%, Placebo: 31%<br>**Location**: USA<br>**Comorbidities**: none<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam (n = 26)<br>**Duration**: 8 weeks |

| | |
|---|---|
| | **Treatment protocol**: flexible dosage; range = 1 to 8 mg, mean = 3.7<br>(2) Imipramine (n = 27)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible dosage; range = 1 to 9 mg, mean = 4.9<br>(3) Placebo (n = 26)<br>**Duration**: 8 weeks<br>**Treatment protocol**: flexible; number of pills: 2 to 10, mean = 6.8 |
| Outcomes | **Time points for assessment**: baseline, weeks 1, 4, 8<br>**Primary outcomes**:<br>(1) Frequency/intensity of panic attacks: panic diary<br>(2) Anxiety: HAMA<br>(3) Depression: Beck Depression Inventory<br>(4) Overall psychiatric symptomatology: SCL-90<br>(5) Global improvement: 7-point scale<br>(6) Work and social disability: 5-point scale<br>(7) Avoidance: Marks/Mathews Fear Questionnaire<br>**Secondary outcome**:<br>(1) Adverse effects: SAFTEE-UP |
| Notes | **Date of study**: not stated<br>**Funding source**: This research was supported in part by National Institute of Mental Health grant 40118 and by a gift from the Upjohn Company.<br>**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 | 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 | **Diagnosis**: DSM-III panic disorder with phobic avoidance<br>**Method of diagnosis**: Structured Clinical Interview for DSM-III-Upjohn version (SCID-UP)<br>**Age**: Alprazolam: mean = 32.8 (SD = 8.9); Clonazepam: mean = 30.5 (SD = 6.5); Placebo: mean = 30.7 (SD = 9.0)<br>**Sex**: Alprazolam: M = 42%; Clonazepam: M = 42%; Placebo: M = 27<br>**Location**: USA (Clinical Psychopharmacology Unit at Massachusetts General Hospital)<br>**Comorbidities**: major depression (if secondary to panic disorder)<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Alprazolam (n = 24)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; range = 1 to 10 mg, mean = 5.39 (SD = 2.89)<br>(2) Clonazepam (n = 26)<br>**Duration**: 6 weeks<br>**Treatment protocol**: flexible dosage; range = 0.5 to 5 mg, mean = 2.5 (SD = 0.94)<br>(3) Placebo arm (n = 22) |

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| | **Duration**: 6 weeks<br>**Treatment protocol**: flexible |
| Outcomes | **Time points for assessment**: baseline, week 3 and 6<br>**Primary outcomes**:<br>(1) Number/intensity/duration of panic attacks: participant's diary<br>(2) Severity of illness: CGI and PGI<br>(3) Phobias: scale derived from 1 developed by Marks and Mathews; overall phobia rating<br>(4) Overall disability: 5-point WSDS<br>(5) Depression: 21-item Beck Depression Inventory<br>**Secondary outcome**:<br>(1) Adverse events: SAFTEE |
| Notes | **Date of study**: not stated<br>**Funding source**: supported in part by a grant from the Upjohn Corporation, Kalamazoo, Michigan<br>**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<br>**Method of diagnosis:** Structured Clinical Interview (SCID)<br>**Age:** M = 35<br>**Sex:** 67% female<br>**Location:** not stated; setting: unclear<br>**Co-morbidities:** not stated<br>**Rescue medication:** not stated; "there was not extensive co-prescription of hypnotics, sedatives or beta-blockers". |
| Interventions | **Participants were randomly assigned to either:**<br>(1) moclobemide arm (n = 182)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, range = 300 - 600 mg, M = 498, SD = 68<br>(2) fluoxetine arm (n = 184)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage, range = 10 - 30 mg, M = 20.5, SD = 2.7 |
| Outcomes | **Time points for assessment:**<br>**Outcomes:**<br>**1.** number of adverse events<br>**2.** severe adverse events |

| | |
|---|---|
| | **3.** clinical global impression of tolerability<br>**4.** panic-free patients<br>**5.** Clinical Global Impression Scale (CGI) |
| Notes | **Date of study:** not stated<br>**Funding source:** sponsored by Hoffmann-La Roche<br>**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)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided. |
| Incomplete outcome data (attrition bias)<br>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<br>**Method of diagnosis:** not specified<br>**Age (years):** some participants > 65, range unclear<br>**Sex:** they show the ratio of gender, however, it is not for the randomised population, but for the population included in the analysis.<br>**Location:** inpatient, multicentre trial all over Japan<br>**Co-morbidities:** excluded<br>**Rescue medication:** lorazepam |
| Interventions | Participants were randomly assigned to either:<br>1. sertraline low-dose arm (randomised n = 59)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage; 75 mg/day<br>2. sertraline high-dose arm (randomised n = 54)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage; 150 mg/day<br>3. placebo arm randomised n = 56)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage; number of tablets not specified |
| Outcomes | **Timepoints for assessment:** baseline and at 12 weeks<br>**Outcomes:**<br>1. response rate (Global Improvement 5-point scale)<br>2. frequency of panic attacks |
| Notes | **Date of study:** not specified<br>**Funding source:** unclear<br>**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)<br>All outcomes | Low risk | Both the participants and the physician were blinded. |

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The assessors were blinded. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM-IV panic disorder<br>**Method of diagnosis:** not stated<br>**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".<br>**Sex:** They show the ratio of gender, however, it is not for the randomised population, but for the population included in the analysis<br>**Location:** in and outpatient setting, all over Japan. (multicentre trial)<br>**Co-morbidities:** excluded<br>**Rescue medication:** lorazepam, zopiclone, brotizolam, lormetazepam, rilmazafone |
| Interventions | Participants were randomly assigned to either:<br>1. paroxetine arm (randomised n = 87)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage 30 mg/day<br>2. placebo arm (randomised n = 84)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage |
| Outcomes | **Timepoints for assessment:** at baseline, at 8 weeks<br>**Outcomes:**<br>1. response rate<br>2. number of panic attacks |
| Notes | **Date of study:** not specified<br>**Funding source:** the study was sponsored by the company marketing the drug<br>**Declarations of interest among the primary researchers:** conflict of interest among primary researchers |

| *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)<br>All outcomes | Low risk | Both the participants and the personnel were blinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | It is unclear whether the researchers were blinded. |
| Incomplete outcome data (attrition bias)<br>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 |

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

***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)<br>All outcomes | Low risk | Both participants and the physicians were blinded. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | It is unclear whether the assessors were blinded or not. |
| Incomplete outcome data (attrition bias)<br>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 | **Diagnosis:** DSM - III panic disorder or agoraphobia with panic attacks<br>**Method of diagnosis:** SCID-UP<br>**Age:** M = 31.54, SD = 7.12<br>**Sex:** 58% female<br>**Location:** USA; setting: outpatients<br>**Co-morbidities:** patients with another primary psychiatric disorder or a physical disorder judged likely to interfere with the study were excluded<br>**Rescue medication:** not stated |
| Interventions | **Participants were randomly assigned to either:**<br>(1) alprazolam 2 mg arm (n = 20)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage 2 mg<br>(2) alprazolam 6 mg arm (n = 21)<br>**Duration:** 8 weeks |

| | |
|---|---|
| | **Treatment protocol:** fixed dosage 6 mg<br>(3) imipramine arm (n = 20)<br>**Duration:** 8 weeks<br>**Treatment protocol:** fixed dosage 225 mg<br>(4) placebo arm (n = 20)<br>**Duration:** 8 weeks |
| Outcomes | **Time points for assessment:** weeks 1, 2, 3, 4, 6, 8<br>**Outcomes:**<br>**1.** number of panic attacks (major, spontaneous, minor, situational)<br>**2.** Marks & Matthews Phobia Scale<br>**3.** disability<br>**4.** Hamilton Rating Scale for Anxiety (HAMA)<br>**5.** Hamilton Rating Scale for Depression (HRSD)<br>**6.** SAFTEE-UP for adverse effects |
| Notes | **Date of study:** not stated<br>**Funding source:** sponsored by Upjohn Company<br>**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<br>**Method of diagnosis**: Structured Clinical Interview for DSM-IV<br>**Age**: Clonazepam group: mean = 37.5 (SD = 6.6); Placebo group: mean = 36.8 (SD = 7.2)<br>**Sex**: M = 10; F = 14<br>**Location**: University of Rio de Janeiro (at the Laboratory of Panic and Respiration)<br>**Comorbidities**: none<br>**Rescue medication**: none |
| Interventions | Participants were randomly assigned to either:<br>(1) Clonazepam (n = 14)<br>**Duration**: 6 weeks<br>**Treatment protocol**: fixed dosage: 2 mg/day<br>(2) Placebo arm (n = 10)<br>**Duration**: 6 weeks |
| Outcomes | **Time points for assessment**: not stated<br>**Primary outcomes**: |

| | |
|---|---|
| | (1) Number of panic attacks: participant's diary<br>(2) Global improvement of panic disorder: CGI<br>(3) Anxiety: HAMA<br>(4) Panic-associated symptom scale (PASS) (panic attacks, anticipatory anxiety, phobias) |
| Notes | **Date of study**: not stated<br>**Funding source**: not stated<br>**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<br>**Method of diagnosis:** SCL-90<br>**Age (years):** 26-49 (mean = 32 SD = 6.4)<br>**Sex:** 27 women, 3 men<br>**Location:** outpatient clinic of the department of Biological Psychiatry of the University Hospital in Utrecht, Netherlands<br>**Co-morbidities:** excluded<br>**Rescue medication:** oxazepam to a maximum of 30 mg daily, if required |
| Interventions | Participants were randomly assigned to either:<br>1. brofaromine arm (randomised n = 15)<br>**Duration:** 12 weeks<br>**Treatment protocol:** flexible dosage; range = 50-150 mg/day, mean = not stated (SD = not stated)<br>2. placebo arm (randomised n = 14)<br>**Duration:** 12 weeks<br>**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)<br>**Outcomes:**<br>1. HAMA<br>2. MADRS<br>3. FQ<br>4. number of panic attacks<br>5. HDRS<br>6. SCL-90<br>7. UPI (Utrecht Panic Inventory)<br>8. STAI |
| Notes | **Date of study:** not specified<br>**Funding source:** none declared<br>**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)<br>All outcomes | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided |
| Incomplete outcome data (attrition bias)<br>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.<br>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.<br>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<br>**Method of diagnosis:** open interview<br>**Age:** M = 35, SD = 7.46<br>**Sex:** 26 women, 6 men<br>**Location:** the Netherlands; setting: outpatients<br>**Co-morbidities:** patients with another anxiety disorder, major affective disorders or psychotic disorder, alcohol or drug abuse and medical problems were excluded<br>**Rescue medication:** oxazepam maximum 30 mg daily |
| Interventions | **Participants were randomly assigned to either:**<br>(1) brofaromine arm (n = 15)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage 150 mg<br>(2) fluvoxamine arm (n = 15)<br>**Duration:** 12 weeks<br>**Treatment protocol:** fixed dosage 150 mg |
| Outcomes | **Time points for assessment:** weekly<br>**Outcomes:**<br>**1.** Hamilton Rating Scale for Anxiety (HAMA)<br>**2.** Montgomery–Åsberg Depression Rating Scale (MADRS)<br>**3.** Fear Questionnaire<br>**4.** number of panic attacks<br>**5.** Hamilton Rating Scale for Depression (HAM-D)<br>**6.** SCL-90 |
| Notes | **Date of study:** not stated<br>**Funding source:** not stated<br>**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<br>**Method of diagnosis:** not specified<br>**Age (years):** mean age in reboxetine arm 36.5 (SD = 10.4), mean age in placebo arm 35.1 (SD = 10.9)<br>**Sex:** 50 women, 25 men<br>**Location:** Brazil and Italy<br>**Co-morbidities:** excluded<br>**Rescue medication:** unclear |
| Interventions | Participants were randomly assigned to either:<br>1. reboxetine arm (randomised n = 42)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage; range = 2-8 mg/day<br>2. placebo arm (randomised n = 40)<br>**Duration:** 8 weeks<br>**Treatment protocol:** flexible dosage |
| Outcomes | **Timepoints for assessment:** weekly for 8 weeks<br>**Outcomes:**<br>1. Sheehan panic Attack and Anxiety Scale<br>2. Phobia Scale<br>3. CGI<br>4. Hamilton Rating Scales for Depression (HAM-D)<br>5. SCL-90<br>6. SDS<br>7. DOTES (Dosage Record and Treatment Emergent Symptom Scale) |
| Notes | **Date of study:** not specified<br>**Funding source:** not specified<br>**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 | **Diagnosis:** DSM-III-R panic disorder<br>**Method of diagnosis:** not stated<br>**Age:** M = 38, SD not provided<br>**Sex:** 70% female, 30 % male<br>**Location:** not stated; setting unclear<br>**Co-morbidities:** patients with depression, organic brain damage, drug/alcohol misuse and other severe psychiatric or somatic disorders were excluded<br>**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. |
| Interventions | **Participants were randomly assigned to either:**<br>(1) citalopram 10-15 mg arm (n = 97)<br>**Duration:** 8 weeks<br>**Treatment protocol:** 10 mg, with the option of increasing to 15 mg if efficacy was not seen<br>(2) citalopram 20-30 mg arm (n = 95)<br>**Duration:** 8 weeks<br>**Treatment protocol:** 20 mg, with the option of increasing to 30 mg if efficacy was not seen<br>(3) citalopram 40-60 arm (n = 89)<br>**Duration:** 8 weeks<br>**Treatment protocol:** 40 mg, with the option of increasing to 60 mg if efficacy was not seen<br>(4) clomipramine (n = 98)<br>**Duration:** 8 weeks<br>**Treatment protocol:** 60 mg, with the option of increasing to 90 mg if efficacy was not seen<br>(5) placebo (n = 96) |
| Outcomes | **Time points for assessment:** baseline, last assessment (no further details provided)<br>**Outcomes:**<br>**1.** number of panic attacks - Clinical Anxiety Scale (CAS)<br>**2.** general improvement (Physician's Global Improvement Scale, Patient's Global Improvement Scale)<br>**3.** Hamilton Anxiety Rating Scale (HAS)<br>**4.** Montgomery–Åsberg Depression Rating Scale (MADRS) |
| Notes | **Date of study:** not stated<br>**Funding source:** not stated<br>**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: "randomised". No further information provided. |
| Allocation concealment (selection bias) | Unclear risk | No information provided. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "double blind". No further information provided. |
| Incomplete outcome data (attrition bias)<br>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 |

| | |
|---|---|
| | **Method of diagnosis:** no available information<br>**Age:** not stated<br>**Sex:** not stated<br>**Location:** China; setting: in and outpatients<br>**Co-morbidities:** none<br>**Rescue medication:** not stated |
| Interventions | **Participants were randomly assigned to either:**<br>(1) paroxetine arm (n = 38)<br>**Duration:** 10 weeks<br>**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<br>(2) clomipramine arm (n = 35)<br>**Duration:** 10 weeks<br>**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 |
| Outcomes | **Time points for assessment:** not stated<br>**Outcomes:** not stated |
| Notes | **Date of study:** not stated<br>**Funding source:** sponsored by the drug company marketing the drug<br>**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)<br>All outcomes | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | No information provided. |
| Incomplete outcome data (attrition bias)<br>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
TCAs: 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) |
| Chounaird 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) |
| Knijnik 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 psychoterapeutic 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 |
| Scieghi 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) |
| Zajecka 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 compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).tw,kf. AND *[RCT filter]:* (controlled clinical trial.pt. or randomised controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomised controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

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

The CCMDCTR-Studies Register 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 befloxatone or benactyzine or binospirone or brofaromine or (buproprion or amfebutamone) or butriptyline or caroxazone or cianopramine or cilobamine or cimoxatone or citalopram or (chlorimipramin* or clomipramin* or chlomipramin* or clomipramine) or clorgyline or clovoxamine or (cx157 or tyrima) or demexiptiline or deprenyl or (desipramine* or pertofrane) or desvenlafaxine or dibenzepin or diclofensine or dimetacrin* or dosulepin or dothiepin or doxepin or duloxetine or desvenlafaxine or dvs-233 or escitalopram or etoperidone or femoxetine or fluotracen or fluoxetine or fluvoxamine or (hyperforin or hypericum or "st john*") or imipramin* or iprindole or iproniazid* or ipsapirone or isocarboxazid* or levomilnacipran or lofepramine* or ("lu aa21004" or vortioxetine) or "lu aa24530" or (ly2216684 or edivoxetine) or maprotiline or melitracen or metapramine or mianserin or milnacipran or minaprine or mirtazapine or moclobemide or nefazodone or nialamide or nitroxazepine or nomifensine or norfenfluramine or nortriptylin* or noxiptilin* or opipramol or oxaflozane or paroxetine or

phenelzine or pheniprazine or pipofezine or pirlindole or pivagabine or pizotyline or propizepine or protriptylin* or quinupramine or reboxetine or rolipram or scopolamine or selegiline or sertraline or setiptiline or teciptiline or thozalinone or tianeptin* or toloxatone or tranylcypromin* or trazodone or trimipramine or venlafaxine or viloxazine or vilazodone or viqualine or zalospirone)
#4. (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or “ethyl loflazepate” or “cm 6912” or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or “wy 3498” or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or (zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or “z drugs”) or *pam or *lam or nonbenzo*)
#5. (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or *piron* or or gabapentin* or pregabalin or mirogabalin or imagabalin)
#6. (#1 and (#2 or #3 or #4 or #5))
*CCDANCTR-Refs Search 2 (ADNOS)*:
#7. ((anxiety or anxious):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:

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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 (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp. (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 loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).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)

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

Search Strategy:

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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 Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp. (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 loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).mp. (95432)

9 (azapirone or alnespirone or binospirone 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)

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

Search Strategy:

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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 Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp. (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 chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).mp. (25520)

15 (azapirone or alnespirone or binospirone 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 subsitut* 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 (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or "St John*") or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or ("Lu AA21004" or Vortioxetine) or "Lu AA24530" or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone):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 norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs or nonbenzo*):ti,ab,kw 23211

#13 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or gabapentin* or pregabalin or mirogabalin or imagabalin):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 |

| | | | | |
|---|---|---|---|---|
| | (-0.71 to 2.00) | (-2.10 to 1.00) | (-0.90 to 1.2) | |

## 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[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]) }
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 #Tsutsui 2000a
1 8 NA 18 37 38 83 NA NA 2 2 NA 1 NA #Tsutsui 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) # calcultate 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) # calcultate 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=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) # calcultate 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) # calcultate 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=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 ofparoxetine 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 clinicaltrial 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 off luvoxamine, cognitive therapy and placebo in the treatment of panic disorder. Archives of General Psychiatry 1993;50:44-50.

### Bradweijn 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.

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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.

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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.

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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. Serotoninergic anxiolytics in the treatment of panic disorder: a controlled study with buspirone. Psychopathology 1989;22(Suppl 1):60-67.

### Pollack 1998 {published data only}

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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.

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# 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 hight 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**

| | Endpoint | | Change from baseline | | | |
|---|---|---|---|---|---|---|
| Comparator | SMD (95% CrI) | Mean Rank (95% CrI) | SMD (95% CrI) | Mean Rank (95% CrI) | No. trials | No. participants |
| 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 (drop out)**

| 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**

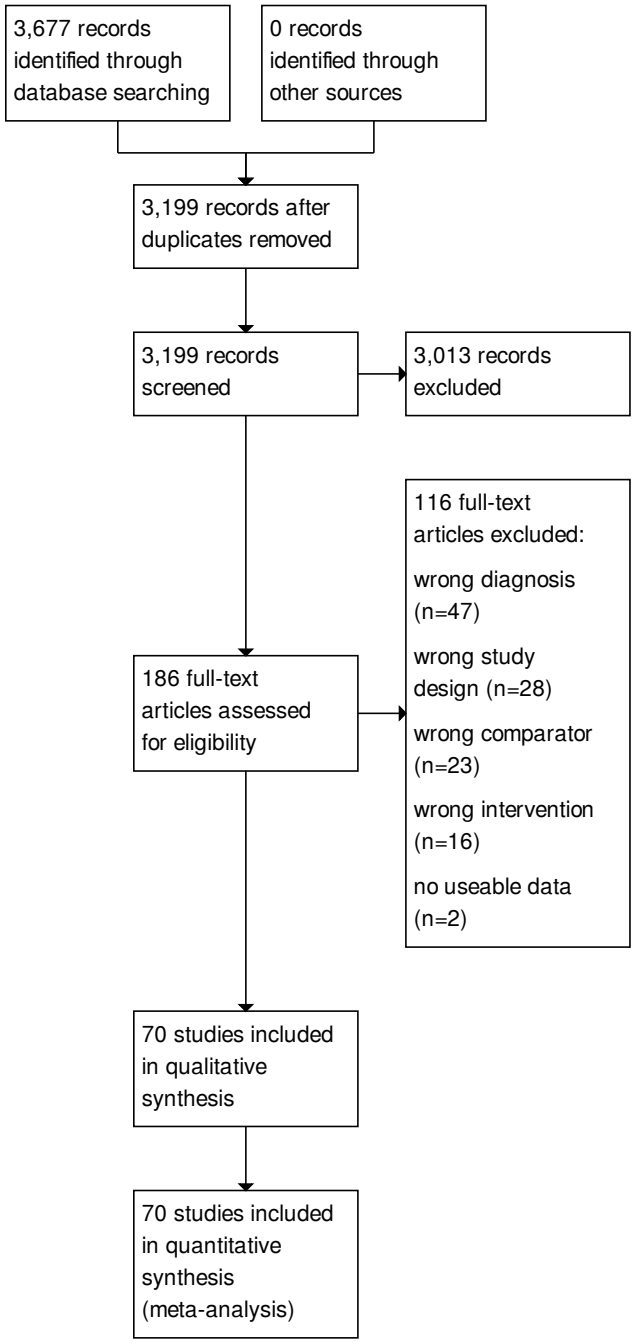



**Figure 2**

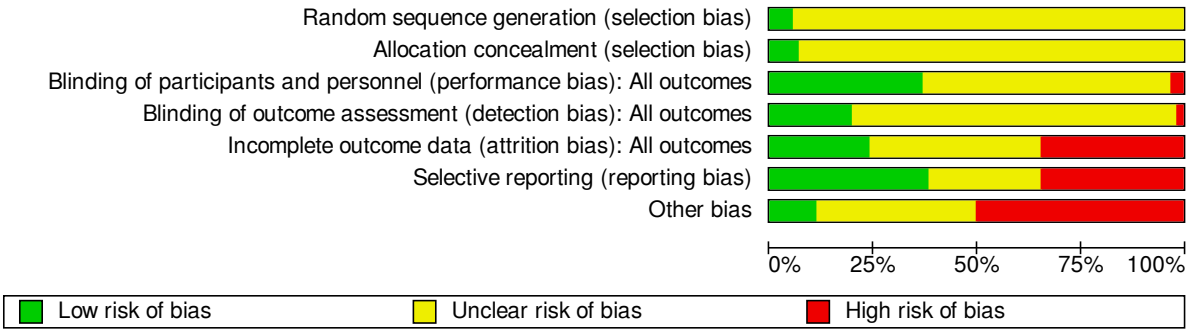
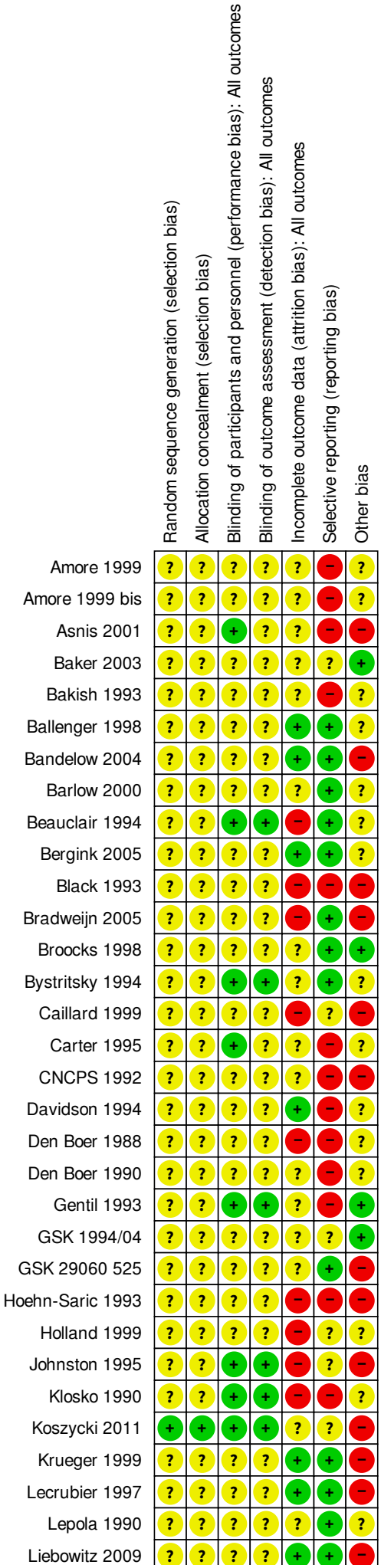

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias): All outcomes
Blinding of outcome assessment (detection bias): All outcomes
Incomplete outcome data (attrition bias): All outcomes
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

**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
Beauclair 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

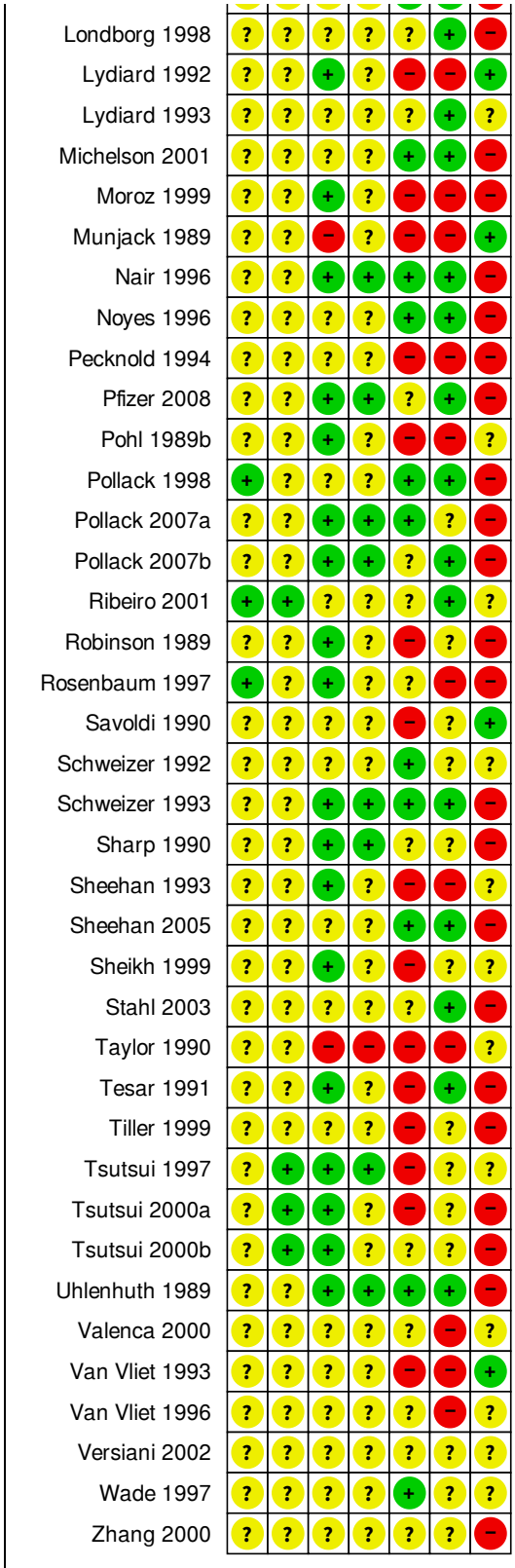
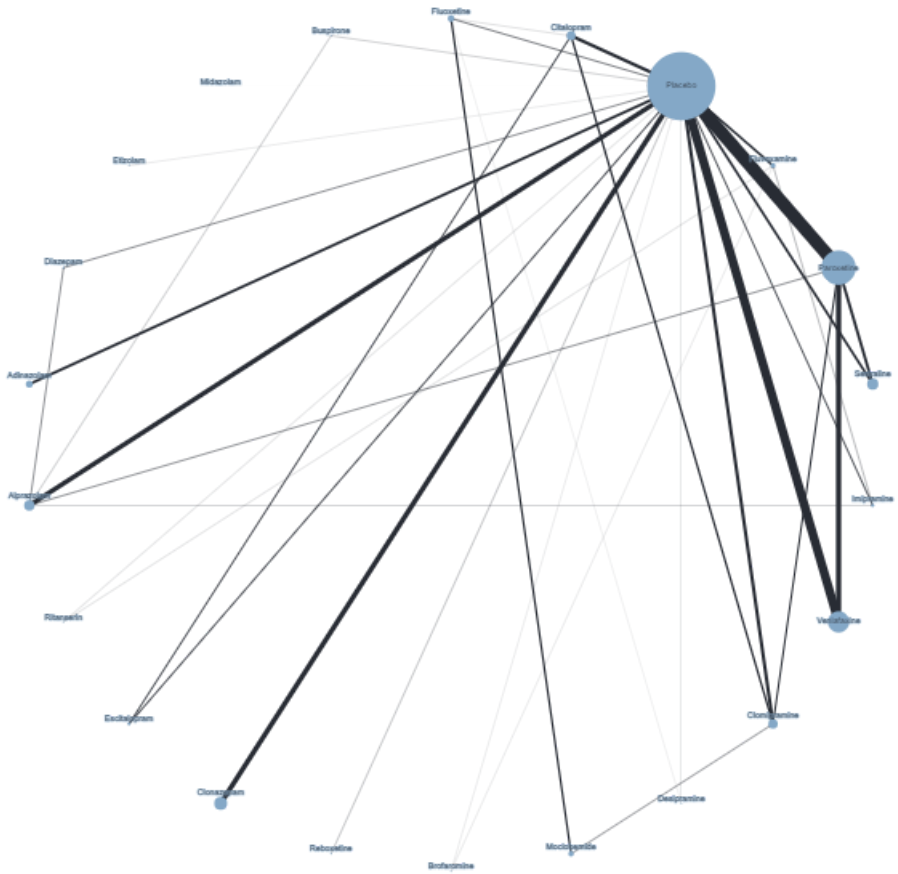

Londborg 1998
Lydiard 1992
Lydiard 1993
Michelson 2001
Moroz 1999
Munjack 1989
Nair 1996
Noyes 1996
Pecknold 1994
Pfizer 2008
Pohl 1989b
Pollack 1998
Pollack 2007a
Pollack 2007b
Ribeiro 2001
Robinson 1989
Rosenbaum 1997
Savoldi 1990
Schweizer 1992
Schweizer 1993
Sharp 1990
Sheehan 1993
Sheehan 2005
Sheikh 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

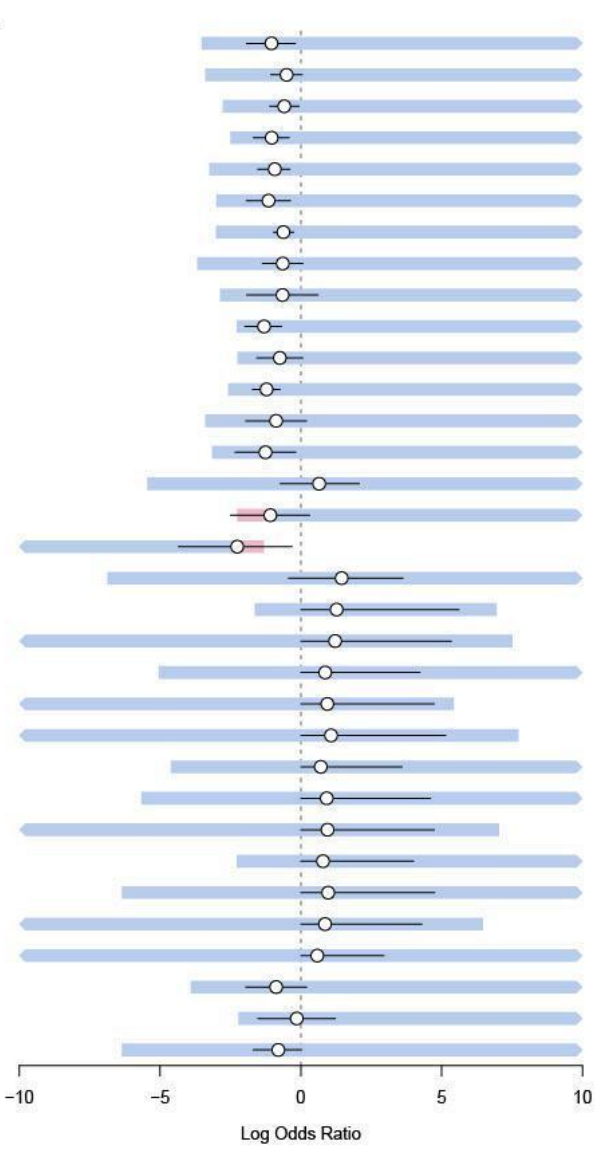
**Figure 4**




Network plot for response outcome (node size and edge width weighted by sample size)

**Figure 5**

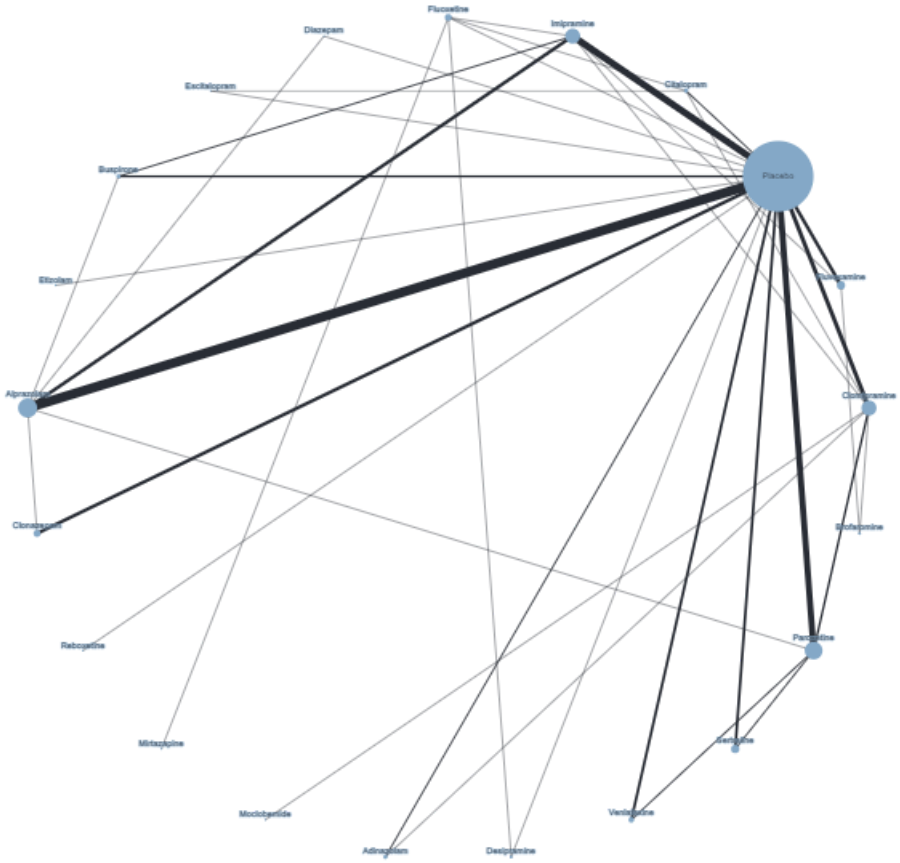
| Contrast | Mean | 95% Credible Interval | | Invariant Interval | |
|---|---|---|---|---|---|
| 2 vs. 1 | −1.04 | (−1.93, −0.20) | 2 | (−3.52, 402.36) | 18 |
| 3 vs. 1 | −0.51 | (−1.07, 0.06) | 3 | (−3.39, 526.63) | 5 |
| 4 vs. 1 | −0.59 | (−1.11, −0.06) | 4 | (−2.77, NT) | – |
| 5 vs. 1 | −1.04 | (−1.69, −0.41) | 5 | (−2.50, 69.38) | 3 |
| 6 vs. 1 | −0.93 | (−1.53, −0.39) | 6 | (−3.25, 86.63) | 18 |
| 7 vs. 1 | −1.15 | (−1.94, −0.37) | 7 | (−3.00, NT) | – |
| 8 vs. 1 | −0.62 | (−0.98, −0.25) | 8 | (−3.02, NT) | – |
| 10 vs. 1 | −0.64 | (−1.37, 0.08) | 10 | (−3.68, 217.24) | 12 |
| 11 vs. 1 | −0.65 | (−1.92, 0.61) | 11 | (−2.87, 262.22) | 20 |
| 12 vs. 1 | −1.31 | (−1.99, −0.68) | 12 | (−2.27, 62.24) | 15 |
| 13 vs. 1 | −0.75 | (−1.57, 0.07) | 13 | (−2.25, 3361.35) | 17 |
| 14 vs. 1 | −1.22 | (−1.72, −0.73) | 14 | (−2.59, 153.83) | 9 |
| 15 vs. 1 | −0.88 | (−1.97, 0.20) | 15 | (−3.39, NT) | – |
| 16 vs. 1 | −1.26 | (−2.34, −0.18) | 16 | (−3.15, NT) | – |
| 17 vs. 1 | 0.65 | (−0.73, 2.07) | 17 | (−5.45, 1397.76) | 18 |
| **18 vs. 1** | −1.08 | (−2.50, 0.31) | 18 | (−2.26, 2226.03) | 2 |
| **19 vs. 1** | −2.26 | (−4.35, −0.31) | – | (NT, −1.31) | 12 |
| 20 vs. 1 | 1.45 | (−0.44, 3.63) | 20 | (−6.86, NT) | – |
| 9 vs. 2 | 1.27 | (0.00, 5.62) | 9 | (−1.63, 6.95) | 2 |
| 10 vs. 2 | 1.22 | (0.00, 5.35) | 10 | (−12.59, 7.51) | 2 |
| 11 vs. 2 | 0.86 | (0.00, 4.23) | 11 | (−5.04, 12.57) | 2 |
| 8 vs. 3 | 0.94 | (0.00, 4.73) | 8 | (−13.08, 5.43) | 3 |
| 8 vs. 4 | 1.07 | (0.00, 5.14) | 8 | (−15.35, 7.72) | 4 |
| 7 vs. 5 | 0.71 | (0.00, 3.59) | 7 | (−4.61, 11.28) | 5 |
| 20 vs. 5 | 0.92 | (0.00, 4.61) | 20 | (−5.66, 67.40) | 5 |
| 8 vs. 6 | 0.95 | (0.00, 4.74) | 8 | (−18.85, 7.04) | 6 |
| 9 vs. 6 | 0.79 | (0.00, 4.01) | 9 | (−2.27, 19.98) | 6 |
| 10 vs. 6 | 0.97 | (0.00, 4.75) | 10 | (−6.36, 12.14) | 6 |
| 14 vs. 7 | 0.86 | (0.00, 4.29) | 14 | (−15.11, 6.47) | 7 |
| 14 vs. 8 | 0.58 | (0.00, 2.95) | 14 | (−11.70, 36.49) | 8 |
| 15 vs. 10 | −0.88 | (−1.97, 0.20) | 15 | (−3.90, 12.31) | 10 |
| 16 vs. 14 | −0.14 | (−1.53, 1.23) | 16 | (−2.22, 21.33) | 14 |
| 17 vs. 14 | −0.80 | (−1.69, 0.03) | 17 | (−6.35, 33.11) | 14 |




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=buspirone, 18=reboxetine, 19=etizolam, 20=ritanserin

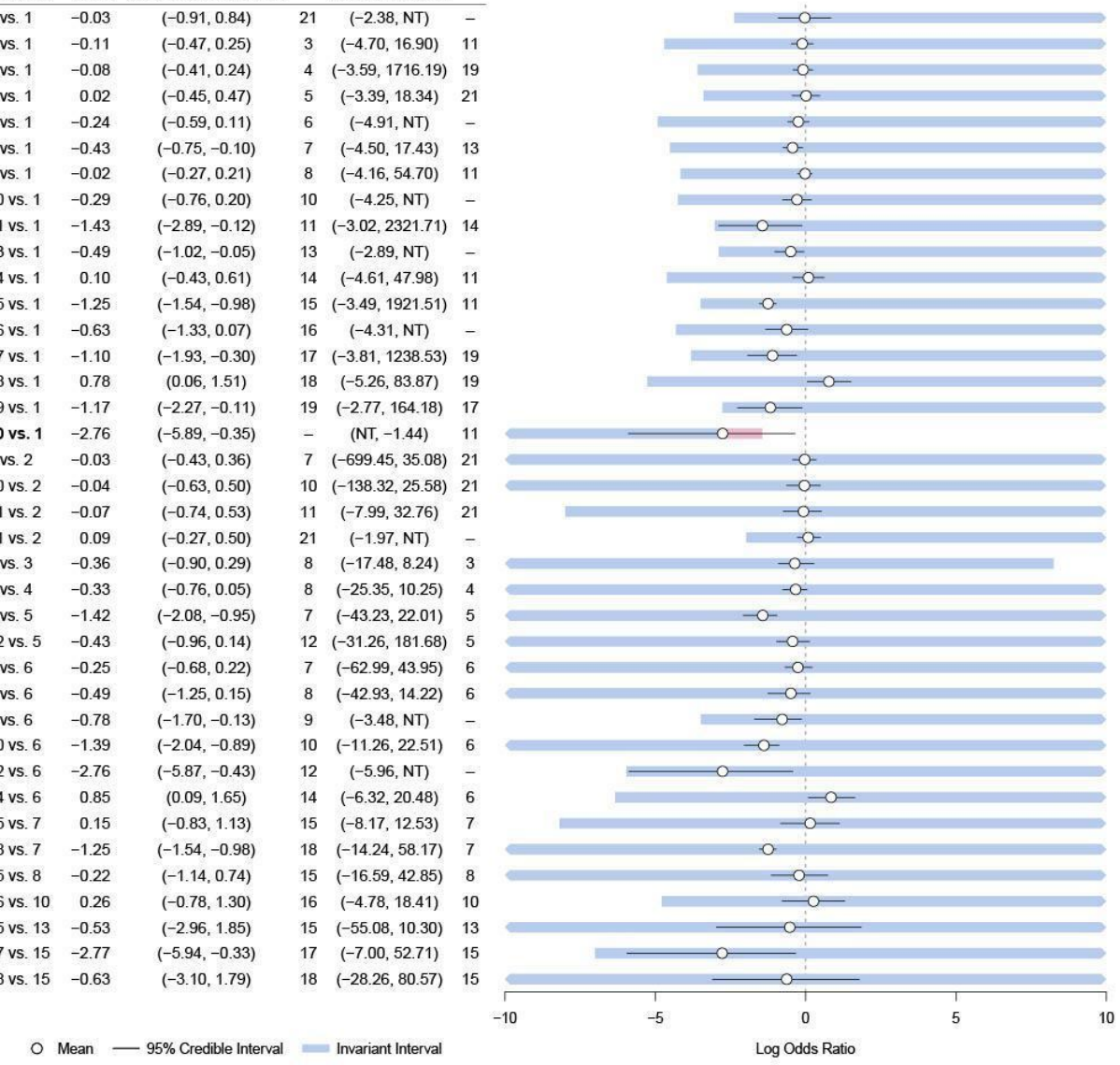
**Figure 6**




Network plot for drop out (node size and edge width weighted by number of studies)

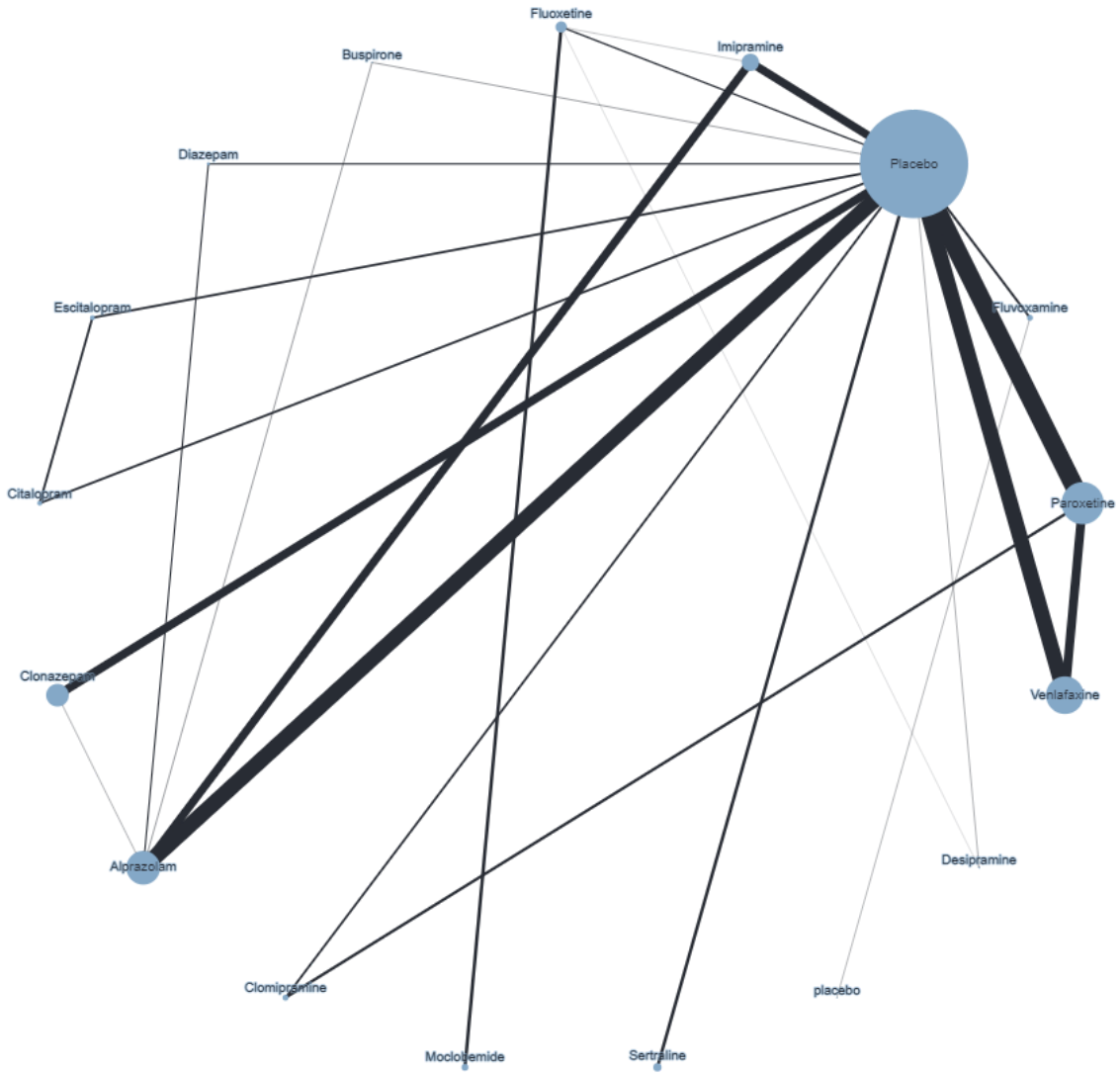
**Figure 7**

| Contrast | Mean | 95% Credible Interval | | Invariant Interval | |
|---|---|---|---|---|---|
| 2 vs. 1 | −0.03 | (−0.91, 0.84) | 21 | (−2.38, NT) | – |
| 3 vs. 1 | −0.11 | (−0.47, 0.25) | 3 | (−4.70, 16.90) | 11 |
| 4 vs. 1 | −0.08 | (−0.41, 0.24) | 4 | (−3.59, 1716.19) | 19 |
| 5 vs. 1 | 0.02 | (−0.45, 0.47) | 5 | (−3.39, 18.34) | 21 |
| 6 vs. 1 | −0.24 | (−0.59, 0.11) | 6 | (−4.91, NT) | – |
| 7 vs. 1 | −0.43 | (−0.75, −0.10) | 7 | (−4.50, 17.43) | 13 |
| 8 vs. 1 | −0.02 | (−0.27, 0.21) | 8 | (−4.16, 54.70) | 11 |
| 10 vs. 1 | −0.29 | (−0.76, 0.20) | 10 | (−4.25, NT) | – |
| 11 vs. 1 | −1.43 | (−2.89, −0.12) | 11 | (−3.02, 2321.71) | 14 |
| 13 vs. 1 | −0.49 | (−1.02, −0.05) | 13 | (−2.89, NT) | – |
| 14 vs. 1 | 0.10 | (−0.43, 0.61) | 14 | (−4.61, 47.98) | 11 |
| 15 vs. 1 | −1.25 | (−1.54, −0.98) | 15 | (−3.49, 1921.51) | 11 |
| 16 vs. 1 | −0.63 | (−1.33, 0.07) | 16 | (−4.31, NT) | – |
| 17 vs. 1 | −1.10 | (−1.93, −0.30) | 17 | (−3.81, 1238.53) | 19 |
| 18 vs. 1 | 0.78 | (0.06, 1.51) | 18 | (−5.26, 83.87) | 19 |
| 19 vs. 1 | −1.17 | (−2.27, −0.11) | 19 | (−2.77, 164.18) | 17 |
| **20 vs. 1** | −2.76 | (−5.89, −0.35) | – | (NT, −1.44) | 11 |
| 7 vs. 2 | −0.03 | (−0.43, 0.36) | 7 | (−699.45, 35.08) | 21 |
| 10 vs. 2 | −0.04 | (−0.63, 0.50) | 10 | (−138.32, 25.58) | 21 |
| 11 vs. 2 | −0.07 | (−0.74, 0.53) | 11 | (−7.99, 32.76) | 21 |
| 21 vs. 2 | 0.09 | (−0.27, 0.50) | 21 | (−1.97, NT) | – |
| 8 vs. 3 | −0.36 | (−0.90, 0.29) | 8 | (−17.48, 8.24) | 3 |
| 8 vs. 4 | −0.33 | (−0.76, 0.05) | 8 | (−25.35, 10.25) | 4 |
| 7 vs. 5 | −1.42 | (−2.08, −0.95) | 7 | (−43.23, 22.01) | 5 |
| 12 vs. 5 | −0.43 | (−0.96, 0.14) | 12 | (−31.26, 181.68) | 5 |
| 7 vs. 6 | −0.25 | (−0.68, 0.22) | 7 | (−62.99, 43.95) | 6 |
| 8 vs. 6 | −0.49 | (−1.25, 0.15) | 8 | (−42.93, 14.22) | 6 |
| 9 vs. 6 | −0.78 | (−1.70, −0.13) | 9 | (−3.48, NT) | – |
| 10 vs. 6 | −1.39 | (−2.04, −0.89) | 10 | (−11.26, 22.51) | 6 |
| 12 vs. 6 | −2.76 | (−5.87, −0.43) | 12 | (−5.96, NT) | – |
| 14 vs. 6 | 0.85 | (0.09, 1.65) | 14 | (−6.32, 20.48) | 6 |
| 15 vs. 7 | 0.15 | (−0.83, 1.13) | 15 | (−8.17, 12.53) | 7 |
| 18 vs. 7 | −1.25 | (−1.54, −0.98) | 18 | (−14.24, 58.17) | 7 |
| 15 vs. 8 | −0.22 | (−1.14, 0.74) | 15 | (−16.59, 42.85) | 8 |
| 16 vs. 10 | 0.26 | (−0.78, 1.30) | 16 | (−4.78, 18.41) | 10 |
| 15 vs. 13 | −0.53 | (−2.96, 1.85) | 15 | (−55.08, 10.30) | 13 |
| 17 vs. 15 | −2.77 | (−5.94, −0.33) | 17 | (−7.00, 52.71) | 15 |
| 18 vs. 15 | −0.63 | (−3.10, 1.79) | 18 | (−28.26, 80.57) | 15 |



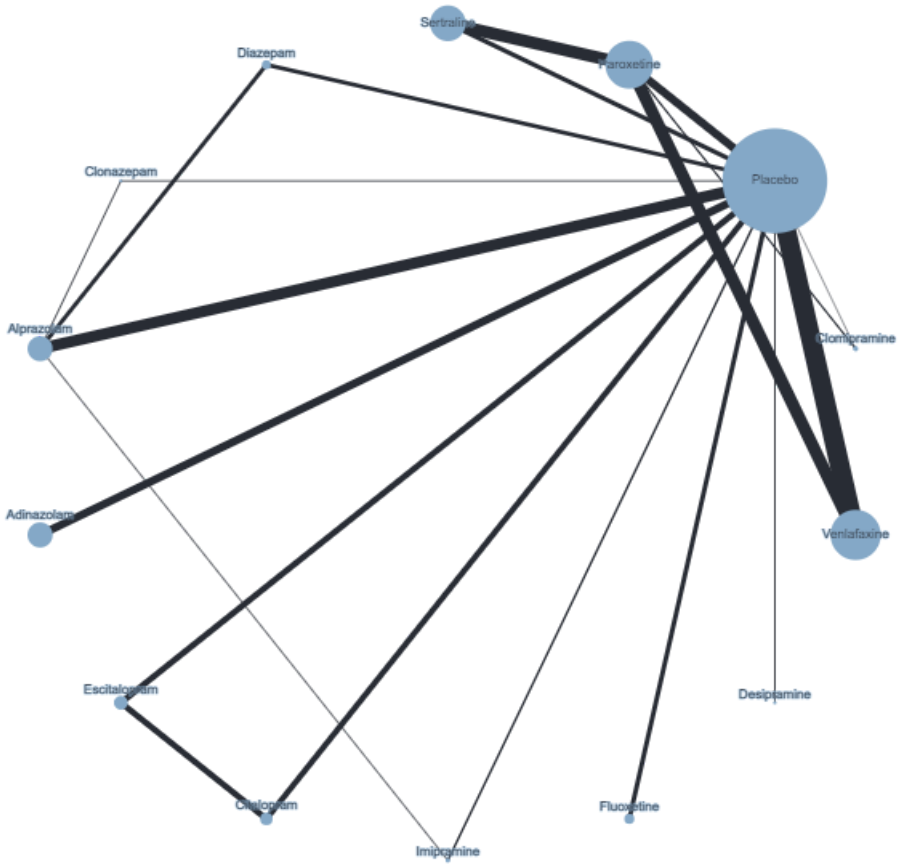

Forest plot of dropout threshold analysis

**Figure 8**



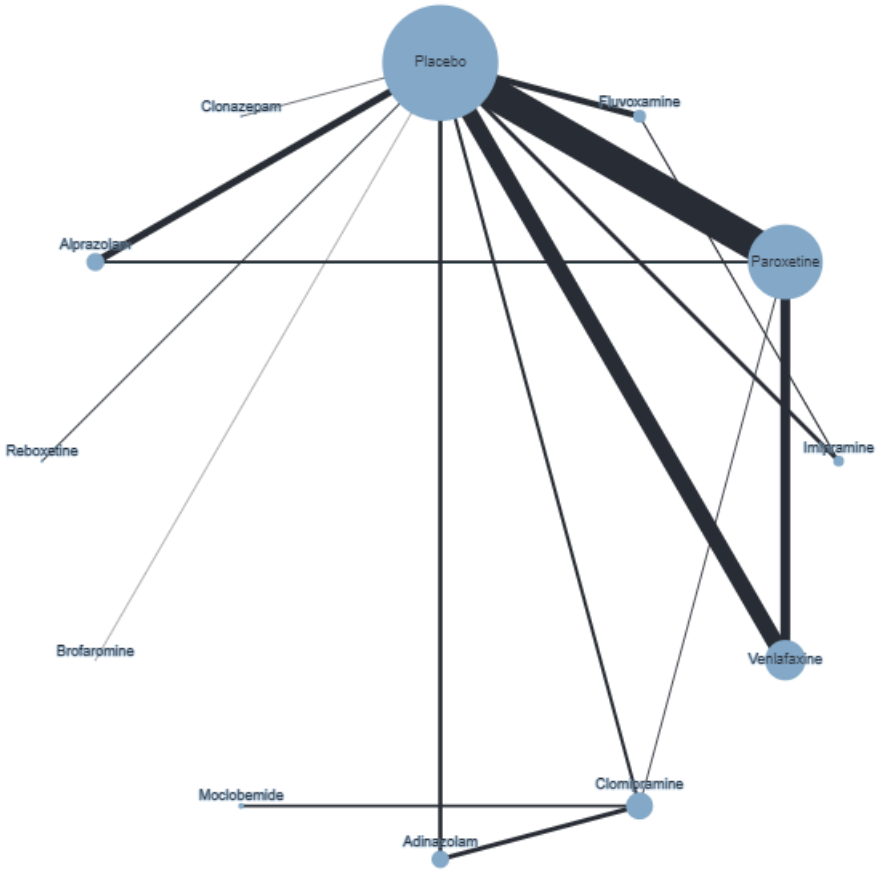

Network plot remission (node size and edge width weighted by sample size)

**Figure 9**



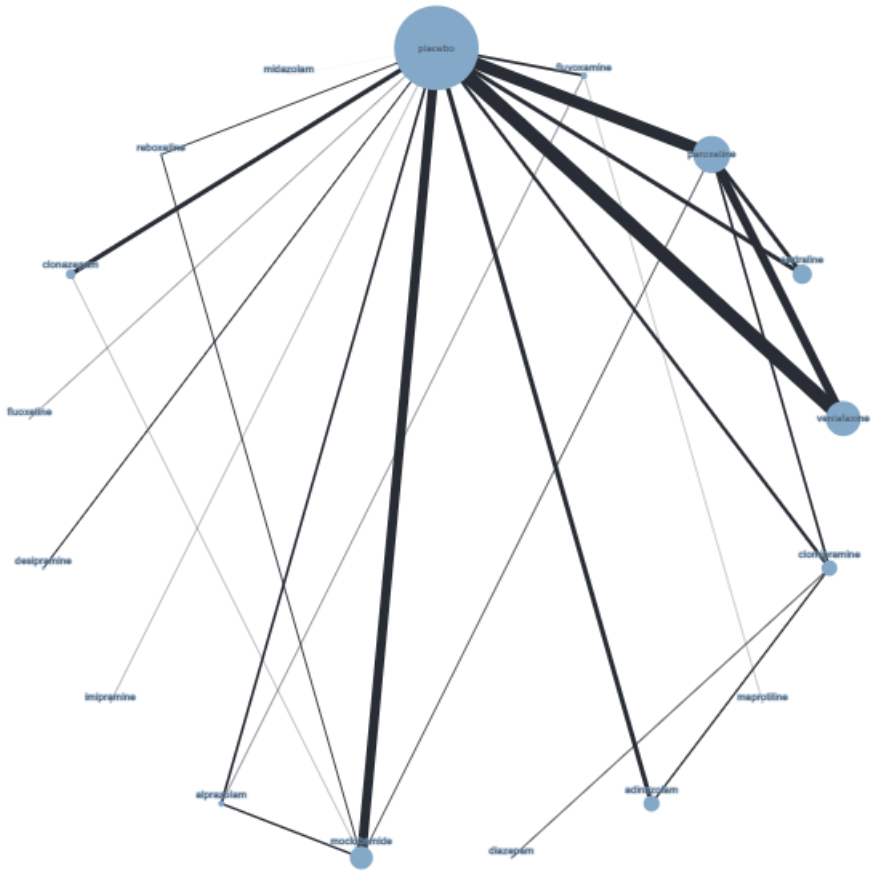

Network plot intervention combinations for panic scales (change from baseline)

**Figure 10**



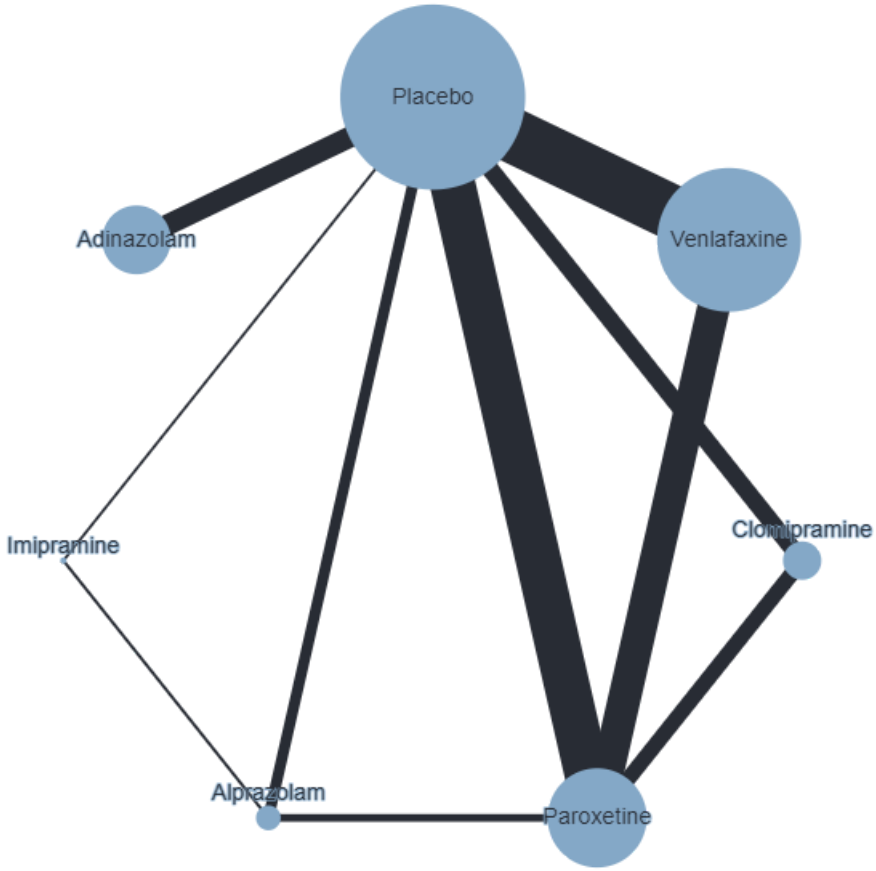
Network plot of intervention comparisons included in network meta-analysis of panic scales (endpoint)

**Figure 11**



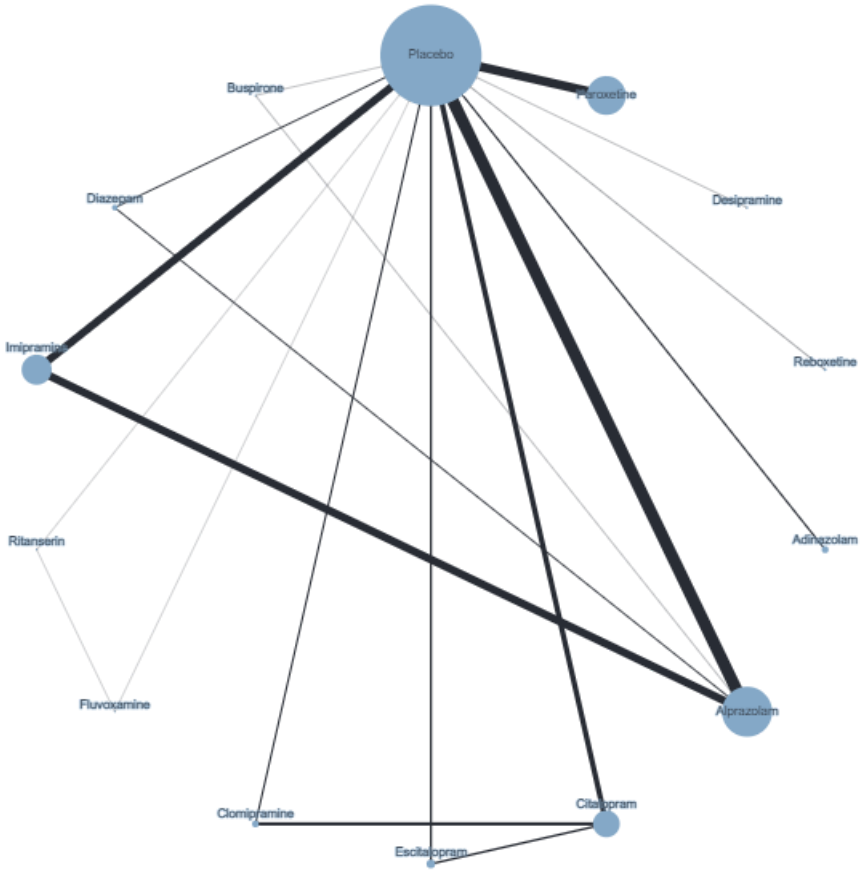

Network plot frequency of panic attacks (node size and edge width weighted by sample size)

**Figure 12**



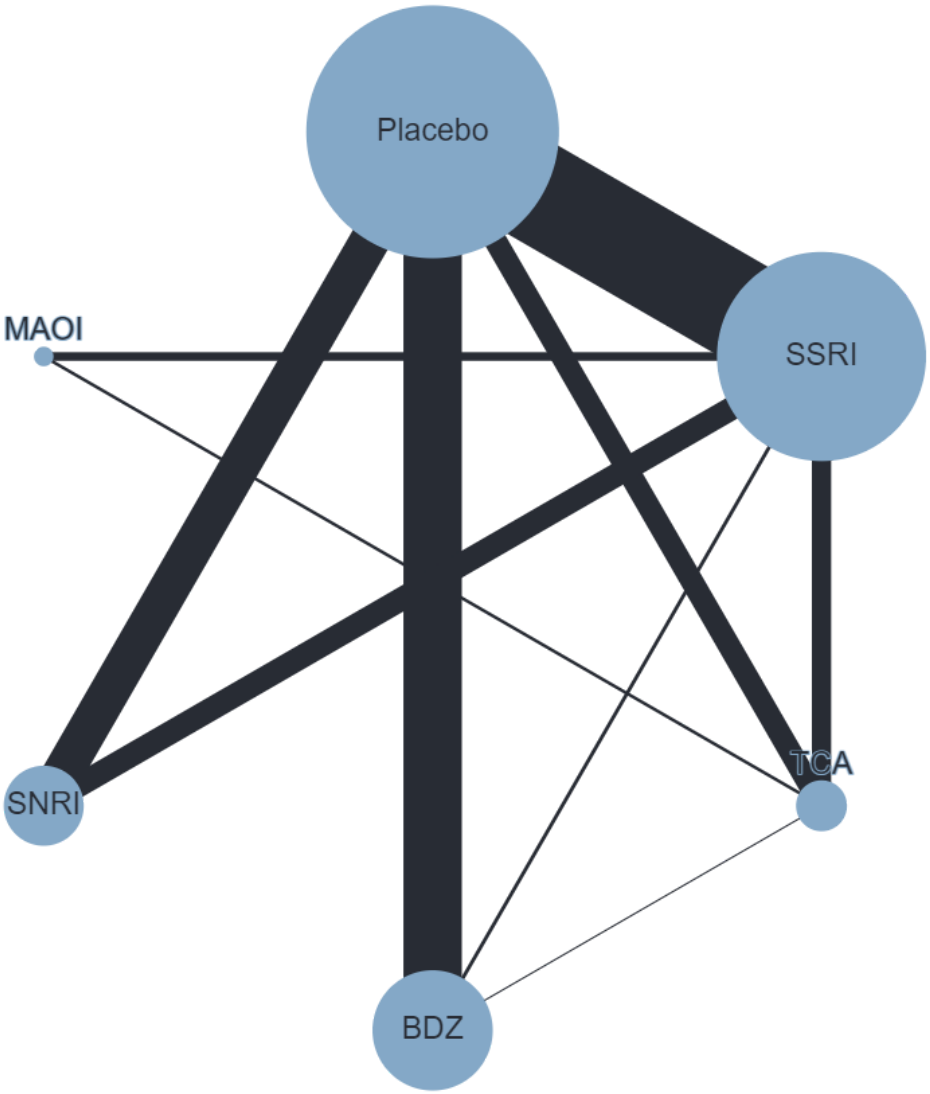

Network plot intervention combinations for agoraphobia (change from baseline)

**Figure 13**



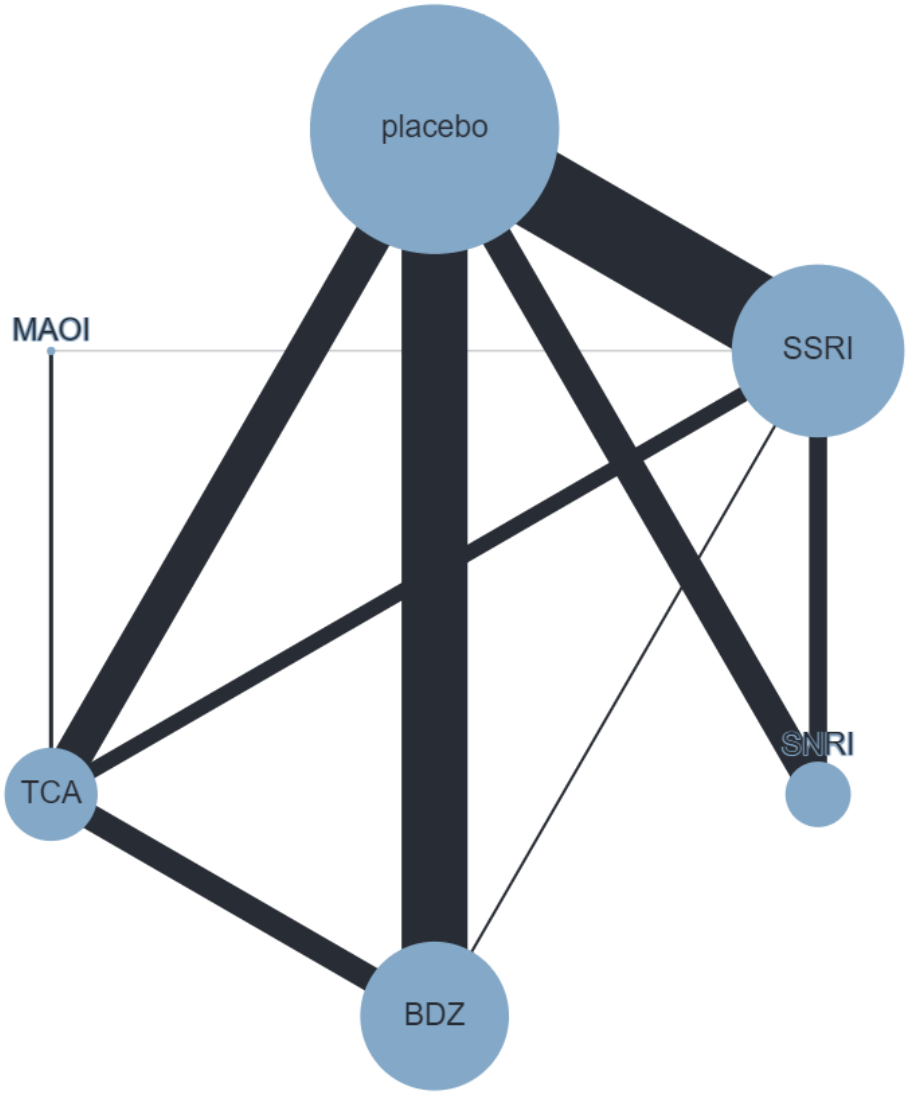
Network plot of intervention combinations for agoraphobia symptoms (endpoint)

**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)