Beroligende lægemidler til kortvarig symptomlindring af nyopståede angst- og urosymptomer hos voksne

Review information

Authors

Sundhedsstyrelsen [1]

[1] [Empty affiliation]

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Characteristics of studies

Characteristics of included studies

Amore 1999

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** SSRI (Fluoxetine) ● Diagnosis: DSM-IV Panic Disorder with or without agoraphobia ● *Age in years, mean (SD)*: 37.0 (SD = 7.1) ● *Females n/N (%)*: 57.89% ● *Duration of anxiety symptoms, years, mean (SD)*: 5.6+5.1 ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: 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 ● *Patients receiving other pharmacological treatment*: All patients meeting inclusion criteria entered a 10-day washout period. Before baseline evaluation, all patients should have discontinued treatment with any psychotropic drug (except benzodiazepines), for at least two weeks. MAOIs should have been discontinued for at least three weeks and fluoxetine or imipramine for at least two months. Oxazepam (up to a maximum daily dose of 30 mg) was the only permitted psychotropic drug during the washout phase and the first four weeks of double-blind treatment Antidepressiva_tricyklisk (Imipramine) ● Diagnosis: DSM-IV Panic Disorder with or without agoraphobia ● *Age in years, mean (SD)*:37.2 (SD = 8.2) ● *Females (%)*: 36.84% ● *Duration of anxiety symptoms, years, mean (SD)*: 5.5+4.2 ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: 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 ● *Patients receiving other pharmacological treatment*: All patients meeting inclusion criteria entered a 10-day washout period. Before baseline evaluation, all patients should have discontinued treatment with any psychotropic drug (except benzodiazepines), for at least two weeks. MAOIs should have been discontinued for at least three weeks and fluoxetine or imipramine for at least two months. Oxazepam (up to a maximum daily dose of 30 mg) was the only permitted psychotropic drug during the washout phase and the first four weeks of double-blind treatment. **Included criteria:** Patients eligible for inclusion could be either sex, aged between 18 and 65 years, suffering from PD with or without agoraphobia according to DSMIV criteria **Excluded criteria:** History of psychosis, current major depression, organic brain syndromes or significant neurological disorders, seizures, a known allergy to one of the study drugs, presence of clinically relevant cardiovascular, hepatic, renal or haematological diseases, alcohol or drug abuse, or narrow angle glaucoma. Women who were pregnant, lactating or of childbearing potential and not using adequate contraception were also excluded.
Interventions	**Intervention Characteristics** SSRI (Fluoxetine) ● *Decsription*: fluoxetine ● *Dose*: flexible dosage; range = 10 - 50 mg, M = 20 mg/day (SD = 10) ● *Duration*: 24 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: All patients meeting inclusion criteria entered a 10-day washout period. Initial dose for the first week of active treatment was 10 mg of fluoxetine once each morning. Fluoxetine was raised by 10 mg weekly increments to a maximum of 50 mg/day (b.i.d.) on the basis of clinical improvement unless unacceptable side-effects appeared Rescue medication: Oxazepam (up to a maximum daily dose of 30 mg) permitted during first four weeks of double-blind treatment Antidepressiva_tricyklisk (Imipramine) ● *Decsription*: imipramine ● *Dose*: : flexible dosage; range = 25 - 250 mg, M = 150 mg/day (SD = 25)

	● *Duration*: 24 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: All patients meeting inclusion criteria entered a 10-day washout period. Initial dose for the first week of active treatment was 25 mg of imipramine once each morning. Imipramine was raised up to 50 mg/day at the end of the first week of treatment. During the following weeks, dose levels were titrated up with increments of 50 mg every week to a maximum of 250 mg/day (b.i.d.), unless unacceptable side-effects appeared. Rescue medication: Oxazepam (up to a maximum daily dose of 30 mg) permitted during first four weeks of double-blind treatment.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Italy **Setting:**: Unclear **Authors name:** Mario Amore **Institution:** Institute of Psychiatry, University of Bologna **Email:** **Address:** Institute of Psychiatry, University of Bologna, Viale Pepoli 5, 40123 Bologna, Italy **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "they were randomly assigned to fluoxetine or imipramine treatment". No further details.
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote: "double blind". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote: "double blind". No further details.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No clear information on incomplete outcome data management.
Selective reporting (reporting bias)	High risk	Judgement Comment: Data on the scales CGI, PASS and HRSD not reported at endpoint.
Other bias	Unclear risk	Judgement Comment: Sponsorship bias cannot be ruled out.

Ansseau 1996

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (alprazolam) ● Diagnosis: DSM-III-R diagnostic criteria for adjustment disorder with mixed emotional feature (anxiety and depression) ● *Age in years, mean (SD)*: 44.2 ± 11.1 ● *Females n/N (%)*: 36/51 (70,6%) ● *Duration of anxiety symptoms, days, mean (SD)*: 60.7 ± 36.6 ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: No information ● *Patients receiving other pharmacological treatment*: No other psychotropic drugs were permitted throughout the study period. Antidepresiva (mianserin) ● Diagnosis: DSM-III-R diagnostic criteria for adjustment disorder with mixed emotional feature (anxiety and depression) ● *Age in years, mean (SD)*: 42.8 ± 12.6 ● *Females n/N (%)*: 36/51 (70,6%) ● *Duration of anxiety symptoms, days, mean (SD)*: 66.2 ± 45.1 ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information

	● *Patients with co-morbidity (%)*: No information ● *Patients receiving other pharmacological treatment*: No other psychotropic drugs were permitted throughout the study period. Antidepresiva (tianeptine) ● Diagnosis:DSM-III-R diagnostic criteria for adjustment disorder with mixed emotional feature (anxiety and depression) ● *Age in years, mean (SD)*: 43.6 ± 10.7 ● *Females n/N (%)*: 36/51 (70,6%) ● *Duration of anxiety symptoms, days, mean (SD)*: 62.5 ±40.2 ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: No information ● *Patients receiving other pharmacological treatment*: No other psychotropic drugs were permitted throughout the study period. **Included criteria:** No specific inclusion cirteria stated. 152 outpatients were included in the study: 49 in the tianeptine group, 52 in the mianserin group, and 51 in the alprazolam group. Patients were 47 males and 105 females, aged 19-73 years, with a mean age (SD) of 43.5 (11.5) years. All subjects fulfilled DSM-III-R diagnostic criteria for adjustment disorder with mixed emotional feature (anxiety and depression) **Excluded criteria:** No specific exclusion cirteria stated.
Interventions	**Intervention Characteristics** Benzodiazepin (alprazolam) ● *Decsription*: Alprazolam ● *Dose*: alprazolam (1.5 mg/day) ● *Duration*: 6 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The trial used a double-blind design with three parallel groups of patients randomly assigned to tianeptine (37.5 mg/day), mianserin(60 mg/day), or alprazolam (1.5 mg/day). After an optional run-in period of 7 days on placebo (3/day), the patients received ascending doses of active compounds during the first 3 days (tianeptine 12.5,25, and 37.5 mg; mianserin 20,40, and 60 mg; and alprazolam 0.5, 1, and 1.5 mg). All active compounds were then administered in three daily intakes. The duration of the study was 6 weeks. The daily dose was kept stable during the initial 2-week treatment period and could then be adapted according to efficacy and tolerability between 25 and 50 mg/day for tianeptine, between 40 and 80 mg/day for mianserin, and between 1and 2 mg/day for alprazolam. No other psychotropic drugs were permitted throughout the study period. Antidepresiva (mianserin) ● *Decsription*: Mianserin ● *Dose*: mianserin(60 mg/day), ● *Duration*: 6 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The trial used a double-blind design with three parallel groups of patients randomly assigned to tianeptine (37.5 mg/day), mianserin(60 mg/day), or alprazolam (1.5 mg/day). After an optional run-in period of 7 days on placebo (3/day), the patients received ascending doses of active compounds during the first 3 days (tianeptine 12.5,25, and 37.5 mg; mianserin 20,40, and 60 mg; and alprazolam 0.5, 1, and 1.5 mg). All active compounds were then administered in three daily intakes. The duration of the study was 6 weeks. The daily dose was kept stable during the initial 2-week treatment period and could then be adapted according to efficacy and tolerability between 25 and 50 mg/day for tianeptine, between 40 and 80 mg/day for mianserin, and between 1and 2 mg/day for alprazolam. No other psychotropic drugs were permitted throughout the study period. Antidepresssiva (tianeptine) ● *Decsription*: Tianeptine ● *Dose*: tianeptine (37.5 mg/day), ● *Duration*: 6 weeks ● *Time of short time follow-up)*: 1 week ● *Detailed description*: The trial used a double-blind design with three parallel groups of patients randomly assigned to tianeptine (37.5 mg/day), mianserin(60 mg/day), or alprazolam (1.5 mg/day). After an optional run-in period of 7 days on placebo (3/day), the patients received ascending doses of active compounds during the first 3 days (tianeptine 12.5,25, and 37.5 mg; mianserin 20,40, and 60 mg; and alprazolam 0.5, 1, and 1.5 mg). All active compounds were then administered in three daily intakes. The duration of the study was 6 weeks. The daily dose was kept stable during the initial 2-week treatment period and could then be adapted according to efficacy and tolerability between 25 and 50 mg/day for tianeptine, between 40 and 80 mg/day for mianserin, and between 1and 2 mg/day for alprazolam. No other psychotropic drugs were permitted throughout the study period.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirknigner, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal

	● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** The study was supported by a grant from the 'Institut de Recherches Internationales Servier" **Country:** Multicentre study in Belgium, Switzerland and France **Setting:**: Outpatients. Multicentre study conducted in seven Belgian, three Swiss, and one French centres **Authors name:** Marc Ansseau **Institution:** Department of Psychiatry and Medical Psychology, C.H. U. du Sart Tilman, B-4000 Liège, Belgium **Email:** **Address:** Department of Psychiatry and Medical Psychology, C.H. U. du Sart Tilman, B-4000 Liège, Belgium **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information on sequence geenration
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The trial used a double-blind design with three parallel groups of patients randomly assigned to tianeptine (37.5 mg/day), mianserin (60 mg/day), or alprazolam (1.5 mg/day)." Judgement Comment: No information on who was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The trial used a double-blind design with three parallel groups of patients randomly assigned to tianeptine (37.5 mg/day), mianserin (60 mg/day), or alprazolam (1.5 mg/day). After" Judgement Comment: No information on who was blinded
Incomplete outcome data (attrition bias)	High risk	Quote: "A total of 33 patients (21.7 per cent) did not complete the study." Judgement Comment: Higher number of dropouts due to adverse events in the group receiving mianserin Uneven reasons between groups.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to a protocol, the trial reports on the outcomes stated in the method section
Other bias	Low risk	Judgement Comment: The trial apperas to be free from other sources of bias

Bakish 1993

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Anitdepressiva (brofaromine) ● Diagnosis: DSM-III panic disorder with or without agoraphobia ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Not stated ● *Patients receiving other pharmacological treatment*: Only hypnotic allowed was chloral hydratem up to 1 g at night Anitdepressiva (clominipramine) ● Diagnosis: DSM-III panic disorder with or without agoraphobia ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Not stated ● *Patients receiving other pharmacological treatment*: Only hypnotic allowed was chloral hydratem up to 1 g at night **Included criteria:** DSM-III panic disorder with or without agoraphobia. No other specific inclusion cirteria stated.

	Excluded criteria: No specific exclusion criteria stated.
Interventions	**Intervention Characteristics** Anitdepressiva MAO (brofaromine) ● *Decsription*: brofaromine ● *Dose*: : flexible dosage; range = 50 - 150 mg, M and SD not provided ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1-week placebo wash out period before randomisation. benzodiazepines were withdrawn 72 hours prior to commencement of the active phase of treatment. Only hypnotic allowed was chloral hydratem up to 1 g at night. Medication started at 50 mg daily and increased by 50 mg each week to achive a maximum tolerable dose. Rescue medication: Chloral hydrate, up to 1 g at night Antidepressiva_tricyklisk (clominipramine) ● *Decsription*: clominipramine ● *Dose*: flexible dosage; range = 25 - 75 mg, M and SD not provided ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1-week placebo wash out period before randomisation. benzodiazepines were withdrawn 72 hours prior to commencement of the active phase of treatment. Only hypnotic allowed was chloral hydratem up to 1 g at night. Medication started at 25 mg daily and increased by 25 mg each week to achive a maximum tolerable dose Rescue medication: Chloral hydrate, up to 1 g at night
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Canada **Setting:** Outpatients **Authors name:** Bakish **Institution:** University of Ottawa and Royal Ottawa Hospital, Ottawa Ontario **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "randomised". No further details
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote: "double blind". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote: "double blind". No further details.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No clear information on incomplete outcome data management.
Selective reporting (reporting bias)	High risk	Judgement Comment: 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	Judgement Comment: Sponsorship bias cannot be ruled out.

CNCPS 1992

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group

Participants	**Baseline Characteristics** Overall ● Diagnosis: DSM-III panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia) ● *Age in years, mean (SD)*: 34, SD not provided ● *Females n/N (%)*: 62% ● *Duration of anxiety symptoms, days, mean (SD)*: no information ● *Outpatient (%)*: Inpatients and outpatients ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Mean score on Hamilton Rating Scale for depression was 14.1 at baseline. Using the DSM-III criteria for majoir depression, 16% of the sample were currently depressed, 16% met the criteria for major depressive episode in the past. 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. ● *Patients receiving other pharmacological treatment*: Patients taking CNS drugs, including benzodiazepines, were excluded from the study Antidepressiva_tricyklisk (Imipramine) ● Diagnosis: DSM-III panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia) ● *Age in years, mean (SD)*: ● *Females n/N (%)*: ● *Duration of anxiety symptoms, days, mean (SD)*: ● *Outpatient (%)*: Inpatients and outpatients ● *Non pharmacological treatment considered or tried (%)*: ● *Patients with co-morbidity (%)*: 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. ● *Patients receiving other pharmacological treatment*: Patients taking CNS drugs, including benzodiazepines, were excluded from the study. Benzodiazepin (alprazolam) ● Diagnosis: DSM-III panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia) ● *Age in years, mean (SD)*: ● *Females n/N (%)*: ● *Duration of anxiety symptoms, days, mean (SD)*: ● *Outpatient (%)*: Inpatients and outpatients ● *Non pharmacological treatment considered or tried (%)*: ● *Patients with co-morbidity (%)*: 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. ● *Patients receiving other pharmacological treatment*: Patients taking CNS drugs, including benzodiazepines, were excluded from the study. Placebo ● Diagnosis: DSM-III panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia) ● *Age in years, mean (SD)*: ● *Females n/N (%)*: ● *Duration of anxiety symptoms, days, mean (SD)*: ● *Outpatient (%)*: Inpatients and outpatients ● *Non pharmacological treatment considered or tried (%)*: ● *Patients with co-morbidity (%)*: 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. ● *Patients receiving other pharmacological treatment*: Patients taking CNS drugs, including benzodiazepines, were excluded from the study. **Included criteria:** DSM-III panic disorder with limited or extensive phobic avoidance (panic attacks with agoraphobia) and Between 18 and 65 years of age. **Excluded criteria:** Patients with acute suicidal ideation, pregnant of lactating, undergoing concurent psychotherapy or behavioralmtherapy. 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. Patients taking CNS drugs, including benzodiacepines were excluded.
Interventions	**Intervention Characteristics** Antidepressiva_tricyklisk (imipramine) ● *Decsription*: Imipramine ● *Dose*: 25-250 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The unit dosage was 25 mg of imipramine. Dosage was increased steadily according to a predetermined scedule that specified a dosage of 150 mg of imipramine at day 19. The dose could be raised or lowered depending on the individual patients clinical state or adverse effect, to a total of 10 identical capsules (10 mg) Rescue medication: Quote "patients taking CNS drugs, including benzodiazepines, were excluded from the study. During

	the washout period, blood was drawn for benzodiazepines screening". Benzodiazepin (alprazolam) ● *Decsription*: alprazolam ● *Dose*: 1-10 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The unit dosage was 1 mg of aprazolam. Dosage was increased steadily according to a predetermined scedule that specified a dosage of 6 mg of alprazolam at day 19. The dose could be raised or lowered depending on the individual patients clinical state or adverse effect, to a total of 10 identical capsules (10 mg). Rescue medication: Quote "patients taking CNS drugs, including benzodiazepines, were excluded from the study. During the washout period, blood was drawn for benzodiazepines screening". Placebo ● *Decsription*: Placebo ● *Dose*: 1-10 placebo capsules ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The number of capsules was increased steadily according to a predetermined scedule of 6 capsules at day 19. The number of capsules could be raised or lowered depending on the individual patients clinical state or adverse effect, to a total of 10 identical capsules. Rescue medication: Quote "patients taking CNS drugs, including benzodiazepines, were excluded from the study. During the washout period, blood was drawn for benzodiazepines screening".
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint Selvmordstanker/selvmordsforsøg ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint Vægtændring, antal patienter ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Numbers with weight gain ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Sponsored by Upjohn Company, Kalamazoo, Michigan **Country:** 12 centres in USA, Spain, Denmark, Germany, England, Italy, Brazil, Mexico, France, Colombia, Austria, Sweden, Canada, Belgium **Setting:** Inpatients and outpatients **Authors name:** Albus **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from:

	Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: 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."
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote "double-blind design". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote "double-blind design". No further details.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: Quote: "of 1168 patients randomized, 1122 met criteria for ITT".
Selective reporting (reporting bias)	High risk	Judgement Comment: 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	Judgement Comment: Sponsored by Upjohn Company, Kalamazoo, Michigan; the role of the funder in planning, conducting and writing the study is not discussed.

DeLeo 1989

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● Diagnosis: Adjustment disorder with depressed mood or with mixed emotional features (DSM-III) ● *Age in years, mean (SD)*: 38.3 ● *Females n/N (%)*: 51/85 (60%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: No information ● *Patients receiving other pharmacological treatment*: No information **Included criteria:** Adjustment disorder **Excluded criteria:** No specific exclusion cirteria stated.
Interventions	**Intervention Characteristics** Antidepressiva (Viloxazine) ● *Decsription*: Viloxazine ● *Dose*: Viloxazine 200 mg/dag orally ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Lormetazepam ● *Decsription*: Lormetazepam ● *Dose*: Lormetazepam 2 mg/dag ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: S-adenosylmetioine ● *Decsription*: ● *Dose*: 100 mg/day intramusculary ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Psychotherapy ● *Decsription*: Psychotherapy psycho analytically oriented ● *Dose*: ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*:

	Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*:
Outcomes	No relevant outcomes reported for our interventions of interest
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Italy **Setting:** Outpatients **Authors name:** Diego De Leo **Institution:** University of Padura School of Medicine, department of Psychiatry **Email:** **Address:** University of Padura School of Medicine, department of Psychiatry, Via Giustiniani 2, 35128 Padua, italy **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: The study writes that each investigator was unaware of the aim of the study.Interventions are given in different ways (oral and intramuscularly) No information on blinding
Blinding of outcome assessment (detection bias)	High risk	Judgement Comment: The investigators don't seem to be blinded and neither the patients it may be supected that this could influence outcome.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No flowchart and no description of dropout
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No reference to a protocol, poorly reported. No usable data
Other bias	Unclear risk	Judgement Comment: CGI evel is measure in different ways between subjects. The study is poorly reported

DenBoer 1988

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Antidepressiva_tricyklisk (Maprotiline) ● Diagnosis: DSM-III panic disorder without phobic avoidance or panic disorder with severe phobic avoidance behaviour. ● *Age in years, mean (SD)*: 35.0 (SD = 7.4) ● *Females n/N (%)*: 20/24 (83%) ● *Duration of anxiety symptoms, years, mean (SD)*: Minimum 1 year, mean duration 9.25 years (SD = 5.8) ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: patients with major affective disorders, schizophrenia, other psychotic disorder or significant medical problems were excluded. ● *Patients receiving other pharmacological treatment*: No information Antidepressiva_tricyklisk (fluvoxamine) ● Diagnosis: DSM-III panic disorder without phobic avoidance or panic disorder with severe phobic avoidance behaviour. ● *Age in years, mean (SD)*: 37.3 (SD = 10.6) ● *Females n/N (%)*: 15/20 (75%) ● *Duration of anxiety symptoms, days, mean (SD)*: Minimum 1 year, mean duration 9.9 years (SD = 6.1) ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: patients with major affective disorders, schizophrenia, other psychotic disorder or significant medical problems were excluded. ● *Patients receiving other pharmacological treatment*: No information **Included criteria:** DSM-III panic disorder without phobic avoidance or panic disorder with severe phobic avoidance behaviour **Excluded criteria:** Patients with major affective disorders (score of 18 or more on Hamilton Rating Scale for Depression), schizophrenia, other psychotic disorder or significant medical problems on the basis of a complete medical evaluatiob, including routine haematological and biochemical laboratory tests were excluded.

Interventions	**Intervention Characteristics** Antidepressiva_tricyklisk (maprotiline) ● *Decsription*: Maprotiline ● *Dose*: Flexible dosage; range = 50 - 150 mg, M and SD not provided. ● *Duration*: 6 weeks ● *Time of short time follow-up*:1 week ● *Detailed description*: Wash out period of 2 weeks before randomisation. Medication was started with 50 mg daily and gradually increased in 2 weeks to 150 mg. Rescue medication: Not stated SSRI (fluvoxamine ● *Decsription*: Fluvoxamine ● *Dose*: Flexible dosage; range = 50 - 150 mg, M and SD not provided ● *Duration*: 6 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Wash out period of 2 weeks before randomisation. Medication was started with 50 mg daily and gradually increased in 2 weeks to 150 mg. Rescue medication: Not stated)
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** The Netherlands **Setting:** Outpatient clinic at the department of Biological Psychiatry of the University Hospital in Utrecth, The Netherlands. **Authors name:** Johan A. Den Boer **Institution:** Department of Biological Psychiatry of the University Hospital in Utrecth, The Netherlands. **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "they were randomly allocated". No further details.
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote "double-blind treatment". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote "double-blind treatment". No further details.
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: 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	Judgement Comment: Continuous outcome data are reported only in graphs.
Other bias	Unclear risk	Judgement Comment: Sponsorship bias cannot be ruled out.

DeWit 1999

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Antidepressiva (Trazodone) ● Diagnosis: HIV and fulfilment of DSM-III-R criteria for the diagnosis of adjustment disorders with anxiety or depressed mood and/or mixed disturbance of emotion and conduct ● *Age in years, median (range)*: Median age was 36.5 years for females (range: 29 - 44), and 27.5 years for males (range: 18 - 46) ● *Females n/N (%)*: 20% ● *Duration of anxiety symptoms, days, mean (SD)*: No information

	● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*:Patients with serious psychiatric disorders were excluded ● *Patients receiving other pharmacological treatment*:Patients taking psychotropic medications were excluded, although zolpidem use was permitted if dosage was constant 7 days prior to study entry. Benzodiazepin (Clorazepate) ● Diagnosis: HIV and fulfilment of DSM-III-R criteria for the diagnosis of adjustment disorders with anxiety or depressed mood and/or mixed disturbance of emotion and conduct ● *Age in years, meadian (range)*: Median age was 36.5 years for females (range: 29 - 44), and 27.5 years for males (range: 18 - 46) ● *Females n/N (%)*: 20% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with serious psychiatric disorders were excluded ● *Patients receiving other pharmacological treatment*: Patients taking psychotropic medications were excluded, although zolpidem use was permitted if dosage was constant 7 days prior to study entry. **Included criteria:** To be eligible, subjects had to meet the following inclusion criteria: age ≥ 18 years; life expectancy well exceeding the study duration; positive blood test for HIV; fulfilment of DSM-III-R criteria for the diagnosis of adjustment disorders with anxiety or depressed mood and/or mixed disturbance of emotion and conduct; and score > 14 on the French version of the Hospital Anxiety and Depression Scale (HADS). **Excluded criteria:** significant history of serious psychiatric disorders, such as major depressive disorder or panic disorder within 1 year prior to study entry; current significant suicide tendency or history of significant suicide attempt; alcohol or drug abuse; other major uncontrolled somatic comorbidities; and receipt of psychotropic medications, although zolpidem use was permitted if dosage was constant 7 days prior to study entry.
Interventions	**Intervention Characteristics** Antidepressiva (Trazodone) ● *Decsription*:Trazodone ● *Dose*: 50-150 mg The mean daily dosages of trazodone were 97.6 mg/day ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: The dosing schedule was one capsule (containing trazodone 50 mg) on Day 1 and Day 2 of treatment, two capsules on Day 3 and Day 4, and three capsules from Day 5 to Day 28. Capsules were taken orally once daily, either with an evening meal or at bedtime with a snack Benzodiazepin (Clorazepate) ● *Decsription*:Clorazepate ● *Dose*: 10-30 mg. The mean daily dosages of clorazepate were 15.6 mg/day ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: The dosing schedule was one capsule (containing clorazepate 10 mg,) on Day 1 and Day 2 of treatment, two capsules on Day 3 and Day 4, and three capsules from Day 5 to Day 28. Capsules were taken orally once daily, either with an evening meal or at bedtime with a snack.
Outcomes	No relevant outcomes reported for our interventions of interest
Notes	**Identification** **Sponsorship source:** Supported by Searle Continental Pharma, Inc., Brussels, Belgium **Country:** Belgium **Setting:** No information **Authors name:** De Wit **Institution:** **Email:** **Address:** **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At Visit 1 subjects were carefully examined and, after verification of inclusion and exclusion criteria, were randomized using a computer-generated list prepared prior to the start of the study."
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "This study was a single-centre, randomized, double-blind, parallel-group" Judgement Comment: The trial was described as double-blilnd, but no information on who was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: The trial was described as double-blilnd, but no information on who was blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "After 2 weeks, one subject receiving trazodone withdrew from the study owing to depression and sleepiness and another subject treated with clorazepate withdrew due to sleepiness, heavy head, vertigo and weakness. Two subjects withdrew due to treatment failure; one from each treatment group." Judgement Comment: Two were excluded form the analyses as they were lost to follow-up. No intention to treat analyses.

Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No reference to a protocol, Only some of our outcomes are reported in the trial.
Other bias	Low risk	Judgement Comment: The trial appears to be free from other sources of bias

EMEA - study 25, 2008

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (Lorazepam) ● Diagnosis: GAD DSM-IV criteria. ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: men and women, no further information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with major depressive disorder and other Axis-1 disorders were excluded. ● *Patients receiving other pharmacological treatment*: No information Pregabalin 150 mg ● Diagnosis: GAD DSM-IV criteria. ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*:men and women, no further information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with major depressive disorder and other Axis-1 disorders were excluded. ● *Patients receiving other pharmacological treatment*: No information Pregabalin 600 mg ● Diagnosis: GAD DSM-IV criteria. ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: men and women, no further information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with major depressive disorder and other Axis-1 disorders were excluded. ● *Patients receiving other pharmacological treatment*: No information Placebo ● Diagnosis: GAD DSM-IV criteria. ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: men and women, no further information ● *Duration of anxiety symptoms, days, mean (SD)*:No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with major depressive disorder and other Axis-1 disorders were excluded. ● *Patients receiving other pharmacological treatment*: No information **Included criteria:** GAD DSM-IV criteria. men and women aged > 18 years **Excluded criteria:** Patients with major depressive disorder and other Axis-1 disorders were excluded.
Interventions	**Intervention Characteristics** Benzodiazepin (Lorazepam) ● *Decsription*: Lorazepam ● *Dose*: 6 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Pregabalin 150 mg ● *Decsription*: Pregabalin 150 mg ● *Dose*: 150 mg given as three dived doses. ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Pregabalin 600 mg ● *Decsription*: Pregabalin 600 mg ● *Dose*: flexible doses, 600 mg given as three dived doses. ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Pregabalin started at 150 mg/day. Based on individual patient response and tolerability the dose may be increased to 300 mg a day after 1 week, and to 450 mg after 2 weeks og to 600 mg after 3 weeks Placebo ● *Decsription*: ● *Dose*: 4 weeks ● *Duration*: 4 weeks

	● *Time of short time follow-up*: ● *Detailed description*:
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed - abstinenssymptomer,* Physician withdrawal checklist (PWC) ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Physician withdrawal checklist (PWC) ● **Range**: ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** **Setting:** Outpatient **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	High risk	Adapted from Slee et al.

Feltner 2003

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (lorazepam) ● Diagnosis: DSM-IV criteria for diagnosis of GAD ● *Age in years, mean (SD)*: 39.2 (11.7) ● *Females n/N (%)*: 58.8 % ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if the suffered from any athoer axis I disorder except dyshyymia, simple phobia, social phobia, somatization disorder or a history of major depressive disorder (current major depressive episode was excluded). In addition, patients with severe personality disorder (antiscocial or borderline), drug or alchohol abuse/dependence (active within the preceding 6 months), and suicidal risk were excluded. In patients with comorbid psychiatric diagnosis GAD was required to be the primary diagnosis ● *Patients receiving other pharmacological treatment*: o psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). Pregabalin 150 mg ● Diagnosis: DSM-IV criteria for diagnosis of GAD ● *Age in years, mean (SD)*: 37.9 (10.9) ● *Females n/N (%)*: 51.4 % ● *Duration of anxiety symptoms, days, mean (SD)*:No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if the suffered from any athoer axis I disorder except

	dyshyymia, simple phobia, social phobia, somatization disorder or a history of major depressive disorder (current major depressive episode was excluded). In addition, patients with severe personality disorder (antiscocial or borderline), drug or alchohol abuse/dependence (active within the preceding 6 months), and suicidal risk were excluded. In patients with comorbid psychiatric diagnosis GAD was required to be the primary diagnosis ● *Patients receiving other pharmacological treatment*: Patients were required to be free of psychotropic medications for 2 weeks (5 for fluoxertine) prior to enrollment. No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). Pregabalin 600 mg ● Diagnosis: DSM-IV criteria for diagnosis of GAD ● *Age in years, mean (SD)*:36.3 (10.9) ● *Females n/N (%)*: 50 % ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if the suffered from any athoer axis I disorder except dyshyymia, simple phobia, social phobia, somatization disorder or a history of major depressive disorder (current major depressive episode was excluded). In addition, patients with severe personality disorder (antiscocial or borderline), drug or alchohol abuse/dependence (active within the preceding 6 months), and suicidal risk were excluded. In patients with comorbid psychiatric diagnosis GAD was required to be the primary diagnosis ● *Patients receiving other pharmacological treatment*: Patients were required to be free of psychotropic medications for 2 weeks (5 for fluoxertine) prior to enrollment. No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). Placebo ● Diagnosis: DSM-IV criteria for diagnosis of GAD ● *Age in years, mean (SD)*:37.8 (10.8) ● *Females n/N (%)*: 50,7 % ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if the suffered from any athoer axis I disorder except dyshyymia, simple phobia, social phobia, somatization disorder or a history of major depressive disorder (current major depressive episode was excluded). In addition, patients with severe personality disorder (antiscocial or borderline), drug or alchohol abuse/dependence (active within the preceding 6 months), and suicidal risk were excluded. In patients with comorbid psychiatric diagnosis GAD was required to be the primary diagnosis ● *Patients receiving other pharmacological treatment*: Patients were required to be free of psychotropic medications for 2 weeks (5 for fluoxertine) prior to enrollment. No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). **Included criteria:**DSM-IV criteria for diagnosis of GAD **Excluded criteria:** Patients were excluded if the suffered from any athoer axis I disorder except dyshyymia, simple phobia, social phobia, somatization disorder or a history of major depressive disorder (current major depressive episode was excluded). In addition, patients with severe personality disorder (antiscocial or borderline), drug or alchohol abuse/dependence (active within the preceding 6 months), and suicidal risk were excluded. In patients with comorbid psychiatric diagnosis GAD was required to be the primary diagnosis. Patients were required to be free of psychotropic medications for 2 weeks (5 for fluoxertine) prior to enrollment.
Interventions	**Intervention Characteristics** Benzodiazepin (lorazepam) ● *Decsription*: lorazepam 2 mg three times a day ● *Dose*: fixed dose 6 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1 week lead-in, neither study drug nor placebo was administered during the lead in phase. Study medication was titrated during the first 6 days of treatment, maintaining a constant number of capsules until the targed dose was reached. Rescue medication: No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). Pregabalin 150 mg ● *Decsription*: Pregabalin 50 mg three times a day ● *Dose*: fixed dose 150 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1 week lead-in, neither study drug nor placebo was administered during the lead in phase. Study medication was titrated during the first 6 days of treatment, maintaining a constant number of capsules until the targed dose was reached. Rescue medication: No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). Pregabalin 600 mg ● *Decsription*: Pregabalin 200 mg three times a day ● *Dose*: fixed dose 600 mg ● *Duration*:4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1 week lead-in, neither study drug nor placebo was administered during the lead in phase. Study medication was titrated during the first 6 days of treatment, maintaining a constant number of capsules until the targed dose was reached.

	Rescue medication: No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit). Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1 week lead-in, neither study drug nor placebo was administered during the lead in phase. Study medication was titrated during the first 6 days of treatment, maintaining a constant number of capsules until the targed dose was reached. Rescue medication: No psychotrofic medications were allowed during the study, with the exception of zolpiderm (5 mg, < 2 nights per week and not the night before a clinical visit).
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed - abstinenssymptomer,* Physician withdrawal checklist (PWC) ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Physician withdrawal checklist (PWC) ● **Range**: ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint Selvmordstanker/selvmordsforsøg ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Funded by Parke-Davis Pharmaceutical research, a division of the Warner-Lambert Company (now Pfiezer) **Country:** USA **Setting:** 4 outpatient centers. **Authors name:** Feltner **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Unclear risk	Adapted from Slee et al.

Khan 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Quetiapin ● Diagnosis: diagnosis of GAD ● *Age in years, mean (SD)*: 44.6 (12.1) ● *Females n/N (%)*: 146/204 (71.6%) ● *Duration of anxiety symptoms, years, mean (SD)*: 15.8 (13.0) ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with any DSM-IV Axis I disorder other than GAD within 6 months prior to enrollment; presence or history of schizophrenia or other psychotic disorders using DSM-IV criteria; any DSM-IV Axis II disorder likely to interfere with the patient's participation in the study; depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] total score > 16 at enrollment or randomization); current serious suicidal or homicidal risk, MADRS Item 10 score 4, or a suicide attempt during the 6 months prior to enrollment; substance or alcohol abuse within 6 months, were excluded. ● *Patients receiving other pharmacological treatment*: All patients received SSRI or SNRI. Chloral hydrate (1 g), zaleplon (20 mg), zolpidem tartrate (10 mg), or zopiclone (7.5 mg) were permitted twice weekly for insomnia up to Day 14 (except before study assessments). Other psychoactive medication was not permitted. Anticholinergics for extrapyramidal symptoms (EPS) were permitted, but were not permitted for prophylactic use. Placebo ● Diagnosis: diagnosis of GAD ● *Age in years, mean (SD)*: 44.2 (10.9) ● *Females n/N (%)*: 150/ 198 (75.8%) ● *Duration of anxiety symptoms, years, mean (SD)*: 15.0 (12.7) ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with any DSM-IV Axis I disorder other than GAD within 6 months prior to enrollment; presence or history of schizophrenia or other psychotic disorders using DSM-IV criteria; any DSM-IV Axis II disorder likely to interfere with the patient's participation in the study; depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] total score > 16 at enrollment or randomization); current serious suicidal or homicidal risk, MADRS Item 10 score 4, or a suicide attempt during the 6 months prior to enrollment; substance or alcohol abuse within 6 months, were excluded. ● *Patients receiving other pharmacological treatment*: All patients received SSRI or SNRI. Chloral hydrate (1 g), zaleplon (20 mg), zolpidem tartrate (10 mg), or zopiclone (7.5 mg) were permitted twice weekly for insomnia up to Day 14 (except before study assessments). Other psychoactive medication was not permitted. Anticholinergics for extrapyramidal symptoms (EPS) were permitted, but were not permitted for prophylactic use. **Included criteria:** Male or female outpatients (aged 18–65 years) with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of GAD as assessed by the Mini International Neuropsychiatric Interview were eligible for inclusion in the study. Patients were required to have a Hamilton Rating Scale for Anxiety (HAM-A) total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores 2 at enrollment, placebo run-in and randomization, and a Clinical Global Impressions-Severity of Illness (CGI-S) score ≥ 4 at enrollment and randomization. During the current anxious episode, patients were required to have a history of partial or no (inadequate) response to duloxetine, escitalopram, paroxetine, or venlafaxine XR. Partial or no (inadequate) response was defined as continuing symptoms following ≥ 8 weeks of therapy prior to enrollment at adequate doses (minimum effective dose according to US label and including ≥ 1 dose increase as permitted by US label). **Excluded criteria:** any DSM-IV Axis I disorder other than GAD within 6 months prior to enrollment; presence or history of schizophrenia or other psychotic disorders using DSM-IV criteria; any DSM-IV Axis II disorder likely to interfere with the patient's participation in the study; depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] total score > 16 at enrollment or randomization); current serious suicidal or homicidal risk, MADRS Item 10 score 4, or a suicide attempt during the 6 months prior to enrollment; substance or alcohol abuse within 6 months prior to enrollment; evidence of clinically relevant disease; clinically significant deviation from reference range in clinical laboratory results. Patients could not have received an antipsychotic, antidepressant (except those listed above), or benzodiazepine (unless ongoing at a stable dose for ≥ 4 weeks prior to enrollment) within 7 days of randomization; mood stabilizers or monoamine oxidase inhibitors within 14 days prior to randomization; or fluoxetine within 28 days. Patients were permitted to continue receiving psychotherapy if it had been ongoing for ≥ 3 months prior to randomization.

Interventions	**Intervention Characteristics** Quetiapin ● *Decsription*: quetiapine XR + SSRI/SNRI ● *Dose: Flexible doses 50-300 mg* ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: one week single blind placebo run in period. Quetiapine XR or placebo was administered orally, once-daily in the evening. Quetiapine XR was initiated at 50 mg/day, with the dose increased to 150 mg/day on Day 3. At Weeks 3 or 4 a mandatory dose increase to 300 mg/day was made in patients with a CGI-S score 4 who tolerated the 150 mg/day dose. No dose increases were permitted after Week 4. Patients unable to tolerate the higher dose returned to 150 mg/day at anytime at the investigator's discretion. Patients continued to receive the same SSRI or SNRI at the same dose as at enrollment throughout the study. Chloral hydrate (1 g), zaleplon (20 mg), zolpidem tartrate (10 mg), or zopiclone (7.5 mg) were permitted twice weekly for insomnia up to Day 14 (except before study assessments). Other psychoactive medication was not permitted. Anticholinergics for extrapyramidal symptoms (EPS) were permitted, but were not permitted for prophylactic use. Placebo ● *Decsription*: placebo + SSRI/SNR ● *Dose*: ● *Duration*: 8 weeks ● *Time of short time follow-up*:1 week ● *Detailed description*: Placebo run-in for 1 week. Placebo tablets were identical in size, color, smell, and taste to quetiapine XR 50 mg or 300 mg tablets and packaging was identical Chloral hydrate (1 g), zaleplon (20 mg), zolpidem tartrate (10 mg), or zopiclone (7.5 mg) were permitted twice weekly for insomnia up to Day 14 (except before study assessments). Other psychoactive medication was not permitted. Anticholinergics for extrapyramidal symptoms (EPS) were permitted, but were not permitted for prophylactic use.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint Selvmordstanker/selvmordsforsøg ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed_abstinenssymptomer* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale:** Treatment discontinuation signs and symptoms ● **Unit of measure**: Points ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Funded by AstraZeneca Pharmaceuticals **Country:** USA **Setting:** Outpatients **Authors name:** **Institution:** **Email:**

	Address: **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "multicenter, randomized, double-blind, paral- lel-group, placebo-controlled study" Quote: "Following placebo run-in, patients were randomized (1:1 ratio using a computer-based system to generate the randomization list)"
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This was an 11-week, multicenter, randomized, double-blind, paral- lel-group, placebo-controlled study (D1441L00016; Palladium; NCT00534599). Eligible patients entered a 1-week single-blind placebo run-in period, followed by an 8-week randomized active treat- ment phase and a 2-week post-treatment period" Judgement Comment: Placebo tablets were identical in size, color, smell, and taste to quetiapine XR 50 mg or 300 mg tablets and packaging was identical.Quetiapine XR or placebo was administered orally, once-daily in the evening. The trial was described as double-blind and placebocontrolled, patients and personel were blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: The trial was described as double-blind and placebocontrolled, presume patients and personel were blinded. No information on blinding of outcome assessors
Incomplete outcome data (attrition bias)	High risk	Quote: "Efficacy analyses used the modified intention-to-treat (MITT) popu- lation (randomized patients who received study drug, and had random- ization and 1 post-randomization HAM-A total score)." Judgement Comment: 32/200 falder fra i kontrolgruppen, 57/209 i quetiapingruppen. Langt flere falder fra pgs. bivirkninger i quetiapingruppen 25 vs 4. Ingen reel ITT analyse. MITT analysen omfatter patienter der har modtaget behandling og har mindst total score på HAM.A post randomisering. imputation med LOCF. Unbalanced reasons for dropout Unbalanced reasons for dropout
Selective reporting (reporting bias)	Low risk	Judgement Comment: Protocol available: https://clinicaltrials.gov/ct2/show/NCT00534599Consistency between protocol and reported outcomes Outcome are reported in accordance with trial registration
Other bias	Low risk	Judgement Comment: The trial appears to be free from other sources of bias

Kruger 1999

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** MAO (moclobemide) ● Diagnosis: DSM - III - R panic disorder with or without agoraphobia ● *Age in years, mean (SD)*: M = 35.0 (SD = 8.9) ● *Females n/N (%)*: 58.2% ● *Duration of anxiety symptoms, present episode, months, mean (SD)*: 23.9 (36.1) ● *Outpatient (%)*: Setting unclear ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: comorbid mental disorder 23.9 % ● *Patients receiving other pharmacological treatment*: No other psychoactive substances were permitted other than chloral hydrate as an occasional night time hypnotic. Anitdepressiva_tricyklisk (clomipramine) ● Diagnosis: DSM - III - R panic disorder with or without agoraphobia ● *Age in years, mean (SD)*: M = 36.0 (SD = 9.5) ● *Females n/N (%)*: 60.3% ● *Duration of anxiety symptoms, present episode, months, mean (SD)*:21.8 (30.1) ● *Outpatient (%)*: Setting unclear ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: comorbid mental disorder 29.4 % ● *Patients receiving other pharmacological treatment*: No other psychoactive substances were permitted other than chloral hydrate as an occasional night time hypnotic. **Included criteria:** Patients aged 18 to 65 years. Currently active panic disorder with or without agoraphobia were enrolled. DSM - III panic disorder with or without agoraphobia. at least 1 panic attack per week in each of the 4 weeks preceding the baseline evaluation. **Excluded criteria:** Patients with organic medtal disorders, dementia, mental retardation, suicidality, schizophrenia, other psychotic disorders and bipolar I and II disorders were excluded. Patients with comorbid (within the past 6 months) obsessive compilsive disorderm major depressive episode, and psychoactive substance use disorders were also excluded. Patients with comorbid generalized anxiety disorders and social phobia of less than moderate severity were included.
Interventions	**Intervention Characteristics** Anitdepressiva_tricyklisk (clomipramine) ● *Decsription*: clomipramine ● *Dose*: fixed-flexible dosage, range = 100 - 200 mg, M and SD not provided ● *Duration*: 8 weeks

	● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week single blind placebo run in period. Patients got the target doses considered effective in the treatment of panic disorders, clomipramine 150 mg day. After 4 weeks of active treatment, there was an option to increase the dose to 200 mg. During the first 4 weeks the dose could be reduced to 100 mg if the patient did not tolerate the dose due to severe side effects. No other changes were permitted. Rescue medication: chloral hydrate as an occasional night time hypnotic MAO (moclobemide) ● *Decsription*: moclobemide ● *Dose*: fixed-flexible dosage, range = 300 - 600 mg, M and SD not provided ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week single blind placebo run in period. Patients got the target doses considered effective in the treatment of panic disorders, moclobemide 450 mg day. After 4 weeks of active treatment, there was an option to increase the dose to 600 mg. During the first 4 weeks the dose could be reduced to 300 mg if the patient did not tolerate the dose due to severe side effects. No other changes were permitted. Rescue medication: chloral hydrate as an occasional night time hypnotic
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Hoffmann - La Roche **Country:** Norway, Sweden, the Netherlands **Setting**: 12 centers in Norway, Sweden, the Netherlands; setting unclear **Authors name:** Krueger **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 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	Judgement Comment: All outcomes were reported.
Other bias	High risk	Judgement Comment: Sponsored by Hoffmann-La Roche; the role of the funder in planning, conducting and writing the study is not discussed.

Lepola 1990

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● Diagnosis: DMS-III panic disorder with or without agoraphobia ● *Age in years, mean (SD)*: M = 37.4, SD not provided ● *Females n/N (%)*: Sex not stated ● *Duration of anxiety symptoms, years, mean (SD)*: at least 3 months. mean 6.4 years. ● *Outpatient (%)*: 0% ● *Non pharmacological treatment considered or tried (%)*: No information

	● *Patients with co-morbidity (%)*: None of the patients suffered from any neurological or other psychiatric disorder. ● *Patients receiving other pharmacological treatment*: The patients did not receive any other treatment during the trial period. **Included criteria:** DMS-III panic disorder with or without agoraphobia. None of the patients suffered from any neurological or other psychiatric disorder. **Excluded criteria:** No specific exclusion cirteria stated.
Interventions	**Intervention Characteristics** Benzodiazepin (alpraxolam) ● *Decsription*: alpraxolam ● *Dose*: flexible dosage, range = 1.5 - 8 mg, M = 4.9, SD not provided ● *Duration*: 9 weeks ● *Time of short time follow-up*: 3 weeks ● *Detailed description*: Rescue medication: "the patients did not receive any other treatment during the trial period" Antidepressiva_tricyklisk (imipramine) ● *Decsription*: imipramine ● *Dose*: flexible dosage, range = 30 - 225 mg, M = 130, SD not provided ● *Duration*: 9 weeks ● *Time of short time follow-up*: 3 weeks ● *Detailed description*: Rescue medication: "the patients did not receive any other treatment during the trial period"
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:**: Finland **Setting:** Inpatients **Authors name:** Lepola **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No information provided about management of incomplete outcome data.
Selective reporting (reporting bias)	Low risk	Judgement Comment: All relevant outcomes were reported.
Other bias	Unclear risk	Judgement Comment: All relevant outcomes were reported.

Li 2016

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Quetiapin ● Diagnosis: DSM-IV criteria major for major depression disorder and GAD ● *Age in years, mean (SD)*: 48.7 (8.92) ● *Females n/N (%)*: 72.73% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information

	● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: major depression disorder was an inclusion criteria ● *Patients receiving other pharmacological treatment*: Rescue medication for sleep such as Zopidem (Ambien 5–10 mg/d or Ambien-CR 6.25–12.5 mg/d) was permitted during the washout period and the double-blinded phase. Except for the aforementioned antidepressant(s), no other medication was allowed. With the exception of antidepressants including selective serotonin re-uptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitor (SSNIs), all other medications were discontinued at least 5 half-lives prior to randomization. The permitted medication(s) was maintained at a stable dose for a minimal 2 week period. Placebo ● Diagnosis: DSM-IV criteria major for major depression disorder and GAD ● *Age in years, mean (SD)*: 52.7 (14.81) ● *Females n/N (%)*: 75 % ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*:No information ● *Patients with co-morbidity (%)*: major depression disorder was an inclusion criteria ● *Patients receiving other pharmacological treatment*: Rescue medication for sleep such as Zopidem (Ambien 5–10 mg/d or Ambien-CR 6.25–12.5 mg/d) was permitted during the washout period and the double-blinded phase. Except for the aforementioned antidepressant(s), no other medication was allowed. With the exception of antidepressants including selective serotonin re-uptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitor (SSNIs), all other medications were discontinued at least 5 half-lives prior to randomization. The permitted medication(s) was maintained at a stable dose for a minimal 2 week period. **Included criteria:** Males and females from 18 to 65 years old who met DSM-IV criteria for major depression disorder, currently depressed with Hamilton Depression Rating Scale-17 items (HAMD-17) total score ≥ 18 at screening and baseline visits, and a current history of GAD with a Hamilton Anxiety Rating Scale (HAM-A) total score ≥ 18 at screening and baseline visits were eligible. In addition, patients were required to be in good physical health. **Excluded criteria:** Patients were excluded if they had: 1) Severe medical or neurological problems; 2) Severe personality disorder; 3) Current suicidal risk judged by a physician; 4) Known history of intolerance or hypersensitivity to any of the medications involved in the study; 5) Treatment with quetiapine ≥ 100 mg/day in the 6 months prior to randomization; 6) Known lack of response to quetiapine in a dosage of ≥ 100 mg/day for 4 weeks at any time, as judged by the investigator; 7) DSM-IV criteria for substance use disorder confirmed by the Substance Use Disorder Module of the Structured Clinical Interview for DSM-IV (SCID), for any substance except for caffeine and nicotine, with substance abuse within last 30 days or substance dependence within last 90 days; 8) Concurrent obsessive compulsive disorder; 9) Use of any cytochrome P450 3A4 inhibitors or cytochrome P450 inducers in 14 days; 10) Unable to wean off benzodiazepines or other unpermitted medication; 12) Female patients who were pregnant, planning to be pregnant or breastfeeding.
Interventions	**Intervention Characteristics** Quetiapin ● *Decsription*: quetiapin ● *Dose*: flexible doses between 150 and 300 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The study medications were started at 50 mg for day 1 and day 2, increased to 150 mg at day 3 and day 4, and finally increased to 300 mg/d at day 5 and onward. For those who could not tolerate 300 mg/d, a 50 mg decrement per week was allowed to a minimum of 150 mg/d. For those who could not tolerate 150 mg/d, they were discontinued from the study. Rescue medication for sleep such as Zopidem (Ambien 5–10 mg/d or Ambien-CR 6.25–12.5 mg/d) was permitted during the washout period and the double-blinded phase. Except for the aforementioned antidepressant(s), no other medication was allowed. Placebo ● *Decsription*: ● *Dose*: ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Rescue medication for sleep such as Zopidem (Ambien 5–10 mg/d or Ambien-CR 6.25–12.5 mg/d) was permitted during the washout period and the double-blinded phase. Except for the aforementioned antidepressant(s), no other medication was allowed.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirknigner, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter*

	● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** This study was supported by AstraZeneca Pharmaceutical Company via an Investigator Initiated study. **Country:** USA **Setting:** The study was conducted in the Mood and Anxiety Clinic within the Mood Disorders Program at Case Western Reserve University/ University Hospitals Case Medical Center, Cleveland, Ohio. **Authors name:** Li **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Random assignment to each arm was balanced for gender, male ver- sus female." Judgement Comment: No information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This study was a randomized, double-blind, 8-week comparison of quetiapine-XR monotherapy or adjunctive therapy to antidepressant(s) versus placebo monotherapy or adjunctive therapy to antidepressant(s)" Judgement Comment: The trial was described as double-blinded, presume patients and personel were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: The trial was described as double-blinded, presume patients and personel were blinded. No information on blinding of outcome assessor
Incomplete outcome data (attrition bias)	High risk	Quote: "There were 34 patients screened, 23 were randomized, and 9 patients completed the 8-week study with 5 in quetiapine-XR group and 4 in placebo group, respectively (Figure 1)." Judgement Comment: over 50% with missing data, ITT analyses but no information on how missing data were imputed Unbalanced reason for dropout. They do however conduct ITT analysis.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available, reports on the outcome stated in the method section
Other bias	Unclear risk	Judgement Comment: Pilot study with very few participants. May have power problems. The trial appears to be free from other sources of bias

Liebowitz 1992

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** MAO (Phenelzine) ● Diagnosis: Social phobia DSM-III criteria ● *Age in years, mean (SD)*: 33.7 (9.0) ● *Females n/N (%)*: 68% ● *Duration of anxiety symptoms, years, mean (SD)*: 16.9 (10.4) ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Medically healthy, free of current major depression or substance abuse and had no history of schizophrenia, organicity or bipolar disorder. ● *Patients receiving other pharmacological treatment*: No other psychotropic medications were permitted. Betablokker (Atenolol) ● Diagnosis: Social phobia DSM-III criteria ● *Age in years, mean (SD)*: 34.5 (9.6) ● *Females n/N (%)*: 65% ● *Duration of anxiety symptoms, years, mean (SD)*:11.3 (9.0)

	● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Medically healthy, free of current major depression or substance abuse and had no history of schizophrenia, organicity or bipolar disorder. ● *Patients receiving other pharmacological treatment*: No other psychotropic medications were permitted. Placebo ● Diagnosis: Social phobia DSM-III criteria ● *Age in years, mean (SD)*: 34.8 (7.3) ● *Females n/N (%)*: 73% ● *Duration of anxiety symptoms, years, mean (SD)*: 16.7 (10.6) ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Medically healthy, free of current major depression or substance abuse and had no history of schizophrenia, organicity or bipolar disorder. ● *Patients receiving other pharmacological treatment*: No other psychotropic medications were permitted. **Included criteria:** Social phobia DSM-III criteria. aged 18-50 years, medically healthy, free of current major depression or substance abuse and had no history of schizophrenia, organicity or bipolar disorder. **Excluded criteria:** Se inclusion
Interventions	**Intervention Characteristics** MAO (Phenelzine) ● *Decsription*: Phenelzine ● *Dose*: 15-90 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week placebo run in period.Treatment begun at 15 mg/day increased to 30 mg/day on day 4, to 45 mg on day 8, and to 60 mg on day 15. After 4 weeks, depending on clinical state and side effects, the dose could be optionally raised to 75 mg/day, and to 90 mg/day after 5 weeks. No other psychotropic medications were permitted. Betablokker (Atenolol) ● *Decsription*: Atenolol ● *Dose*: 50-100 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week placebo run in period. Treatment begun at 50 mg/day given in themorning and raised to 100 mg/day if tolerated, after 2 weeks. No other psychotropic medications were permitted. Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week placebo run in period. No other psychotropic medications were permitted.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Parke-Davis Phamaceutical Co now Pfeizer (phelenzine) and Stuart Pharmaceuticals (atenolol) supplied for medication. **Country:** **Setting:** Outpatients **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D J, Ipser, J. Pharmacological treatments for social anxiety disorder in adults: a systematic review and network meta-analysis. Acta neuropsychiatrica 2020;32(4):169-176

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Williams et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Williams et al.
Blinding of participants and personnel (performance bias)	Unclear risk	Adapted from Williams et al.

Blinding of outcome assessment (detection bias)	Unclear risk	Adapted from Williams et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Williams et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Williams et al.
Other bias	Unclear risk	Adapted from Williams et al.

Llorca 2002

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (bromazepam) ● Diagnosis: diagnosis of GAD according to DSM-IV criteria ● *Age in years, mean (SD)*: 44.9 (11.5) ● *Females n/N (%)*:79/116 (68%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with Known alcohol or drug dependence, major depressive episode within the preceding 6 months, a score ≥ 7 on the Raskin Severity of Depression and Mania Scale, psychotic or delusional disorders within the preceding 3 years, concomitant chronic disseases were excluded. ● *Patients receiving other pharmacological treatment*: Psychotropic drugs were not allowed during the study. Antihistamin (hydroxyzine) ● Diagnosis: diagnosis of GAD according to DSM-IV criteria ● *Age in years, mean (SD)*: 43.6 (11.7) ● *Females n/N (%)*:74/105 (70.5%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with Known alcohol or drug dependence, major depressive episode within the preceding 6 months, a score ≥ 7 on the Raskin Severity of Depression and Mania Scale, psychotic or delusional disorders within the preceding 3 years, concomitant chronic disseases were excluded. ● *Patients receiving other pharmacological treatment*: Psychotropic drugs were not allowed during the study. Placebo ● Diagnosis: diagnosis of GAD according to DSM-IV criteria ● *Age in years, mean (SD)*: 41.5 (11.9) ● *Females n/N (%)*: 75/ 113 (66,4 %) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with Known alcohol or drug dependence, major depressive episode within the preceding 6 months, a score ≥ 7 on the Raskin Severity of Depression and Mania Scale, psychotic or delusional disorders within the preceding 3 years, concomitant chronic disseases were excluded. ● *Patients receiving other pharmacological treatment*: Psychotropic drugs were not allowed during the study. **Included criteria:** Criteria for the run-in period: between 18 and 65 years, diagnosis of GAD according to DSM-IV criteria, HAM-A score ≥ 20. Criteria for the 12 wweks treatment periode:HAM-A difference ≤ 7, HAM-A score ≥ 20, satisfactory treetment compliance during the run-in period. **Excluded criteria:** Known alcohol or drug dependence, major depressive episode within the preceding 6 months, a score≥ 7 on the Raskin Severity of Depression and Mania Scale, psychotic or delusional disorders within the preceding 3 years, concomitant chronic disseases. Treatment with antidepressants, neuroleptics, mood regulators, morphine or derivatesm hydroxyzine or bromazepam within the preceding 4 weeks, treatment with benzodiazepines > 2 days per week during the previous 30 days or benzodiazepines intake during the previous 2 weeks, and need for psychotherapy unless psychotherapy was conducted on a continunous basis for at least 6 months. Psychotropic drugs or other treatments likely to impact the central nervous system or non pharmacologicaal treatments, such as psychotherapy or accupuncture, were not allowed during the study.
Interventions	**Intervention Characteristics** Benzodiazepin (bromazepam) ● *Decsription*: bromazepam 6 mg ● *Dose*: fixed doses, 6 mg ● *Duration*: 12 weeks ● Time of short time follow-up: 3 weeks ● Detailed description: 2 weeks of single-blind placebo run-in and 12 weeks of double-blind treatment. Daily medication was given as oral capsules in 3 divied doses (t.i.d.). During the doubled blind period of the study the daily dose of bromazepam was 6 mg (1,5 mg in the morning and at noon and 3 mg in the evening) Antihistamin (Hydroxyzine) ● Decsription: Hydroxyzine 50 mg ● Dose:fixed doses, 50 mg ● Duration: 12 weeks ● Time of short time follow-up: 3 weeks ● Detailed description: 2 weeks of single-blind placebo run-in and 12 weeks of double-blind treatment. Daily medication was given as oral capsules in 3 divied doses (t.i.d.). During the doubled blind period of the study the daily

	dose of hydroxyzine was 50 mg (12,5 mg in the morning and at noon and 25 mg in the evening) Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 12 weeks ● *Time of short time follow-up*: 3 weeks ● *Detailed description:* 2 weeks of single-blind placebo run-in and 12 weeks of double-blind treatment. Daily placebo was given as oral capsules in 3 divied doses *(t.i.d.).*
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** UCB-pharma **Country:** France **Setting** Outpatients **Authors name: Llorca** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Unclear risk	Adapted from Slee et al.

Merideth 2012

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Quetiapin 150 mg ● Diagnosis: DSM-IV-TR diagnosis of GAD ● *Age in years, mean (SD)*: 38.2 (11.5) ● *Females n/N (%)*: 143 (68%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded from the study if they had been diagnosed with a DSM-IV-TR axis I disorder other than GAD within 6 months before enrollment, if they had either the presence or a history of schizophrenia or other psychotic disorders according to DSM-IV-TR, or if they had any DSM-IV-TR axis II disorder that was likely to interfere with their ability to participate in the study. Additional exclusion criteria included

substance/alcohol abuse or dependence, as defined by the DSM-IV-TR criteria, within 6 months before enrollmen
- *Patients receiving other pharmacological treatment*: The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically.

Quetiapin 300 mg
- Diagnosis: DSM-IV-TR diagnosis of GAD
- *Age in years, mean (SD)*: 39.0 (12.6)
- *Females n/N (%)*: 143 (71%)
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: Patients were excluded from the study if they had been diagnosed with a DSM-IV-TR axis I disorder other than GAD within 6 months before enrollment, if they had either the presence or a history of schizophrenia or other psychotic disorders according to DSM-IV-TR, or if they had any DSM-IV-TR axis II disorder that was likely to interfere with their ability to participate in the study. Additional exclusion criteria included substance/alcohol abuse or dependence, as defined by the DSM-IV-TR criteria, within 6 months before enrollmen
- *Patients receiving other pharmacological treatment*: The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically.

SSRI (escitalopram)
- Diagnosis: DSM-IV-TR diagnosis of GAD
- *Age in years, mean (SD)*: 40.4 (11.6)
- *Females n/N (%)*: 133 (66%)
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: Patients were excluded from the study if they had been diagnosed with a DSM-IV-TR axis I disorder other than GAD within 6 months before enrollment, if they had either the presence or a history of schizophrenia or other psychotic disorders according to DSM-IV-TR, or if they had any DSM-IV-TR axis II disorder that was likely to interfere with their ability to participate in the study. Additional exclusion criteria included substance/alcohol abuse or dependence, as defined by the DSM-IV-TR criteria, within 6 months before enrollmen
- *Patients receiving other pharmacological treatment*: The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically.

Placebo
- Diagnosis:DSM-IV-TR diagnosis of GAD
- *Age in years, mean (SD)*: 36.6 (12.3)
- *Females n/N (%)*: 135 (64%)
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: Patients were excluded from the study if they had been diagnosed with a DSM-IV-TR axis I disorder other than GAD within 6 months before enrollment, if they had either the presence or a history of schizophrenia or other psychotic disorders according to DSM-IV-TR, or if they had any DSM-IV-TR axis II disorder that was likely to interfere with their ability to participate in the study. Additional exclusion criteria included substance/alcohol abuse or dependence, as defined by the DSM-IV-TR criteria, within 6 months before enrollmen
- *Patients receiving other pharmacological treatment*: The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically.

Included criteria: Male or female outpatients aged 18–65 years, with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of GAD (300.02) were eligible for inclusion in the study. Patients were required to have a Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) total score of 20 or more, HAMA item 1 (anxious mood) and item 2 (tension) scores of 2 or more, Montgomery-A˚sberg Depression Rating Scale (MADRS; Montgomery and A˚sberg, 1979) total score of 16 or less, and Clinical Global Impressions (CGI) - Severity of illness (CGI-S; National Institutes of Mental Health, 1970) score of 4 or more at enrollment and randomization
Excluded criteria: Patients were excluded from the study if they had been diagnosed with a DSM-IV-TR axis I disorder other than GAD within 6 months before enrollment, if they had either the presence or a history of schizophrenia or other psychotic disorders according to DSM-IV-TR, or if they had any DSM-IV-TR axis II disorder that was likely to interfere with their ability to participate in the study. Additional exclusion criteria included substance/alcohol abuse or dependence, as defined by the DSM-IV-TR criteria, within 6 months before enrollment, any clinically relevant disease (including renal or hepatic impairment, significant coronary artery disease or cerebrovascular disease); or clinically significant deviation from the reference range in laboratory test results at enrollment. Patients who posed a serious suicidal or homicidal risk, or had a MADRS item 10 score of 4 or more, or had made a suicide attempt during the 6 months before enrollment were also excluded

Interventions	**Intervention Characteristics** Quetiapin 150 mg ● *Decsription*: Quetiapine XR 150 mg ● *Dose*: Quetiapine XR 150 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The study consisted of three defined treatment periods: a washout period of 28 days or less, in which earlier psychotropic medications were withdrawn, a randomly assigned 8-week active treatment phase, followed by a 2-week follow-up period, in which discontinuation symptoms were assessed. Quetiapine XR treatment was initiated at 50 mg/day on days 1 and 2 of the randomized treatment period, and increased to 150 mg/day on days 3 and 4. All study medication was administered orally, once daily, in the evening. The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically. Quetiapin 300 mg ● *Decsription*: Quetiapine XR 300 mg ● *Dose*: Quetiapine XR 300 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The study consisted of three defined treatment periods: a washout period of 28 days or less, in which earlier psychotropic medications were withdrawn, a randomly assigned 8-week active treatment phase, followed by a 2-week follow-up period, in which discontinuation symptoms were assessed. Quetiapine XR treatment was initiated at 50 mg/day on days 1 and 2 of the randomized treatment period, and increased to 150 mg/day on days 3 and 4; patients randomized to the 300 mg/day group had their dose increased to 300 mg/day on day 5. All study medication was administered orally, once daily, in the evening. The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically. SSRI Escitalopram ● *Decsription*: Escitalopram 10 mg ● *Dose*: Escitalopram 10 mg ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The study consisted of three defined treatment periods: a washout period of 28 days or less, in which earlier psychotropic medications were withdrawn, a randomly assigned 8-week active treatment phase, followed by a 2-week follow-up period, in which discontinuation symptoms were assessed. Escitalopram was administered at 10 mg/day from day 1 to day 56. All study medication was administered orally, once daily, in the evening. The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically. Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The study consisted of three defined treatment periods: a washout period of 28 days or less, in which earlier psychotropic medications were withdrawn, a randomly assigned 8-week active treatment phase, followed by a 2-week follow-up period, in which discontinuation symptoms were assessed. To ensure blinding, packaging was identical for all treatments. Placebo tablets/capsules were identical in size, color, smell, and taste to their respective active treatment (quetiapine XR or escitalopram) tablets/capsules. All study medication was administered orally, once daily, in the evening. The use of other psychoactive medications was not permitted during the study, except medications for insomnia. The following medications were permitted twice weekly up to week 2, but not on the night before study assessments: zolpidem tartrate of 10 mg; chloral hydrate of 1 g; zaleplon of 20 mg; and zopiclone of 7.5 mg. During the randomized treatment period, anticholinergic medication was permitted for extrapyramidal symptoms (EPS) but was not given prophylactically.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint

	Afhængighed_abstinenssymptomer ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale:** Treatment discontinuation signs and symptoms (TDSS) ● **Unit of measure**: Points ● **Direction**: Lower is better ● **Data value**: Endpoint Vægtændring, antal patienter ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Number of patients with over 7% increase in body weight ● **Direction**: Lower is better ● **Data value**: Endpoint Ekstrapyramidale bivirkninger, antal patienter ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** This study (Gold; D1448C00010; Clinical Trials Registry NCT00329446) was sponsored by AstraZeneca. The authors thank Robin McCoy RN and Jeris Minor BA from AstraZeneca for their valuable contribution to the conduct of the study and Gail Gilmour PhD, from Complete Medical Communications, who provided medical writing support funded by AstraZeneca. **Country:** 64 centers in the United States. **Setting:** Outpatients **Authors name:** Meridith **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Low risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Low risk	Adapted from Slee et al.

Michelson 2013

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (lorazepam) ● Diagnosis: DSM-IV criteria for generalized anxiety disorder ● *Age in years, mean (SD)*: 36.4 (10.8) ● *Females n/N (%)*: 39 (56.5%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information

- *Outpatient (%)*: No information
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: patients were required to have a Raskin Depression Scale (Raskin et al. 1969) score ≤ 8
- *Patients receiving other pharmacological treatment*: Patients could not be taking any of the following therapies: fluoxetine or investigational compounds within 4 wk of randomization; long-acting benzodiazepines or monoamine oxidase inhibitors within 2 wk of randomization; short-acting benzodiazepines or other psychotropic drugs within 1 wk of randomization

L-759274

- Diagnosis: DSM-IV criteria for generalized anxiety disorder
- *Age in years, mean (SD)*: 38.3 (10.5)
- *Females n/N (%)*: 30 (41.1%)
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*:
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: patients were required to have a Raskin Depression Scale (Raskin et al. 1969) score ≤ 8
- *Patients receiving other pharmacological treatment*: Patients could not be taking any of the following therapies: fluoxetine or investigational compounds within 4 wk of randomization; long-acting benzodiazepines or monoamine oxidase inhibitors within 2 wk of randomization; short-acting benzodiazepines or other psychotropic drugs within 1 wk of randomization

Placebo

- Diagnosis: DSM-IV criteria for generalized anxiety disorder
- *Age in years, mean (SD)*: 41.3 (11.4)
- *Females n/N (%)*: 40 (56.3%)
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: No information
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: patients were required to have a Raskin Depression Scale (Raskin et al. 1969) score ≤ 8
- *Patients receiving other pharmacological treatment*: Patients could not be taking any of the following therapies: fluoxetine or investigational compounds within 4 wk of randomization; long-acting benzodiazepines or monoamine oxidase inhibitors within 2 wk of randomization; short-acting benzodiazepines or other psychotropic drugs within 1 wk of randomization

Included criteria: Patients were men and women, aged 18–60 yr, who met DSM-IV criteria for generalized anxiety disorder (APA, 1994) based on a clinical interview by a physician, and who had a Hamilton Anxiety Scale (HAMA; Hamilton, 1959) total score ≥ 20, with scores ≥ 2 on both the anxious mood and tension items (items 1 and 2) at their initial visit. In addition, patients were required to have a Raskin Depression Scale (Raskin et al. 1969) score ≤ 8 and no single item >3 at the initial visit, as well as a Covi Anxiety Scale (Lipman, 1982) score greater than the Raskin Depression Scale score.
Excluded criteria: Patients could not be taking any of the following therapies: fluoxetine or investigational compounds within 4 wk of randomization; long-acting benzodiazepines or monoamine oxidase inhibitors within 2 wk of randomization; short-acting benzodiazepines or other psychotropic drugs within 1 wk of randomization.

Interventions

Intervention Characteristics
Benzodiazepin (lorazepam)

- *Decsription*: 1-6 mg
- *Dose*: flexible doses 1–6 mg lorazepam
- *Duration*: 6 weeks
- *Time of short time follow-up*: 1 week
- *Detailed description*: a 1-wk, single-blind, placebo run-in period. Lorazepam was initiated at 1 mg/d and could be increased to a maximum of 6 mg/d based on the investigator's assessment of symptom response

L-759274

- *Decsription*:
- *Dose*: 40 mg L-759274
- *Duration*: 6 weeks
- *Time of short time follow-up*: 1 week
- *Detailed description*: a 1-wk, single-blind, placebo run-in period. 40 mg L-759274. L-759274 is a novel NK1 antagonist, in patients with generalized anxiety disorder. L-759274 is a potent antagonist of the NK1 receptor

Placebo

- *Decsription*: Placebo
- *Dose*: 6 weeks
- *Duration*: 1 week
- *Time of short time follow-up*: 1 week
- *Detailed description*: a 1-wk, single-blind, placebo run-in period.

Outcomes

Angstsymptomer målt med HAM-A, mean final (SD)

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Hamilton Anxiety Scale
- **Range**: 0-56
- **Unit of measure**: points
- **Direction**: Lower is better
- **Data value**: Endpoint

	Avorlige bivirkninger, antal patienter ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** The studies described here were funded by Merck. The authors thank N. Agrawal (Merck, PET plasma sample analyses), R. Vogt (Merck, trial administration), Turku PET Center staff (PET and MRI scans) and M. Nyman, O. Eskola, J. Kajander, O. Solin (Turku PET Center), M. Kramer, M. Goldberg, A. Majumdar, K. Petty, and D. Sciberras (all formerly of Merck) for their academic contributions to the studies. **Country:** USA **Setting:** Six academic and private research sites in the United States **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Low risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Unclear risk	Adapted from Slee et al.

Møller 2001

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (alprazolam) ● Diagnosis: a diagnosis of GAD according to ICD-10 code F41.1 ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients without significant other psychiatric disorders such as panic disorder, major depression, or known substance abuse, nor relevant concomitant other diseases (e.g., epilepsy, severe renal or hepatic impairment, cancer). Approximately 66% had concomitant diseases ● *Patients receiving other pharmacological treatment*: Neither psychotropic comedication (anxiolytics, antidepressants, neuroleptics, sedatives) nor psychotherapeutic interventions were allowed during the study period. In the case of severe sleep disturbances, up to 1 g of chloral hydrate per day could be administered. Antidepressiva_tricyklisk (Opipramol) ● Diagnosis: a diagnosis of GAD according to ICD-10 code F41.1 ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 %

	● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients without significant other psychiatric disorders such as panic disorder, major depression, or known substance abuse, nor relevant concomitant other diseases (e.g., epilepsy, severe renal or hepatic impairment, cancer). Approximately 66% had concomitant diseases ● *Patients receiving other pharmacological treatment*: Neither psychotropic comedication (anxiolytics, antidepressants, neuroleptics, sedatives) nor psychotherapeutic interventions were allowed during the study period. In the case of severe sleep disturbances, up to 1 g of chloral hydrate per day could be administered. Placebo ● Diagnosis: a diagnosis of GAD according to ICD-10 code F41.1 ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients without significant other psychiatric disorders such as panic disorder, major depression, or known substance abuse, nor relevant concomitant other diseases (e.g., epilepsy, severe renal or hepatic impairment, cancer). Approximately 66% had concomitant diseases ● *Patients receiving other pharmacological treatment*: Neither psychotropic comedication (anxiolytics, antidepressants, neuroleptics, sedatives) nor psychotherapeutic interventions were allowed during the study period. In the case of severe sleep disturbances, up to 1 g of chloral hydrate per day could be administered. **Included criteria:** Outpatients aged 18 to 65 years with a diagnosis of GAD according to ICD-10 code F41.1 without significant other psychiatric disorders such as panic disorder, major depression, or known substance abuse, nor relevant concomitant other diseases (e.g., epilepsy, severe renal or hepatic impairment, cancer) were included in this multicenter, randomized, placebo-controlled clinical trial. The total score on the Hamilton Rating Scale for Anxiety (HAM-A) had to be at least 17, and the score on the 21-item Hamilton Rating Scale for Depression (HAM-D) could not be greater than 20. **Excluded criteria:** without significant other psychiatric disorders such as panic disorder, major depression, or known substance abuse, nor relevant concomitant other diseases (e.g., epilepsy, severe renal or hepatic impairment, cancer)
Interventions	**Intervention Characteristics** Benzodiazepin (alprazolam) ● *Decsription*: alprazolam ● *Dose*: 2 mg of alprazolam ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The patients underwent a 7-day, single-blind, placebo-washout period (day 7 to 1). This was followed by a 4-week, double blind treatment (days 0–28), which preceded a 7-day (days 29–35) period during which the doses were reduced to avoid withdrawal phenomena after the cessation of the benzodiazepine. Medication was prepared in capsules of identical appearance. Capsules contained 0.5 mg of alprazolam. Neither psychotropic comedication (anxiolytics, antidepressants, neuroleptics, sedatives) nor psychotherapeutic interventions were allowed during the study period. In the case of severe sleep disturbances, up to 1 g of chloral hydrate per day could be administered. On day 0 of the first 3 days of the double-blind treatment period, one of the two evening capsules contained active medication in the opipramol and alprazolam groups. On day 1, two capsules in the evening were active, and on day 2, the morning capsules also contained active medication. From day 3 onward, the final doses of 200 mg of opipramol and 2 mg of alprazolam given in four capsules were reached, whereas patients receiving placebo were only given inert capsules (days 7 to 35) Antidepressiva_tricyklisk (opipramol) ● *Decsription*: opipramol ● *Dose*: 200 mg of opipramol ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The patients underwent a 7-day, single-blind, placebo-washout period (day 7 to 1). This was followed by a 4-week, double blind treatment (days 0–28), which preceded a 7-day (days 29–35) period during which the doses were reduced to avoid withdrawal phenomena after the cessation of the benzodiazepine. Medication was prepared in capsules of identical appearance. Capsules contained 50 mg of opripramol. Neither psychotropic comedication (anxiolytics, antidepressants, neuroleptics, sedatives) nor psychotherapeutic interventions were allowed during the study period. In the case of severe sleep disturbances, up to 1 g of chloral hydrate per day could be administered. On day 0 of the first 3 days of the double-blind treatment period, one of the two evening capsules contained active medication in the opipramol and alprazolam groups. On day 1, two capsules in the evening were active, and on day 2, the morning capsules also contained active medication. From day 3 onward, the final doses of 200 mg of opipramol and 2 mg of alprazolam given in four capsules were reached, whereas patients receiving placebo were only given inert capsules (days 7 to 35) Placebo ● *Decsription*: Placebo ● *Dose*: Medication was prepared in capsules of identical appearance ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The patients underwent a 7-day, single-blind, placebo-washout period (day 7 to 1). This was followed by a 4-week, double blind treatment (days 0–28), which preceded a 7-day (days 29–35) period during which the doses were reduced to avoid withdrawal phenomena after the cessation of the benzodiazepine. Medication was prepared in capsules of identical appearance. Capsules contained placebo. Neither psychotropic comedication (anxiolytics, antidepressants, neuroleptics, sedatives) nor psychotherapeutic interventions were allowed during the study period. In the case of severe sleep disturbances, up to 1 g of chloral hydrate per day could be administered.

Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Frakturer, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Germany **Setting:** Outpatients **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Low risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Unclear risk	Adapted from Slee et al.

Nguyen 2006

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (lorazepam) ● Diagnosis: Adjustment Disorder With Anxiety (ADWA) (DSM IV) ● *Age in years, mean (SD)*: 42.0 (13.1) ● *Females n/N (%)*: 69.8% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with major depressive disorder any other evolutive psychiatric disorder (e.g. generalized anxiety disorder, anxiety related to mourning, panic disorder and psychosis) were excluded. ● *Patients receiving other pharmacological treatment*: Patients were not allowed to have a regular treatment with BZD or other psychotropic drug Anxiolytika (etifoxine) ● Diagnosis: Adjustment Disorder With Anxiety (ADWA) (DSM IV)

	● *Age in years, mean (SD)*: 44.0 (13.4) ● *Females n/N (%)*: 62.4% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with major depressive disorder any other evolutive psychiatric disorder (e.g. generalized anxiety disorder, anxiety related to mourning, panic disorder and psychosis) were excluded. ● *Patients receiving other pharmacological treatment*: Patients were not allowed to have a regular treatment with BZD or other psychotropic drug **Included criteria:** Adjustment Disorder With Anxiety (ADWA). To be eligible for inclusion, the patients, male or female, aged from 18– 65 years had to meet the criteria for ADWA as defined in the Diagnostic and Statistical Manual of mental disorders (DSM-IV): marked anxiety, with impairment of social functioning, occurring within 3 months after the onset of an identifiable psychological stressor. They were required to have a baseline HAM-A total score ≥ 20. Other inclusion criteria were a score 5 in at least one of the sub-scales of the Sheehan disability scale, rating a significant impairment, and a score < 20 in the Montgomery-Asberg Depression Rating scale (MADRS) (Montgomery et al., 1985) excluding significant depressive symptomatology. **Excluded criteria:** Patients who met clinical criteria for major depressive disorder were also excluded, as well as patients presenting with any other evolutive psychiatric disorder (e.g. generalized anxiety disorder, anxiety related to mourning, panic disorder and psychosis). Other non-inclusion criteria were contra-indications to the study drugs, i.e. a history of myasthenia, decompensated respiratory insufficiency, alcohol or drugs abuse, hypersensitivity to the study drugs and pregnant or lactating women. Patients were not allowed to have a regular treatment with BZD or other psychotropic drug, beta blocker therapy nor any drug that could have effects on the nervous system, or medication that could interfere with the study treatments metabolism (carbamazepine, phenytoine, primidone, rifampicine, griseofulvine, phenobarbital and probenecide), within the month preceding inclusion or during the study
Interventions	**Intervention Characteristics** Benzodiazepin (lorazepam) ● *Decsription*: lorazepam ● *Dose*: lorazepam (2 mg/day) ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: They were asked to take the study drug daily during 28 days, at usual dosages (0.5–1 mg by day for lorazepam) Anxiolytika (etifoxine) ● *Decsription*: etifoxine ● *Dose*: etifoxine (150 mg/day) ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: They were asked to take the study drug daily during 28 days, at usual dosages (50 mg 3 times a day for etifoxine)
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Supported by Biocodex, Compiègne, France **Country:** France **Setting:** outpatients, four regions in France (Arras, Marseille, Dijon and Rennes) **Authors name:** **Institution:** **Email:** **Address:** **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Randomization was realized by the coordinator centre, by a centralized procedure
Allocation concealment (selection bias)	Low risk	Quote: "Rando- mization was realized by the coordinator centre, by a centralized procedure."
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: ADWA patients included in the study wererandomly assigned to receive per os one of thetreatments, etifoxine (150 mg/day) or lorazepam(2 mg/day). They were asked to take the study drugdaily during 28 days, at usual dosages (50 mg 3 times aday for etifoxine, and 0.5–1 mg by day for lorazepam),dosages in conformity with the French Summary ofProduct Characteristics (SPC) for each drug. Studymedications (provided to the investigators by Biocodex laboratory) were presented as identical-appearingcapsules to maintain the double-blind fashion

Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: The intervention is given in identical-appearing capsules and the participants are unaware of allocation and therefore it suspected that outcome cannot be influenced.
Incomplete outcome data (attrition bias)	Low risk	Quote: "The intent-to-treat population (ITT) was composed of 185 patients (E: 91; L: 94) who received at least one dose of treatment and had at least one on- treatment HAM-A data (primary assessment para-meter). Two patients from etifoxine group and two from lorazepam group were excluded from ITT because of premature withdrawal before the first on-treatment evaluation (on Day 7), one patient for withdrew consent and one for adverse events in each group of treatment." Judgement Comment: From the 191 ADWA patients enrolled in the study, 189 patients were analysed, 93 in etifoxine group, and96 in lorazepam group. Overall, 176 patients completed the study, 87 in etifoxine group (93.5%) and 89 in lorazepam group (92.7%). Compliance (as assessed by therapeutic units return) to treatment was respectively of 95.2% and 95.5%. six patients from the etifoxine group (6.5%) and seven from the lorazepam group (7.3%) discontinued the study, maimlu form adverse events (E:2, L:5)
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to a protocol, the trail reports on all the outcomes stated in the method section
Other bias	Low risk	Judgement Comment: The trial appears to be free from other sources of bias

Noyes 1996

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks ● *Age in years, mean (SD)*: : M = 36.6; SD = 10.5 ● *Females n/N (%)*: 157/ 241 (65%) ● *Duration of anxiety symptoms, years, mean (SD)*: 9.1 (10.1) ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: patients with major psychiatric co-morbidities, head trauma or seizures were excluded ● *Patients receiving other pharmacological treatment*: Patients were required to have discontinued any psychoactive medication at least 7 days prior to begining study medication. During the study, subjects recieved no other psychoactive drug or psylogical treatment Benzodiazepin (diazepam) ● Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks ● *Age in years, mean (SD)*: ● *Females n/N (%)*: ● *Duration of anxiety symptoms, days, mean (SD)*: ● *Outpatient (%)*: ● *Non pharmacological treatment considered or tried (%)*: ● *Patients with co-morbidity (%)*: ● *Patients receiving other pharmacological treatment*: Benzodiazepin (alprazolam) ● Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks ● *Age in years, mean (SD)*: ● *Females n/N (%)*: ● *Duration of anxiety symptoms, days, mean (SD)*: ● *Outpatient (%)*: ● *Non pharmacological treatment considered or tried (%)*: ● *Patients with co-morbidity (%)*: Patients with major psychiatric co-morbidities, head trauma or seizures were excluded. Current major depressive disorder was identified in 13.3 % of subjects. ● *Patients receiving other pharmacological treatment*: Placebo ● Diagnosis: DSM-III panic disorder or agoraphobia with panic attacks ● *Age in years, mean (SD)*: ● *Females n/N (%)*: ● *Duration of anxiety symptoms, days, mean (SD)*: ● *Outpatient (%)*: ● *Non pharmacological treatment considered or tried (%)*: ● *Patients with co-morbidity (%)*: Patients with major psychiatric co-morbidities, head trauma or seizures were excluded ● *Patients receiving other pharmacological treatment*: **Included criteria:** DSM-III panic disorder or agoraphobia with panic attacks. at least one panic attack in each of the 3 weeks prior to the study, **Excluded criteria:** patients with major psychiatric co-morbidities (major depressive disorder dominating the clinical pisture, bipolar disorder, psychosis, dementia, melancholia suicidallity) were excluded, as were patients with uncontrolled physical ilness, abnormal labatory values, a history of substance abuse within 6 mnonths, head trauma or seizures.
Interventions	**Intervention Characteristics** Benzodiazepin (diazepam) ● *Decsription*: diazepam ● *Dose*: capusels containing 10 mg, flexible dosage, range = 10 - 100 mg, M = 43, SD not provided

	● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: capsules were administered in divided doses four times daily. Medication was gradually increased according to a standardized schedule until maximum benefits was achieved or dose limiting side-effects appeared. an effort was made to achiede a dose of 6 capsules per day by the end of the 3 week. but the maximum allowed dose was 10 capsules per day. Rescue medication: none Benzodiazepin (alprazolam) ● *Decsription*: alprazolam ● *Dose*: capusels containing 1 mg, flexible dosage, range = 1 - 10 mg, M = 4.9, SD not provided ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: capsules were administered in divided doses four times daily. Medication was gradually increased according to a standardized schedule until maximum benefits was achieved or dose limiting side-effects appeared. an effort was made to achiede a dose of 6 capsules per day by the end of the 3 week. but the maximum allowed dose was 10 capsules per day. Rescue medication: none Placebo ● *Decsription*: Placebo ● *Dose*: capusels containing placebo ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: capsules were administered in divided doses four times daily. Medication was gradually increased according to a standardized schedule until maximum benefits was achieved or dose limiting side-effects appeared. an effort was made to achiede a dose of 6 capsules per day by the end of the 3 week. but the maximum allowed dose was 10 capsules per day. Rescue medication: none
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Vægtændring, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal patinter med vægtøgning eller vægttab ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtid, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Supported by a grant from the Upjohn Company **Country:** USA, Australia **Setting:** Outpatients **Authors name:** Noyes **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Quote: "double-blind". No further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Quote: "double-blind". No further details.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 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	Judgement Comment: All outcomes were reported.
Other bias	High risk	Judgement Comment: Supported by a grant from the Upjohn Company; the role of the funder in planning, conducting and writing the study is not discussed.

Pande 2003

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (lorazepam) ● Diagnosis: a diagnosis of generalized anxiety disorder according to DSM-IV criteria ● *Age in years, mean (SD)*: 33.9 (9.7) ● *Females n/N (%)*: 63.2% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they suffered from any axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder. Also, patients at suicide risk, as judged by the clinician on the basis of history or current severity of suicidal ideation, were excluded. ● *Patients receiving other pharmacological treatment*: No psychotropic medications were allowed during the study with the exception of zolpidem (5 mg), which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit Pregabalin 150 mg ● Diagnosis: a diagnosis of generalized anxiety disorder according to DSM-IV criteria ● *Age in years, mean (SD)*: 37.9 (11.8) ● *Females n/N (%)*: 49.3% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they suffered from any axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder. Also, patients at suicide risk, as judged by the clinician on the basis of history or current severity of suicidal ideation, were excluded. ● *Patients receiving other pharmacological treatment*: No psychotropic medications were allowed during the study with the exception of zolpidem (5 mg), which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit Pregabalin 600 mg ● Diagnosis: a diagnosis of generalized anxiety disorder according to DSM-IV criteria ● *Age in years, mean (SD)*: 35.5 (11.2) ● *Females n/N (%)*: 57.1% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they suffered from any axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder. Also, patients at suicide risk, as judged by the clinician on the basis of history or current severity of suicidal ideation, were excluded. ● *Patients receiving other pharmacological treatment*: No psychotropic medications were allowed during the study with the exception of zolpidem (5 mg), which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit Placebo ● Diagnosis: a diagnosis of generalized anxiety disorder according to DSM-IV criteria ● *Age in years, mean (SD)*: 35.7 (11.5) ● *Females n/N (%)*: 68.1% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they suffered from any axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder. Also, patients at

	suicide risk, as judged by the clinician on the basis of history or current severity of suicidal ideation, were excluded. ● *Patients receiving other pharmacological treatment*: No psychotropic medications were allowed during the study with the exception of zolpidem (5 mg), which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit **Included criteria:** a diagnosis of generalized anxiety disorder according to DSM-IV criteria **Excluded criteria:** Patients were excluded if they suffered from any axis I disorder except dysthymia, simple phobia, social phobia, somatization disorder, or a history of major depressive disorder. Also, patients at suicide risk, as judged by the clinician on the basis of history or current severity of suicidal ideation, were excluded. Patients were required to be free of psychotropic medications for 2 weeks (5 weeks for fluoxetine) before enrollment. A urine drug screen was performed at screening and at termination, although a positive result at screening was not exclusionary. No psychotropic medications were allowed during the study with the exception of zolpidem (5 mg), which was permitted on an as-needed basis for extreme sleeplessness. Zolpidem was not to be taken for more than 2 nights per week and not to be taken the night before a clinic visit. Women of childbearing potential were required to be using contraception. If patients still met study inclusion criteria at the end of the lead-in phase, as confirmed by a second clinical interview with the psychiatrist, they were randomly assigned to one of the four treatment conditions
Interventions	**Intervention Characteristics** Benzodiazepin (lorazepam) ● *Decsription*: lorazepam 6 mg ● *Dose*: 6 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: lorazepam, 6 mg/day (2 mg t.i.d). The study had three phases: a 1-week placebo lead-in, a 4-week doubleblind phase, and a 1-week taper. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, subjects received one-sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Pregabalin 150 mg ● *Decsription*: Pregabalin 150 mg ● *Dose*: 150 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: pregabalin, 150 mg/day (50 mg t.i.d.). The study had three phases: a 1-week placebo lead-in, a 4-week doubleblind phase, and a 1-week taper. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, subjects received one-sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Pregabalin 600 mg ● *Decsription*: Pregabalin 600 mg ● *Dose*: 600 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: pregabalin, 600 mg/day (200 mg t.i.d.). The study had three phases: a 1-week placebo lead-in, a 4-week doubleblind phase, and a 1-week taper. Study medication was titrated during the first 6 days of double-blind treatment. On day 1, subjects received one-sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached. Placebo ● *Decsription*: ● *Dose*: ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Study medication was titrated during the first 6 days of double-blind treatment. On day 1, subjects received one-sixth of the randomly assigned dose, which was then increased daily until the targeted dose was reached.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed - abstinenssymptomer,* Physician withdrawal checklist (PWC) ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Physician withdrawal checklist (PWC) ● **Range**: ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal

	● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** USA **Setting:** five outpatient clinical research sites based in Seattle; Portland, Ore.; Lansing, Mich.; Los Angeles; and Durham, **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Low risk	Adapted from Slee et al.

Razavi 1999

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Antidepressiva (Trazodone) ● Diagnosis: Female breast cancer patients with fulfilment of DSM-III-R criteria for the diagnosis of adjustment disorders with anxiety or depressed mood and/or mixed disturbance of emotion and conduct. ● *Age in years, mean (SD)*: The median age was 56.5 years (range 33 - 71 years) ● *Females n/N (%)*: 100% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 8 (72.7%) patients in the trazodone group were ambulatory. ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*:Patients with serious psychiatric disorders were excluded ● *Patients receiving other pharmacological treatment*: Patients taking psychotropic medications were excluded, although zolpidem use was permitted if dosage was constant 7 days prior to study entry. Benzodiazepin (Clorazepate) ● Diagnosis: Female breast cancer patients with fulfilment of DSM-III-R criteria for the diagnosis of adjustment disorders with anxiety or depressed mood and/or mixed disturbance of emotion and conduct ● *Age in years, mean (SD)*: The median age was 56.5 years (range 33 - 71 years) ● *Females n/N (%)*: 100% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: five (71.4%) patients receiving clorazepate were ambulatory ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with serious psychiatric disorders were excluded ● *Patients receiving other pharmacological treatment*: Patients taking psychotropic medications were excluded, although zolpidem use was permitted if dosage was constant 7 days prior to study entry. **Included criteria:** female patients diagnosed with breast cancer and who were receiving treatment for this condition. To be included, patients had to meet the Diagnostic and Statistical Manual of Mental Disorders (3rd edn., revised; DSMIII-R) criteria for adjustment disorders with anxious or depressed mood and/or mixed disturbance of emotion and conduct. Patients also had to have a score of ≥ 14 on the French version of the Hospital Anxiety and Depression Rating Scale

	(HADS). **Excluded criteria:** Patients were not eligible if they had a clinically significant history of serious psychiatric disorders, or if they were receiving psychiatric or psychoactive medication; zolpidem use was permitted if the dose was constant 7 days prior to study entry.
Interventions	**Intervention Characteristics** Antidepressiva (Trazodone) ● *Decsription*: ● *Dose*: 150 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: The dosing schedule was one capsule (containing trazodone 50 mg) on day 1 and day 2, two capsules on day 3 and day 4, and three capsules per day from day 5 to day 28. Study medication was taken once daily with an evening meal or at bedtime with a snack. Benzodiazepin (Clorazepate) ● *Decsription*: Clorazepate 10-30 mg ● *Dose*: 30 mg ● *Duration*:4 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: The dosing schedule was one capsule (clorazepate 10 mg) on day 1 and day 2, two capsules on day 3 and day 4, and three capsules per day from day 5 to day 28. Study medication was taken once daily with an evening meal or at bedtime with a snack.
Outcomes	No relevant outcomes reported for our interventions of interrest
Notes	**Identification** **Sponsorship source:** This study was supported by Searle Continental Pharma Inc., Brussels, Belgium **Country:** Belgium **Setting:** in and outpatients **Authors name:** **Institution:** **Email:** **Address:** **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At visit 1, patients gave informed consent and, after review of inclusion and exclusion criteria, were assigned to receive either trazodone or clorazepate according to a computer-generated randomization list prepared prior to the start of the study."
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: No information of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: No information of blinding Not clear if outcome assessors are blinded
Incomplete outcome data (attrition bias)	High risk	Quote: "In this study, 27 patients were enrolled; however, nine were not included in the efficacy analysis. Major protocol violations resulted in the withdrawal of six patients (three patients took unauthorized drugs, two of whom were men and should not have been included, and one patient had alkaline phosphatase levels of 469 DIII [hepatic metastases]), two patients refused to take the study medication and one patient was lost to follow-up almost immediately after inclusion. Henceforth, all results of efficacy analysis are based on 18 patients; 11 were randomized to receive trazodone and seven were administered clorazepate." Judgement Comment: Major protocol violations resulted in the withdrawal of six patients (three patients took unauthorized drugs, twoof whom were men and should not have been included, and one patient had alkaline phosphatase levels of 469 DIII [hepatic metastases]), two patients refused to take the study medication and one patient was lost to follow-up almost immediately afterinclusion.all results of efficacy analysis are based on 18 patients; 11 were randomized to receive trazodone and seven were administered clorazepate
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to a protocol, Only some of our outcomes are reported in the trial.
Other bias	Low risk	Judgement Comment: The trial appears to be free from orher sources of bias

Rickels 2005

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (alprazolam) ● Diagnosis: DSM-IV criteria for GAD ● *Age in years, mean (SD)*: 40 ± 12 ● *Females n/N (%)*: 66% ● *Duration of anxiety symptoms, days, mean (SD)*: No information

- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: exclusion criteria: a Raskin Depression Scale score of greater than 7, current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessivecompulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse;
- *Patients receiving other pharmacological treatment*: concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night before a scheduled clinic appointment)

Pregabalin 300 mg
- Diagnosis: DSM-IV criteria for GAD
- *Age in years, mean (SD)*: 38 ± 10
- *Females n/N (%)*: 64%
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: exclusion criteria: a Raskin Depression Scale score of greater than 7, current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessivecompulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse;
- *Patients receiving other pharmacological treatment*: concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night before a scheduled clinic appointment)

Pregabalin 450 mg
- Diagnosis: DSM-IV criteria for GAD
- *Age in years, mean (SD)*: 38 ± 12
- *Females n/N (%)*: 59%
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: exclusion criteria: a Raskin Depression Scale score of greater than 7, current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessivecompulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse;
- *Patients receiving other pharmacological treatment*: concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night before a scheduled clinic appointment)

Pregabalin 600 mg
- Diagnosis: DSM-IV criteria for GAD
- *Age in years, mean (SD)*: 39 ± 12
- *Females n/N (%)*: 67%
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: exclusion criteria: a Raskin Depression Scale score of greater than 7, current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessivecompulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse;
- *Patients receiving other pharmacological treatment:* concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night before a scheduled clinic appointment)

Placebo
- Diagnosis: DSM-IV criteria for GAD
- *Age in years, mean (SD)*: 41 ± 12
- *Females n/N (%)*: 63%
- *Duration of anxiety symptoms, days, mean (SD)*: No information
- *Outpatient (%)*: 100%
- *Non pharmacological treatment considered or tried (%)*: No information
- *Patients with co-morbidity (%)*: exclusion criteria: a Raskin Depression Scale score of greater than 7, current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessivecompulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse;
- *Patients receiving other pharmacological treatment*: concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night

	before a scheduled clinic appointment) **Included criteria:** Male or female outpatients who were 18 years or older, met the DSM-IV criteria for GAD based on a structured Mini-International Neuropsychiatric Interview, and had screening and baseline scores of 20 or greater on the Hamilton Anxiety Rating Scale (HAM-A) and 9 or greater on the Covi Anxiety Scale were eligible for enrollment. **Excluded criteria:** Patients were excluded for any of the following reasons: (1) a Raskin Depression Scale score of greater than 7; (2) being a fertile woman having a positive pregnancy test result, not using a medically accepted contraceptive, or currently nursing; (3) current or past history of bipolar, schizophrenic, schizoaffective, psychotic, or factitious disorder and dementia; (4) current but not lifetime major depressive disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessivecompulsive disorder, posttraumatic or acute stress disorders, and eating disorders at the diagnostic threshold but not subthreshold level and alcohol or other substance dependence and/or abuse; (5) positive urine drug screen result (including benzodiazepines); (6) any clinically significant acute or unstable medical condition or clinically significant electrocardiographic (ECG) result or laboratory abnormalities; (7) concurrent psychotherapy for GAD, unless undergoing stable treatment for longer than 3 months; (8) concomitant treatment with a psychotropic medication during the study and for at least 2 weeks before the screening visit (5 weeks for fluoxetine) (zolpidem tartrate, 5 mg, for up to 2 nights per week was permitted during the study as needed for extreme sleeplessness, except for the night before a scheduled clinic appointment); (9) current or past history of a seizure disorder or requiring anticonvulsant therapy for any indication; or (10) suicide risk either currently or based on history.
Interventions	**Intervention Characteristics** Benzodiazepin (alprazolam) ● *Decsription*: Alprazolam ● *Dose*: fixed dosages, 1.5 mg alprazolam ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1-week drug-free screening period, during which no placebo was administered and prohibited medications were washed out. At the conclusion of the 4-week double-blind treatment period, medication was discontinued during a 1-week taper period, followed by a 1-week medication-free period. Treatment with alprazolam was initiated at 0.5 mg/d and was increased to 1.0 mg/d on day 4 and to 1.5 mg/d on day 7. Study drug was administered in divided doses using a 3 times a day schedule. Pregabalin 300 mg ● *Decsription*: Pregabalin 300 mg ● *Dose*: fixed dosages of pregabalin 300 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1-week drug-free screening period, during which no placebo was administered and prohibited medications were washed out. At the conclusion of the 4-week double-blind treatment period, medication was discontinued during a 1-week taper period, followed by a 1-week medication-free period. Pregabalin treatment was initiated at 300 mg/d for all 3 dosages; for patients assigned to 450 and 600 mg of pregabalin, the dosage was titrated to 450 mg/d on day 4; and for those assigned to 600 mg of pregabalin, the dosage was titrated to 600 mg/d on day 7. Study drug was administered in divided doses using a 3 times a day schedule. Pregabalin 450 mg ● *Decsription*: Pregabalin 450 mg ● *Dose*: fixed dosages of pregabalin 450 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1-week drug-free screening period, during which no placebo was administered and prohibited medications were washed out. At the conclusion of the 4-week double-blind treatment period, medication was discontinued during a 1-week taper period, followed by a 1-week medication-free period. Pregabalin treatment was initiated at 300 mg/d for all 3 dosages; for patients assigned to 450 and 600 mg of pregabalin, the dosage was titrated to 450 mg/d on day 4; and for those assigned to 600 mg of pregabalin, the dosage was titrated to 600 mg/d on day 7. Study drug was administered in divided doses using a 3 times a day schedule. Pregabalin 600 mg ● *Decsription*: Pregabalin 600 mg ● *Dose*: fixed dosages of pregabalin 600 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1-week drug-free screening period, during which no placebo was administered and prohibited medications were washed out. At the conclusion of the 4-week double-blind treatment period, medication was discontinued during a 1-week taper period, followed by a 1-week medication-free period. Pregabalin treatment was initiated at 300 mg/d for all 3 dosages; for patients assigned to 450 and 600 mg of pregabalin, the dosage was titrated to 450 mg/d on day 4; and for those assigned to 600 mg of pregabalin, the dosage was titrated to 600 mg/d on day 7. Study drug was administered in divided doses using a 3 times a day schedule. Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description:* 1-week drug-free screening period, during which no placebo was administered and prohibited medications were washed out. At the conclusion of the 4-week double-blind treatment period, medication was discontinued during a 1-week taper period, followed by a 1-week medication-free period.

Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed - abstinenssymptomer,* Physician withdrawal checklist (PWC) ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Physician withdrawal checklist (PWC) ● **Range**: ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint Kardielle bivirkninger, *antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** This study was supported by Pfizer Inc, New York, NY. **Country:** USA **Setting:** Outpatients, The study was conducted at 29 US centers **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Low risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Low risk	Adapted from Slee et al.

Rocca 1997

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (delorazepam) ● Diagnosis: DSM-IV diagnosis of GAD ● *Age in years, mean (SD)*: 37.5 (11.1) ● *Females n/N (%)*: 57% overall population ● *Duration of anxiety symptoms, years, mean (SD)*: Age at onset 30.0 (6.6). For 60% of the patients the duration of the current episode was more than 1 year. ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Subjects with other significant axis-1 diagnoses such as panioc disorder, major mental ilness, including major depression or substance abuse, were excluded form the study. ● *Patients receiving other pharmacological treatment*: No other psychoactive drugr were allowed during the treatment period SSRI (Paroxetine) ● Diagnosis: DSM-IV diagnosis of GAD ● *Age in years, mean (SD)*: 35.3 (9.3) ● *Females n/N (%)*: 57% overall population ● *Duration of anxiety symptoms, years,, mean (SD)*: Age at onset 28 5 (7.4). For 60% of the patients the duration of the current episode was more than 1 year. ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Subjects with other significant axis-1 diagnoses such as panioc disorder, major mental ilness, including major depression or substance abuse, were excluded form the study. ● *Patients receiving other pharmacological treatment*: No other psychoactive drugr were allowed during the treatment period Antidepressiva_tricyklisk (imipramine) ● Diagnosis: DSM-IV diagnosis of GAD ● *Age in years, mean (SD)*: 37.6 (9.3) ● *Females n/N (%)*: 57% overall population ● *Duration of anxiety symptoms, years,, mean (SD)*: Age at onset 29.4 (6.7). For 60% of the patients the duration of the current episode was more than 1 year. ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Subjects with other significant axis-1 diagnoses such as panioc disorder, major mental ilness, including major depression or substance abuse, were excluded form the study. ● *Patients receiving other pharmacological treatment*: No other psychoactive drugr were allowed during the treatment period **Included criteria:** DSM-IV diagnosis of GAD.a score of at least 18 on HAM-A, a score of at least 38 on the State and Trait Anxeity inventory, and a score of 14 or less on the Hamilton Rating Scale for Depressiob. **Excluded criteria:** Subjects with other significant axis-1 diagnoses such as panioc disorder, major mental ilness, including major depression or substance abuse, were excluded form the study.
Interventions	**Intervention Characteristics** Benzodiazepin (delorazepam) ● *Decsription*: delorazepam ● *Dose*: flexible doses, range 3-6 mg (daily), mean daily dose 74.2 mg, SD 1.1 ● *Duration*: 8 weeks ● *Time of short time follow-up*: 2 weeks ● *Detailed description:* The optimal dose was reached within 1 week, No other psychoactive drugr were allowed during the treatment period SSRI (Paroxetine) ● *Decsription*: Paroxetine ● *Dose*: 20 mg daily dose ● *Duration*: 8 weeks ● *Time of short time follow-up*: 2 weeks ● *Detailed description*: The optimal dose was reached within 1 week, No other psychoactive drugr were allowed during the treatment period Antidepressiva_tricyklisk (imipramine) ● *Decsription*: Imipramine ● *Dose*: Flexible doses, range 50-100 mg daily, mean daily dose 75 mg, SD 16, ● *Duration*: 8 weeks ● *Time of short time follow-up*: 2 weeks ● *Detailed description:* The optimal dose was reached within 1 week, No other psychoactive drugr were allowed during the treatment period
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale

	● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Italy **Setting:** Psychiatric Clinic University of Turin, outpatients **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Slee et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Slee et al.
Blinding of participants and personnel (performance bias)	High risk	Adapted from Slee et al.
Blinding of outcome assessment (detection bias)	High risk	Adapted from Slee et al.
Incomplete outcome data (attrition bias)	High risk	Adapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Slee et al.
Other bias	Unclear risk	Adapted from Slee et al.

Schweizer 1993

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (alprazolam) ● Diagnosis: DSM - III panic disorder ● *Age in years, mean (SD)*: M = 33, SD = 7 ● *Females n/N (%)*: 75% ● *Duration of anxiety symptoms, days, mean (SD)*: 84% had suffered from panic disorder at least 1 year and 59% for at least 3 years. ● *Outpatient (%)*: Probably outpatients ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: none ● *Patients receiving other pharmacological treatment*: no concomitant centrally active medication therapy was permitted during the study. Patients were excluded if they were taking any psychoactive medication. 54% of the study patients had received previous treatment for panic disorder, mostly in the form of low-dose or intermittent benzodiazephine therapy. Antidepressiva_tricyklisk (Imipramine) ● Diagnosis: DSM - III panic disorder ● *Age in years, mean (SD)*: M = 33, SD = 7 ● *Females n/N (%)*: 75% ● *Duration of anxiety symptoms, days, mean (SD)*: 84% had suffered from panic disorder at least 1 year and 59% for at least 3 years. ● *Outpatient (%)*: Probably outpatients ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: none ● *Patients receiving other pharmacological treatment*: no concomitant centrally active medication therapy was permitted during the study. Patients were excluded if they were taking any psychoactive medication. 54% of the study patients had received previous treatment for panuc disorder, mostly in the form of low-dose or intermittent benzodiazephine therapy. Placebo ● Diagnosis: DSM - III panic disorder ● *Age in years, mean (SD)*:M = 33, SD = 7 ● *Females n/N (%)*: 75% ● *Duration of anxiety symptoms, days, mean (SD)*: 84% had suffered from panic disorder at least 1 year and 59% for at least 3 years. ● *Outpatient (%)*: Probably outpatients ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: none ● *Patients receiving other pharmacological treatment*: no concomitant centrally active medication therapy was permitted during the study. Patients were excluded if they were taking any psychoactive medication. 54% of the

	study patients had received previous treatment for panuc disorder, mostly in the form of low-dose or intermittent benzodiazephine therapy. **Included criteria:** DSM - III panic disorder or agoraphobia with panic attacks. Between 18 and 65 of age **Excluded criteria:** Patients were excluded if their primary diagnosis consisted of any other axis I DSM-III disorder, if they had suffered in the past 6 months from alchohol or drug dependence, if they had major depression in the past 2 years or if they had a history of bipolar disorder, cyclothymic disorderm schizophrenia, obsessive-compulsive disorderm epilepsy, seizures of dementia. Patients were also excluded if they had any acute or unstable medical problems or if they were taking any psychoactive medication, if they were currently undergoing any psychotherapy or behavoir therapy or if they gave evidence of suicide.
Interventions	**Intervention Characteristics** Benzodiazepin (alprazolam) ● *Decsription*: alprazolam ● *Dose*: Flexible dosage, range = 2 - 10 mg, M = 5.4, SD = 2.1. ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week placebo run in period. Flexible dosage, range = 1 - 10 mg, M = 5.4, SD = 2.1. Capsules containing 1 mg of alprazolam. Treatment was initiated at one capsule in the evening. Stepwise increasaes in daily doses were mase every 3 to 4 days according to following schedule: two capsules per day for 3 days, 3 capsuels per day for 4 days, four capsules per day for 4 days, 5 capsules for 4 days and so on as tolerated. Every effort was made to increase the dosage of all patients to a minimum of 6 capsuels per day (6 mg alprazolam). The maximum permitted dose was 10 capsules (10 mg alprazolam). when patients reported advesre effects, the dose titration was slowed, or if necessary, the daily dose was reduced. Medications were taken 4 times daily. Patients were allowed to remain in the study while taklen daily doses af low as one pill per day. Rescue medication: Quote: "no concomitant centrally active medication therapy was permitted during the study" Antidepressiva_tricyklisk (Imipramine) ● *Decsription*: Imipramine ● *Dose*: Flexible dosage, range = 50 - 250 mg, M = 152, SD = 65. ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: one week placebo run in period. Flexible dosage, range = 25 - 250 mg, M = 152, SD = 65. Capsules containing 25 mg of imipramine. Treatment was initiated at one capsule in the evening. Stepwise increasaes in daily doses were mase every 3 to 4 days according to following schedule: two capsules per day for 3 days, 3 capsuels per day for 4 days, four capsules per day for 4 days, 5 capsules for 4 days and so on as tolerated. Every effort was made to increase the dosage of all patients to a minimum of 6 capsuels per day (150 mg imipraamine). The maximum permitted dose was 10 capsules (250 mg imipramine). when patients reported advesre effects, the dose titration was slowed, or if necessary, the daily dose was reduced. Medications were taken 4 times daily. Patients were allowed to remain in the study while taklen daily doses af low as one pill per day. Rescue medication: Quote: "no concomitant centrally active medication therapy was permitted during the study" Placebo ● *Decsription*: Placebo ● *Dose*: Flexible dosage, 1-10 capsules. ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Capsules containing lacotse filler as placebo. Treatment was initiated at one capsule in the evening. Stepwise increasaes in daily doses were mase every 3 to 4 days according to following schedule: two capsules per day for 3 days, 3 capsuels per day for 4 days, four capsules per day for 4 days, 5 capsules for 4 days and so on as tolerated. Every effort was made to increase the dosage of all patients to a minimum of 6 capsuels per day. The maximum permitted dose was 10 capsules. when patients reported advesre effects, the dose titration was slowed, or if necessary, the daily dose was reduced. Medications were taken 4 times daily. Patients were allowed to remain in the study while taklen daily doses af low as one pill per day. Rescue medication: Quote: "no concomitant centrally active medication therapy was permitted during the study"
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed_abstinenssymptomer, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal personer med abstinens sympomer ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint

Notes	**Identification** **Sponsorship source:** Research grant from the Upjohn Co, Kalamazoo, Mich and by Publich Health Service Grant Country: USA **Setting:** No information **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: Quote: "patients were dispensed identical capsules containing either 1 mg of alprazolam or 25 mg of imipramine".
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Quote: "patients were dispensed identical capsules containing either 1 mg of alprazolam or 25 mg of imipramine".
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 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 statystical 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	Judgement Comment: All relevant outcomes were reported.
Other bias	Low risk	Judgement Comment: Sponsored by Upjohn Co; the role of the funder in planning, conducting and writing the study is not discussed.

Song 2017

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (diazepam + paroxetine) ● Diagnosis: GAD based on DSM-V ● *Age in years, mean (SD)*: 47.94 ± 12.10 ● *Females n/N (%)*: 28/49 (57.7%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 0% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: we also determined Hamilton depression scale (HAMD) for each participant and those with score ≥ 7 were excluded in the present study. Furthermore, those patients with evidence of drug abuse, drinking, cognitive impairment, and physical illness such as diabetes, severe hypertension, cardiovascular and cerebrovascular diseases, malignant diseases, respiratory diseases, or autoimmune infections were also excluded. ● *Patients receiving other pharmacological treatment*: The doses of paroxetine were (40.40 ± 8.80) mg in the paroxetine group, (38.98 ± 7.70) mg in the paroxetinediazepam group, and (38.00 ± 9.69) mg in the paroxetineMSZRT group.They were not statistically different among the three groups (??? = 0.62, ??? = 0.54). Placebo (paroxetine) ● Diagnosis: GAD based on DSM-V ● *Age in years, mean (SD)*: 50.60 ± 12.84 ● *Females n/N (%)*: 26/43 (60.5 %) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 0% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: we also determined Hamilton depression scale (HAMD) for each participant and those with score ≥ 7 were excluded in the present study. Furthermore, those patients with evidence of drug abuse, drinking, cognitive impairment, and physical illness such as diabetes, severe hypertension, cardiovascular and cerebrovascular diseases, malignant diseases, respiratory diseases, or autoimmune infections were also excluded. ● *Patients receiving other pharmacological treatment*: The doses of paroxetine were (40.40 ± 8.80) mg in the paroxetine group, (38.98 ± 7.70) mg in the paroxetinediazepam group, and (38.00 ± 9.69) mg in the paroxetineMSZRT group.They were not statistically different among the three groups (??? = 0.62, ??? = 0.54).

	Chinese_herbs (MSZRT) + paroxetine ● Diagnosis: GAD based on DSM-V ● *Age in years, mean (SD)*: 48.96 ± 12.87 ● *Females n/N (%)*: 28/50 (56%) ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 0% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: we also determined Hamilton depression scale (HAMD) for each participant and those with score ≥ 7 were excluded in the present study. Furthermore, those patients with evidence of drug abuse, drinking, cognitive impairment, and physical illness such as diabetes, severe hypertension, cardiovascular and cerebrovascular diseases, malignant diseases, respiratory diseases, or autoimmune infections were also excluded. ● *Patients receiving other pharmacological treatment*: The doses of paroxetine were (40.40 ± 8.80) mg in the paroxetine group, (38.98 ± 7.70) mg in the paroxetinediazepam group, and (38.00 ± 9.69) mg in the paroxetineMSZRT group.They were not statistically different among the three groups (??? = 0.62, ??? = 0.54). **Included criteria:** Inpatients of Psychosomatic Disorders Department in our hospital, diagnosed as GAD by two experienced psychiatrists based on DSM-V and treatmentfree within 2 months, were recruited. Participants were required to have a score ≥ 14 on Hamilton Anxiety Scale (HAMA) and ≥50 on Self-Rating Anxiety Scale (SAS) at baseline. **Excluded criteria:** we also determined Hamilton depression scale (HAMD) for each participant and those with score ≥ 7 were excluded in the present study. Furthermore, those patients with evidence of drug abuse, drinking, cognitive impairment, and physical illness such as diabetes, severe hypertension, cardiovascular and cerebrovascular diseases, malignant diseases, respiratory diseases, or autoimmune infections were also excluded.
Interventions	**Intervention Characteristics** Benzodiazepin (diazepam + paroxetine) ● *Decsription*: diazepam + paroxetine ● *Dose*: 7.5 mg diazepam + paroxetine 20-60 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Subjects in three groups took paroxetine 20 mg/day half an hour after breakfast in the first week. From second week, they were allowed to increase paroxetine dose. The maximum dose during the study period was 60 mg/day if judged clinically necessary by the investigator. Meanwhile, the paroxetine-diazepam group received 2.5 mg of diazepam three times daily as recommended by the manufacturer. No other medications or psychotherapy were permitted during study period. Diazepam (2.5 mg/tablet) was purchased from Beijing Yimin Pharmaceutical Co., Ltd., China. Paroxetine (20 mg/tablet) was obtained from Tianjin Smith Kline & French laboratories Ltd., China. Placebo (paroxetine) ● *Decsription*: paroxetine ● *Dose*: paroxetine 20-60 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Subjects in three groups took paroxetine 20 mg/day half an hour after breakfast in the first week. From second week, they were allowed to increase paroxetine dose. The maximum dose during the study period was 60 mg/day if judged clinically necessary by the investigator. No other medications or psychotherapy were permitted during study periodParoxetine (20 mg/tablet) was obtained from Tianjin Smith Kline & French laboratories Ltd., China Chinese herbs (MSZRT) + paroxetine ● *Decsription*: chinese herbs + paroxetine ● *Dose*: MSZRT 400 ml + paroxetine 20-60 mg ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Subjects in three groups took paroxetine 20 mg/day half an hour after breakfast in the first week. From second week, they were allowed to increase paroxetine dose. The maximum dose during the study period was 60 mg/day if judged clinically necessary by the investigator. Daily dose of MSZRT formula for each patient comprised Suanzaoren (Semen Zizyphi Spinosae) 15 g, Zhimu (Rhizoma Anemarrhena) 12 g, Fuling (Sclerotium Poriae Cocos) 15 g, Chuanxiong (Radix Ligustici Chuanxiong) 10 g, Zhizi (Gardenia jasminoides fruit) 10 g, Dandouchi (Fermented Soybean) 6 g, Chanyi (periostracum cicada) 6 g, and Zhigancao (Radix Glycyrrhizae) 6 g. All herbs were purchased from Medicinal Materials Co. Ltd. (Lin'an City, Zhejiang Province, China). They were mixed and prepared as 400 ml of decoction solution according to traditional methods and packed into two bags. Paroxetine (20 mg/tablet) was obtained from Tianjin Smith Kline & French laboratories Ltd., China
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint

	Træthed i dagtiden, antal patienter ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** This work was supported by National Natural Science Foundation of China [Grant no. 81601183] and Science and Technology Council of Hangzhou [Grant nos. 20160533B28 and 20140733Q49]. **Country:** China **Setting:** Inpatients of Psychosomatic Disorders Department **Authors name:** Song **Institution:** **Email:** **Address:** **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All subjects were randomly assigned to receive the treatments of paroxetine, paroxetine-diazepam, or paroxetine-MSZRT." Judgement Comment: No information on how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: The trial is not described as blinded or placebo controlled. No blinding of SZRT, presume no blinding of diazepam.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "as mean ± standard deviation. primary outcome measurement by a trained clinician, who was blind to the treatment for each patient. Subjects also performed SAS test" Judgement Comment: HAMA total scores at baseline and weeks 1, 2, 3, and 4 after treatment were evaluated as the primary outcome measurement by a trained clinician, who was blind to the treatment for each patient.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No information on number screened for eligibillity, number randomized or number of withdrawal. No flow diagram.
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No protocol available. Only one of our outcomes of interest is rapported
Other bias	Low risk	Judgement Comment: The trial appears to be free from other sources of bias

Stein 2008a

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall (agomelatin and placebo) ● Diagnosis: Primary diagnosis of GAD DSM-IV. ● *Age in years, mean (SD)*: 41.7, SD 12.2 ● *Females n/N (%)*: 68.6 % ● *Duration of anxiety symptoms, years, mean (SD)*: mean duration of GAD symptoms was 9.6 years, SD 10.5 ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Subjects wiht other psychiatri disordes, a history or bipolar or psychotic disorders, neurological disordersm severe personality disorders (antiscoial or borderline), drug or alcohol abuse/dependence, and suciude risk, or who had made serious suicide attemt within the past year were excluded. ● *Patients receiving other pharmacological treatment*: Subjects receiving pcychotropic agentsm psychoactive herbal remedies or have recently begun psychotherapy were excluded. **Included criteria:** Primary diagnosis of GAD DSM-IV. a score of at least 22 on HAM-A, a score of at least 2 on both HAM-A items (anxiety mood) and 2 (tension), a Hospital anxiety and depression (HAD) Scale score of 11 or greater, af HAD Anxiety > depressions coren and a Monggomery_asberg Depression Rating Scale score of 16 or less. **Excluded criteria:** Subjects with a decreas of greather than 20% on the HAM-A dueing 1 week single-blind run-in period were excluded. Subjects wiht other psychiatri disordes, a history or bipolar or psychotic disorders, neurological disordersm severe personality disorders (antiscoial or borderline), drug or alcohol abuse/dependence, and suciude risk, or who had made serious suicide attemt within the past year were excluded. Subjects receiving pcychotropic agentsm psychoactive herbal remedies or have recently begun psychotherapy were excluded.

Interventions	**Intervention Characteristics** Melatonin (agomelatin) ● *Decsription*: agomelatin ● *Dose*: 25-50 mg ● *Duration*: 12 weeks ● *Time of short time follow-up*: 2 weeks ● *Detailed description*: one week single blind placebo run in period. Dosage of agomelatin could be increased from 25-50 mg daily based on insufficient improvement from week 2 weeks onward. Placebo ● *Decsription*: Placebo ● *Dose*: ● *Duration*: 12 weeks ● *Time of short time follow-up*: 2 weeks ● *Detailed description*: one week single blind placebo run in period
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Afhængighed - abstinenssymptomer,* Discontinuation-Emergent Signs and Symptoms (DESS) Scale ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Discontinuation-Emergent Signs and Symptoms (DESS) Scale ● **Range**: ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Finland and South Africa **Setting:** Outpatients, Finland (5 centers,80 subjects) South Africa 6 centers, 41 subjects) **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Slee A, Nazareth I, Bondaronek P, Lui Y, Chjeng Z Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet 2019; 393: 768-77

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Apapted from Slee et al.
Allocation concealment (selection bias)	Low risk	Apapted from Slee et al.
Blinding of participants and personnel (performance bias)	Low risk	Apapted from Slee et al.
Blinding of outcome assessment (detection bias)	Low risk	Apapted from Slee et al.
Incomplete outcome data (attrition bias)	Low risk	Apapted from Slee et al.
Selective reporting (reporting bias)	Unclear risk	Apapted from Slee et al.
Other bias	Low risk	Apapted from Slee et al.

Stein 2015a

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (alprazolam) ● Diagnosis: Adjustment disorder with anxiety (ADWA) as defined by the DSM-IV ● *Age in years, mean (SD)*: 38.9 (12.8) ● *Females n/N (%)*: 70.3% ● *Duration of anxiety symptoms, days, mean (SD)*: No information. ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information. ● *Patients with co-morbidity (%)*: Participants had no comorbid psychiatric or substance use disorder, no suicidal thoughts, present or past history of epilepsy, no medical disorder physiologically responsible for anxiety ● *Patients receiving other pharmacological treatment*: Current or past (previous month) treatment with benzodiazepines or other psychotropic agents (including alternative medicines) was not allowed. Anxiolytika (Etifoxine) ● Diagnosis: Adjustment disorder with anxiety (ADWA) as defined by the DSM-IV ● *Age in years, mean (SD)*: 40.0 (11.8) ● *Females n/N (%)*: 76.0 % ● *Duration of anxiety symptoms, days, mean (SD)*: No information. ● *Outpatient (%)*:100% ● *Non pharmacological treatment considered or tried (%)*: No information. ● *Patients with co-morbidity (%)*: Participants had no comorbid psychiatric or substance use disorder, no suicidal thoughts, present or past history of epilepsy, no medical disorder physiologically responsible for anxiety. ● *Patients receiving other pharmacological treatment*: Current or past (previous month) treatment with benzodiazepines or other psychotropic agents (including alternative medicines) was not allowed. **Included criteria:** To be eligible for inclusion, male or female outpatients aged 18–65 years had to meet the criteria for ADWA as defined by the DSM-IV. In addition, baseline score on the Hamilton Anxiety Rating Scale (HAM-A) was ≥ 20, with a baseline score in at least one of three subscales (work, family and social life) of the Sheehan Disability Scale (SDS) ≥ 5, and a baseline score on the Montgomery– Asberg Depression Rating Scale (MADRS) < 20. **Excluded criteria:** Participants had no comorbid psychiatric or substance use disorder (as assessed by the Mini International Neuropsychiatric Interview, no suicidal thoughts, present or past history of epilepsy, no medical disorder physiologically responsible for anxiety, and were not pregnant nor breast feeding. Current or past (previous month) treatment with benzodiazepines or other psychotropic agents (including alternative medicines) was not allowed. Current treatment with drugs likely to interfere with the metabolism of the study treatments was also an exclusion criterion.
Interventions	**Intervention Characteristics** Benzodiazepin (alprazolam) ● *Decsription*: ● *Dose*: 1.5 mg/day for alprazolam ● *Duration*: 4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: 1.5 mg/day for alprazolam for 28 days. Study drug was to be taken daily for 28 days (one capsule in the morning, at noon and in the evening), at usual dosages (1.5 mg/day for alprazolam), in conformity with the summary of product characteristics (SmPC) of the two drugs. Study treatments were presented as capsules identical in their appearance. Anxiolytika (Etifoxine) ● *Decsription*: ● *Dose*: 150 mg/day for etifoxine ● *Duration*:4 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*:150 mg/day for etifoxine for 28 days. Study drug was to be taken daily for 28 days (one capsule in the morning, at noon and in the evening), at usual dosages (150 mg/day for etifoxine), in conformity with the summary of product characteristics (SmPC) of the two drugs. Study treatments were presented as capsules identical in their appearance.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Sponsorship and article processing charges for this study were provided by Biocodex, Gentilly, France **Country:** South Africa **Setting:** Outpatients from seventeen centres in two locations (Cape Town, Johannesburg) participated. **Authors name:** **Institution:** **Email:**

	Address: **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: A randomization list was established and study treatments were assigned by each investigator in ascending order of numbering based on thechronological enrollment order. No information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Study treatments were presented as capsules identical in their appearance." Judgement Comment: the trial was described as double blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: No information on blinding of outcome assessors It is unclear if outcome assessors were blinded to allocation
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "Thirteen patients from the etifoxine group (13.0%) and 11 from the alprazolam group (10.9%) prematurely discontinued the study, mainly for adverse events (etifoxine: 4, alprazolam: 6) and consent withdrawal (etifoxine: 3, alprazolam: 2). Overall, 177 patients completed the study, 87 in the etifoxine group (87.0%) and 90 in the alprazolam group (89.1%). The mean" Judgement Comment: No intention to treat analyses
Selective reporting (reporting bias)	Low risk	Judgement Comment: Not reffering to a protocol but report on relevant outcomes.
Other bias	Low risk	Judgement Comment: The trial appears to be free from other sources of bias

Stein 2017

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Melatonin (Agomelatin 10 mg) ● Diagnosis: Primary diagnosis of GAD according to DSM-IV-TR criteria. ● *Age in years, mean (SD)*: 43.6 (13.4) ● *Females n/N (%)*: 67.9% ● *Duration of anxiety symptoms, years mean (SD)*: 3.7 ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with other psychiatric disorders including major depressive disorder, drug or alcohol abuse dependence, severe personality disorders, a history of psychotic disorder, neurological disorders, and suicide risk (as judged by the clinician, a score > 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year), were excluded. ● *Patients receiving other pharmacological treatment*: Patients receiving psychotropic agents or other treatments likely to impact on the central nervous system or on study evaluations, or having recently begun psychotherapy, were excluded. Melatonin (Agomelatin 25 mg) ● Diagnosis: Primary diagnosis of GAD according to DSM-IV-TR criteria. ● *Age in years, mean (SD)*: 44.1 (15.2) ● *Females n/N (%)*: 71.9 % ● *Duration of anxiety symptoms, yearxs, mean (SD)*: 4.2 ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with other psychiatric disorders including major depressive disorder, drug or alcohol abuse dependence, severe personality disorders, a history of psychotic disorder, neurological disorders, and suicide risk (as judged by the clinician, a score > 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year), were excluded. ● *Patients receiving other pharmacological treatment*: Patients receiving psychotropic agents or other treatments likely to impact on the central nervous system or on study evaluations, or having recently begun psychotherapy, were excluded. ● Placebo ● Diagnosis: Primary diagnosis of GAD according to DSM-IV-TR criteria. ● *Age in years, mean (SD)*: 44.1 (13.1) ● *Females n/N (%)*: 63.4 % ● *Duration of anxiety symptoms, years, mean (SD)*: 3.6 ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients with other psychiatric disorders including major depressive disorder, drug or alcohol abuse dependence, severe personality disorders, a history of psychotic disorder, neurological disorders, and suicide risk (as judged by the clinician, a score > 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year), were excluded. ● *Patients receiving other pharmacological treatment*: Patients receiving psychotropic agents or other treatments likely to impact on the central nervous system or on study evaluations, or having recently begun psychotherapy, were

	excluded. **Included criteria:** Primary diagnosis of GAD according to DSM-IV-TR criteria. Patients were required to have a HAMA (Hamilton, 1959) total score ≥ 22, a score ≥ 2 on both HAM-A items 1 and 2, HAM-A items 1+2 > 5, a Hospital Anxiety and Depression (HAD) (Zigmond and Snaith, 1983) Anxiety score > Depression score at selection and inclusion, and a MontgomeryÅsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score ≤ 16 at selection. **Excluded criteria:** Patients with a decrease greater than 20% on the HAM-A total score between selection and inclusion were excluded. Patients with current (within 6 months prior to the selection visit) anxiety disorders other than GAD, including panic disorder, posttraumatic stress disorder, agoraphobia, social phobia, obsessive-compulsive disorder according to DSM-IV-TR criteria and confirmed by the MINI, were excluded. Regarding specific phobia, only patients with symptoms present almost daily or which could interfere with study evaluation were excluded. Patients with anxiety symptoms due to a general medical condition or substance use were also excluded. Patients with other psychiatric disorders including major depressive disorder, drug or alcohol abuse dependence, severe personality disorders, a history of psychotic disorder, neurological disorders, and suicide risk (as judged by the clinician, a score > 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year), were excluded. Women of childbearing potential without effective contraception, pregnant women, and patients with severe or uncontrolled organic disease, likely to interfere with the conduct of the study were also excluded. Patients receiving psychotropic agents or other treatments likely to impact on the central nervous system or on study evaluations, or having recently begun psychotherapy, were excluded. However, menopause hormone replacement therapy, and treatment with thyroid hormones or beta-blockers were allowed when used at a stable dosage (start, stop or modification within the 3 months [4 weeks for beta-blockers] prior to inclusion)
Interventions	**Intervention Characteristics** Melatonin (Agomelatin 10 mg) ● *Decsription*: Agomelatin 10 mg ● *Dose*: Agomelatin 10 mg ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Agomelatine 10 mg in the evening for 12 weeks. Treatments were identically labeled Melatonin (Agomelatin 25 mg) ● *Decsription*: Agomelatin 25 mg ● *Dose*: Agomelatin 25 mg ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Agomelatine 25 mg o in the evening for 12 weeks. Treatments were identically labeled Placebo ● *Decsription*: Palcebo ● *Dose*: ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: Placebo in the evening for 12 weeks. Treatments were identically labeled
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Avorlige bivirkninger, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint *Svimmelhed, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** This study was funded by Servier. Servier employees were involved in the collection and analysis of data. **Country:** Finland (6 centres), Russia (6 centres), Poland (9 centres), Slovakia (6 centres), and Ukraine (8 centres) **Setting:** Outpatients

	Authors name: Stein **Institution:** **Email:** **Address:** **Notes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive agomelatine 10 mg, agomelatine 25 mg or placebo in the evening for 12 weeks. The treatments were assigned at the inclusion visit by a balanced (non-adaptive and non- centralized) randomization with stratification by centre. Treatments were identically labeled." Judgement Comment: No information on how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to receive agomelatine 10 mg, agomelatine 25 mg or placebo in the evening for 12 weeks. The treatments were assigned at the inclusion visit by a balanced (non-adaptive and non- centralized) randomization with stratification by centre. Treatments were identically labeled. After" Judgement Comment: No information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "12-week, placebo-controlled, double-blind, international study in patients with a primary diagnosis of GAD. The" Judgement Comment: Treatments were identically labeled.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: The trial was described as double-blind, presume patients and personel were blinded. No information on blinding of outcome assessors
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "patients). A total of 61 patients did not complete the trial (85.2% completer rate). Reasons for withdrawal were mainly lack of efficacy and non-medical; while rates of withdrawal for non-medical reasons were the same same across treatment arms, it is noteworthy that only 1 patient on agomelatine 25 mg withdrew due to lack of efficacy versus 8 patients on agomelatine 10 mg daily and 20 patients on placebo" Judgement Comment: The efficacy analyses were performed in the full analysis set (FAS) (all included and randomized patients having taken at least one dose of study medication, and having a value at baseline and at least one post-baseline visit for the primary efficacy measure.modified ITT analyse med LOCF.Kun 4 deltagere er ikke inkluderet i analyserne.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol availabe. The trial reports on all the outcomes stated in the methods section. all our critical outcomes of interest are reported.
Other bias	Low risk	Judgement Comment: The trial appears to be free from other sources of bias There were no clinically relevant differences between the treatment groups for demographic criteria and clinical characteristics

Taylor 1990

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (alprazolam) ● Diagnosis: Panic disorder. ● *Age in years, mean (SD)*: Mean = 35.0; ● *Females n/N (%)*: 81% ● *Duration of anxiety symptoms, days, mean (SD)*:No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*:No information ● *Patients with co-morbidity (%)*: none ● *Patients receiving other pharmacological treatment*: Willing to stop all psychoactive medications was stated as an inclusion criteria Antidepressiva_tricyklisk (Imipramine) ● Diagnosis: Panic disorder. ● *Age in years, mean (SD)*: Mean=34.1 ● *Females n/N (%)*: 65.9 % ● *Duration of anxiety symptoms, days, mean (SD)*:No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: none ● *Patients receiving other pharmacological treatment*: Willing to stop all psychoactive medications was stated as an inclusion criteria Placebo ● Diagnosis: Panic disorder. ● *Age in years, mean (SD)*: Mean= 34.9 ● *Females n/N (%)*: 65.1 % ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: none ● *Patients receiving other pharmacological treatment*: Willing to stop all psychoactive medications was stated as an inclusion criteria

	Included criteria: One panick attack or more per week for the last 3 weeks, have panic attacks with dour symptoms occuring during an attack, not have an organic cause for the panic attack. If the patient had a current major depressive episode, then the panic attack had to develop before the cureent major depressive episode, and if patients had a past major depressive episode, then their panic disorder needed to begin before the past major depressive episode. no previous adequate treatment with imipramine of alprazolam, willing to stop all psychoactive medications. **Excluded criteria:** Patients were excluded for a diagnosis of alchohol or drug abuse or dependence, mania, cyclothymia, psychotic disorder, obssesive.compulsive disorder or acute suicidality.
Interventions	**Intervention Characteristics** Benzodiazepin (alprazolam) ● *Decsription*:alprazolam ● *Dose*: Flexible dosage; range = 1 - 8 mg, M = 3.7 ● *Duration*: 8 weeks ● *Time of short time follow-up*: 1 weeks ● *Detailed description*: Medications were dispensed in identical capsules of placebo, alprazolam 1 mg or imipramine 30 mg. Medications were uncreased until patients were free of panic attacksm suffered from unplessant side effects or were taking 10 tablets per day. Rescue medication: none Antidepressiva_tricyklisk (Imipramine) ● *Decsription*:Imipramine ● *Dose*: Flexible dosage; range = 30 - 270 mg, M = 147 ● *Duration*: 8 weeks ● *Time of short time follow-up*:1 weeks ● *Detailed description*: Medications were dispensed in identical capsules of placebo, alprazolam 1 mg or imipramine 30 mg. Medications were uncreased until patients were free of panic attacksm suffered from unplessant side effects or were taking 10 tablets per day. Rescue medication: none Placebo ● *Decsription*:Placebo ● *Dose*: Identical capsules up to 10 tablets per day. ● *Duration*: 8 weeks ● *Time of short time follow-up*:1 weeks ● *Detailed description*: Medications were dispensed in identical capsules of placebo, alprazolam 1 mg or imipramine 30 mg. Medications were uncreased until patients were free of panic attacksm suffered from unplessant side effects or were taking 10 tablets per day. Rescue medication: none
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** This research was supported in part by NIMH grant 40118 and by a giN from the Up- john Company. **Country:** USA **Setting:** Outpatients **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Bighelli I, Trespidi C, Castellazzi M, Cipriani A, Furukawa TA, Girlanda F, Guaiana G, Koesters M, Barbui C. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011567. DOI: 10.1002/14651858.CD011567.pub2. Accessed 22 April 2022.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: "Double blind": no further information provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: "Double blind": no further information provided.

Incomplete outcome data (attrition bias)	High risk	Judgement Comment: Completer analysis only, unequal drop-out rate (Alprazolam: 8%, Imipramine: 19%)
Selective reporting (reporting bias)	High risk	Judgement Comment: Almost all 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	High risk	Judgement Comment: This research was supported in part by NIMH grant 40118 and by a giN from the Upjohn Company. The role of the funder in planning, conducting and writing the study is not discussed.

vanVliet 1992

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** overall (MAO (Brofaromine) and placebo) ● Diagnosis: Social phobia according to DSM-III-R criteria ● *Age in years, mean (SEM)*: Mean age (± SEM) was 32.8 ± 2.0 years ● *Females n/N (%)*: 21/30 (70%) ● *Duration of anxiety symptoms, years, mean (SD)*: the mean duration of illness was 12.4 ± 2.5 years. ● *Outpatient (%)*: 100 % ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Excluded were patients with another anxiety disorder, major affective disorder or psychotic disorder, alcohol abuse and those patients suffering from medical problems ● *Patients receiving other pharmacological treatment*: the use of other psychotropic drugs was not allowed except oxazepam, which was permitted if required to a maximum of 30 mg daily. **Included criteria:** Included in the study were patients suffering from social phobia according to DSM-III-R criteria. **Excluded criteria:** Excluded were patients with another anxiety disorder, major affective disorder or psychotic disorder, alcohol abuse and those patients suffering from medical problems on the basis of a complete medical evaluation. During treatment, the use of other psychotropic drugs was not allowed except oxazepam, which was permitted if required to a maximum of 30 mg daily.
Interventions	**Intervention Characteristics** MAO (Brofaromine) ● *Decsription*: MAO (Brofaromine) ● *Dose*: 150 mg daily ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: The dose of brofaromine was gradually increased from 50 to 150 mg daily (75 mg b.i.d.) in 3 weeks. If patients judged themselves to be improved they could continue their medication under doubleblind conditions in a follow-up period which lasted another 12 weeks. Placebo ● *Decsription*: ● *Dose*: ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: If patients judged themselves to be improved they could continue their medication under doubleblind conditions in a follow-up period which lasted another 12 weeks.
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** The Netherlands **Setting:** Patients were recruited from the outpatient clinic of the department of Biological Psychiatry of the University Hospital in Utrecht. **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D J, Ipser, J. Pharmacological treatments for social anxiety disorder in adults: a systematic review and network meta-analysis. Acta neuropsychiatrica 2020;32(4):169-176

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Williams et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Williams et al.
Blinding of participants and personnel (performance bias)	Unclear risk	Adapted from Williams et al.
Blinding of outcome assessment (detection bias)	Unclear risk	Adapted from Williams et al.
Incomplete outcome data (attrition bias)	Low risk	Adapted from Williams et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Williams et al.
Other bias	Low risk	Adapted from Williams et al.

vanVliet 1997

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Anxiolytika (Buspirone) ● Diagnosis: Social phobia, specific or generalized subtype, according to DSM-IV cirteria ● *Age in years, mean (SD)*: 41.6, SD 8.1 ● *Females n/N (%)*: 36.7 % overall ● *Duration of anxiety symptoms, years mean (SD)*: age at onset 19.4, SD 7.3. Duration of ilness 22.2 years, SD 4.7 ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Excluded were patiets with another anxiety disorderm major affective disorder or psychotic disorder, alcohol or drug abuse. Patients with a personality disorder were also excluded ● *Patients receiving other pharmacological treatment*: During treatment the use of other psychotroopic drugs as well as sympathicomimetrics and cimetidine was not allowed. Occasional use of oxazepam to a mixamum of 30 mg daily was permitted if required. Placebo ● Diagnosis: Social phobia, specific or generalized subtype, according to DSM-IV cirteria ● *Age in years, mean (SD)*: 32.9, SD 9.6 ● *Females n/N (%)*: 36.7 % overall ● *Duration of anxiety symptoms, years, mean (SD)*:age at onset 17.1, SD 4.7 Duration of ilness 15.8 years, SD 9.7 ● *Outpatient (%)*: 100% ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Excluded were patiets with another anxiety disorderm major affective disorder or psychotic disorder, alcohol or drug abuse. Patients with a personality disorder were also excluded ● *Patients receiving other pharmacological treatment*: During treatment the use of other psychotroopic drugs as well as sympathicomimetrics and cimetidine was not allowed. Occasional use of oxazepam to a mixamum of 30 mg daily was permitted if required. **Included criteria:** Social phobia, specific or generalized subtype, according to DSM-IV cirteria. **Excluded criteria:** Excluded were patiets with another anxiety disorderm major affective disorder or psychotic disorder, alcohol or drug abuse. Patients with a personality disorder were also excluded. A score of 15 or higher on the Hamilton Rating Scale for Depression was an exclusion criteria. During treatment the use of other psychotroopic drugs as well as sympathicomimetrics and cimetidine was not allowed. Occasional use of oxazepam to a mixamum of 30 mg daily was permitted if required
Interventions	**Intervention Characteristics** Anxiolytika (Buspirone) ● *Decsription*: Buspirone ● *Dose*: 30 mg daily ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*: the dose of buspirone was gradually increased from 15 mg in the first week to 30 mg from the third week on (10 mg t.i.d.) Placebo ● *Decsription*:Placebo ● *Dose*: ● *Duration*: 12 weeks ● *Time of short time follow-up*: 1 week ● *Detailed description*:
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint

Notes	**Identification** **Sponsorship source:** Not stated **Country:** The Netherlands **Setting:** Outpatient clinic at the Department of psychiatry of the University Hospital in Utrecht **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D J, Ipser, J. Pharmacological treatments for social anxiety disorder in adults: a systematic review and network meta-analysis. Acta neuropsychiatrica 2020;32(4):169-176

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Williams et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Williams et al.
Blinding of participants and personnel (performance bias)	Unclear risk	Adapted from Williams et al.
Blinding of outcome assessment (detection bias)	Unclear risk	Adapted from Williams et al.
Incomplete outcome data (attrition bias)	Low risk	Adapted from Williams et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Williams et al.
Other bias	Unclear risk	Adapted from Williams et al.

Versiani 1992

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Mao (Moclobemide) ● Diagnosis: DSM-III-R criteria for social phobia, ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Patients with significant medical illness e.g. essential tremor or Parkinson's diseasethat could mimic certainsocial phobic symptoms were also excluded ● *Patients receiving other pharmacological treatment*: Patients had to have been free from any psychotropic medication for at least one month. Both concomitant psychotropic drugs and psycho therapeutic interventions of any kind were forbidden during the study. Mao (Phenelzine) ● Diagnosis: DSM-III-R criteria for social phobia, ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Patients with significant medical illness e.g. essential tremor or Parkinson's diseasethat could mimic certainsocial phobic symptoms were also excluded ● *Patients receiving other pharmacological treatment*: Patients had to have been free from any psychotropic medication for at least one month. Both concomitant psychotropic drugs and psycho therapeutic interventions of any kind were forbidden during the study. Placebo ● Diagnosis: DSM-III-R criteria for social phobia, ● *Age in years, mean (SD)*: No information ● *Females n/N (%)*: No information ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more

	stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Patients with significant medical illness e.g. essential tremor or Parkinson's diseasethat could mimic certainsocial phobic symptoms were also excluded ● *Patients receiving other pharmacological treatment*: Patients had to have been free from any psychotropic medication for at least one monthBoth concomitant psychotropic drugs and psycho therapeutic interventions of any kind were forbidden during the study. **Included criteria:** The patients were of either sex, and aged 19-60 years. The disorder had to meet the followingcriteria: by CGI severity score of ≥ 4;(ii) global score on the Sheehan Disabilities Scale of ≥3; and clinical judgementthat a drugtreatment was indicated.All patients met the DSM-III-R criteria for social phobia, as diagnosed by the StructuredClinicalInterviewfor DSM-III-R (SCID). They had to have been free from any psychotropic medication for at least one month **Excluded criteria:** Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Patients with significant medical illness e.g. essential tremor or Parkinson's diseasethat could mimic certainsocial phobic symptoms were also excluded. Inability to fill in self-rating scales or to adhere to the study requirements, as well as concomitant psychotherapy or lack of protection against pregnancy, were other exclusion criteria. Both concomitant psychotropic drugs and psycho therapeutic interventions of any kind were forbidden during the study.
Interventions	**Intervention Characteristics** Mao (Moclobemide) ● *Decsription*: Moclobemide ● *Dose*: flexible doses, 100-600 mg, the mean (s.d.) daily doses were: moclobemidegroup, 580.7 (55.6) mg/day (end of phase 1, 8 weeks) ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Medication was provided in capsules of identical appearance containing moclobemide (100 mg). The initial dose was one capsule twice daily, morning, and afternoon; if tolerated, this dose was increasedon day 4 to four capsules a day - two in the morning, one in the afternoon, and one at bedtime. This dose was maintained until the end of week 4. At week5, if the dosewastolerated, it wasincreasedagain to five capsulesper day - two in the morning, two in the afternoon, and one at bedtime. At week 6, there was a further option to increase the dose to two capsules thrice daily; attempts were made to reach this maximum dose (600 mg/day moclobemide) Mao (Phenelzine) ● *Decsription*: ● *Dose*: flexible doses, 30-90 mg. the mean (s.d.) daily doses were: phenelzine group, 67.5 (15.0) mg/day (end of phase 1, 8 weeks) ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Medication was provided in capsules of identical appearance containing phenelzine (15 mg) The initial dose was one capsule twice daily, morning, and afternoon; if tolerated, this dose was increased on day 4 to four capsules a day - two in the morning, one in the afternoon, and one at bedtime. This dose was maintained until the end of week 4. At week 5, if the dose was tolerated, it was increased again to five capsulesper day - two in the morning, two in the afternoon, and one at bedtime. At week 6, there was a further option to increase the dose to two capsules thrice daily; attempts were made to reach this maximum dose (90 mg/day phenelzine) Placebo ● *Decsription*: Phenelzine ● *Dose*: capsules of identical appearance. mean (s.d.) daily doses were: placebogroup,5.9(0.4) (end of phase 1, 8 weeks) ● *Duration*: 8 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*: Medication was provided in capsules of identical appearance containing placebo. The initial dose was one capsule twice daily, morning, and afternoon; if tolerated, this dose was increasedon day 4 to four capsules a day - two in the morning, one in the afternoon, and one at bedtime. This dose was maintained until the end of week 4. At week 5, if the dosewastolerated, it wasincreasedagain to five capsulesper day - two in the morning, two in the afternoon, and one at bedtime. At week 6, there was a further option to increase the dose to two capsules thrice daily; attempts were made to reach this maximum dose (600 mg/day moclobemide, 90 mg/day phenelzine)
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Switzerland. **Setting:** Not stated **Authors name:** **Institution:** **Email:**

	Address: **Notes:** Data regtarding 'Risk of bias' obtained from: Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D J, Ipser, J. Pharmacological treatments for social anxiety disorder in adults: a systematic review and network meta-analysis. Acta neuropsychiatrica 2020;32(4):169-176

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Williams et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Williams et al.
Blinding of participants and personnel (performance bias)	Unclear risk	Adapted from Williams et al.
Blinding of outcome assessment (detection bias)	Unclear risk	Adapted from Williams et al.
Incomplete outcome data (attrition bias)	Low risk	Adapted from Williams et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Williams et al.
Other bias	Low risk	Adapted from Williams et al.

Versiani 1997

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Benzodiazepin (bromazepam) ● Diagnosis: social phobias DSM-III criteria ● *Age in years, mean (SD)*: 34.7 (9.8) ● *Females n/N (%)*: 40% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Relative to mood disorders only past major depression (non bipolar, non-psychotic, and non-melancholic) or secondary dysthomia were allowed. Personality disorders (cluster A+B) were excluded. Patients with significant medical illness were also excluded. ● *Patients receiving other pharmacological treatment*: Both concomitant medications and psychotherapy were forbidden during the study Placebo ● Diagnosis: social phobias DSM-III criteria ● *Age in years, mean (SD)*: 38.7 (10) ● *Females n/N (%)*: 30% ● *Duration of anxiety symptoms, days, mean (SD)*: No information ● *Outpatient (%)*: No information ● *Non pharmacological treatment considered or tried (%)*: No information ● *Patients with co-morbidity (%)*: Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Relative to mood disorders only past major depression (non bipolar, non-psychotic, and non-melancholic) or secondary dysthomia were allowed. Personality disorders (cluster A+B) were excluded. Patients with significant medical illness were also excluded. ● *Patients receiving other pharmacological treatment*: Both concomitant medications and psychotherapy were forbidden during the study **Included criteria:** The patients were of either sex and aged 19-60 years. CGI severity score equal to or greather than 4 and a Sheehan global disability of at least 3. All patient met criteria for social phobias DSM-III criteria. **Excluded criteria:** Patients were excluded if they had, or had a history of, any other DSM-III-R diagnoses to which social phobia could have been secondary. These included organic mental disorders, abuse of psychoactive substances, other anxiety disorders except generalised anxiety disorder, panic disorder (with a more stringent criterion than those of DSM-III R, i.e. history of a single un expected panic attack), and psychosis. Relative to mood disorders only past major depression (non bipolar, non-psychotic, and non-melancholic) or secondary dysthomia were allowed. Personality disorders (cluster A+B) were excluded. Patients with significant medical illness were also excluded. Inability to fill in self-rating scales or to adhere to the study requirements, was also reasons for exclusion. Patients had to have been free from any psychotropic medication for at least one month. Both concomitant medications and psychotherapy were forbidden during the study
Interventions	**Intervention Characteristics** Benzodiazepin (bromazepam) ● *Decsription*: bromazepam ● *Dose*: flexible doses 9-27 mg, mean final dose was 21 mg. ● *Duration*: 12 weeks

	● *Time of short time follow-up*: 4 weeks ● *Detailed description*: flexible doses 9-27 mg, tablets of 3 mg of bromazepam. doses started at 9 mg (3 mg. three simes a day), and increased by 3 mg. every week until week 7 were the doses were 27 mg, (9 mg three times a day). Doses were decreased if not tolerated. Efforts were made to attain the maximum doses. Mean final dose was 21 mg Placebo ● *Decsription*: Placebo ● *Dose*: tablets of identical appearance ● *Duration*: 12 weeks ● *Time of short time follow-up*: 4 weeks ● *Detailed description*:
Outcomes	*Angstsymptomer målt med HAM-A, mean final (SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Hamilton Anxiety Scale ● **Range**: 0-56 ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Funktion* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Sheehan Disability Scale, work dimention, social dimention and family dimention ● **Range**: 0-10 at each subscale ● **Unit of measure**: points ● **Direction**: Lower is better ● **Data value**: Endpoint *Træthed i dagtiden, antal patienter* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Unit of measure**: Antal ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Identification** **Sponsorship source:** Not stated **Country:** Brasil **Setting:** Not stated **Authors name:** **Institution:** **Email:** **Address:** **Notes:** Data regtarding 'Risk of bias' obtained from: Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D J, Ipser, J. Pharmacological treatments for social anxiety disorder in adults: a systematic review and network meta-analysis. Acta neuropsychiatrica 2020;32(4):169-176

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Adapted from Williams et al.
Allocation concealment (selection bias)	Unclear risk	Adapted from Williams et al.
Blinding of participants and personnel (performance bias)	Unclear risk	Adapted from Williams et al.
Blinding of outcome assessment (detection bias)	Unclear risk	Adapted from Williams et al.
Incomplete outcome data (attrition bias)	Low risk	Adapted from Williams et al.
Selective reporting (reporting bias)	Unclear risk	Adapted from Williams et al.
Other bias	Unclear risk	Adapted from Williams et al.

Footnotes

Characteristics of excluded studies

Altmann 2020

Reason for exclusion	Wrong intervention

Amodeo 2012

Reason for exclusion	Wrong comparator

Amore 1999a

Reason for exclusion	Wrong intervention

Asakura 2007

Reason for exclusion	Wrong intervention

Bandelow 2010

Reason for exclusion	Wrong outcomes

Barnett 2002

Reason for exclusion	Wrong outcomes

Blanco 2010

Reason for exclusion	Wrong outcomes

Bystritsky 1994

Reason for exclusion	Wrong outcomes

Careri 2015

Reason for exclusion	Wrong intervention

Christensen 2019

Reason for exclusion	Wrong intervention

Connor 1998

Reason for exclusion	Wrong outcomes

Davidson 1993

Reason for exclusion	Wrong outcomes

DenBoer 1990

Reason for exclusion	Wrong intervention

Durgam 2016

Reason for exclusion	Wrong intervention

Fahln 1995

Reason for exclusion	Wrong outcomes

Furmark 2005

Reason for exclusion	Wrong intervention

Gao 2009

Reason for exclusion	sprog

Garvey 1989

Reason for exclusion	Wrong outcomes

Gentil 1993

Reason for exclusion	Wrong outcomes

Goddard 2015

Reason for exclusion	Wrong outcomes

Gommoll 2015

Reason for exclusion	Wrong intervention

Gong 2016

Reason for exclusion	Wrong outcomes

GSKClinicalStudiesRegister 2018

Reason for exclusion	Wrong outcomes

Guo 2009

Reason for exclusion	sprog

Heimberg 1998

Reason for exclusion	Wrong outcomes

Holland 1999

Reason for exclusion	Wrong outcomes

Huang 2005

Reason for exclusion	sprog

Ichitovkina 2014

Reason for exclusion	Wrong study design

Jia 2009

Reason for exclusion	sprog

Katschnig 1997

Reason for exclusion	Wrong outcomes

Khan 2011a

Reason for exclusion	Wrong outcomes

Khan 2016

Reason for exclusion	Wrong intervention

Klerman 1986

Reason for exclusion	Protocol

Klosko 2016

Reason for exclusion	Wrong outcomes

Lecrubier 1997

Reason for exclusion	Wrong outcomes

Li 2005

Reason for exclusion	sprog

Li 2011

Reason for exclusion	sprog

Liu 2004

Reason for exclusion	sprog

Liux 2005

Reason for exclusion	sprog

Lott 1997

Reason for exclusion	Wrong outcomes

Meco 1989

Reason for exclusion	Wrong comparator

Mirzaei 2021

Reason for exclusion	Wrong intervention

Moller 2003

Reason for exclusion	already included from systematic review

Muehlbacher 2005

Reason for exclusion	Wrong outcomes

Nair 1996

Reason for exclusion	Wrong outcomes

Niu 2004

Reason for exclusion	sprog

Noyes 1997

Reason for exclusion	Wrong outcomes

Oosterbaan 2001

Reason for exclusion	Wrong outcomes

Peng 2012

Reason for exclusion	sprog

Ribeiro 2001

Reason for exclusion	Wrong outcomes

Rothschild 2012

Reason for exclusion	Wrong intervention

Sasson 1999

Reason for exclusion	Wrong outcomes

Schneider 2020

Reason for exclusion	Wrong outcomes

Schneier 1998

Reason for exclusion	Wrong outcomes

Schutters 2010

Reason for exclusion	Wrong outcomes

Sedighi 2020

Reason for exclusion	Wrong comparator

Servant 1998

Reason for exclusion	sprog

Shahrokhi 2021

Reason for exclusion	Wrong patient population

Sheikh 1999

Reason for exclusion	Wrong outcomes

Song 2007

Reason for exclusion	sprog

Stein 2002

Reason for exclusion	Wrong outcomes

Stein 2015

Reason for exclusion	already included from systematic review

Stein 2018

Reason for exclusion	Wrong outcomes

Syunyakov 2016

Reason for exclusion	sprog

Tesar 1991

Reason for exclusion	Wrong outcomes

Uhlenhuth 1989

Reason for exclusion	Wrong outcomes

Vaishnavi 2007

Reason for exclusion	Wrong outcomes

VanAmeringen 2007

Reason for exclusion	Wrong intervention

Vicente 2020

Reason for exclusion	

Wade 1997

Reason for exclusion	Wrong outcomes

Wang 2009

Reason for exclusion	sprog

Wang 2015

Reason for exclusion	Wrong intervention

Westenberg 1989

Reason for exclusion	Wrong outcomes

Wolitzky Taylor 2018

Reason for exclusion	Wrong intervention

Yang 2005

Reason for exclusion	sprog

Young 2017

Reason for exclusion	Wrong intervention

Zammit 2019

Reason for exclusion	Wrong patient population

Zammit 2020

Reason for exclusion	Wrong patient population

Zullino 2015

Reason for exclusion	Wrong intervention

Footnotes

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Excluded studies

Altmann 2020

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Data and analyses

1 Benzodiazepine vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Anxiety symptoms - HAM-A	13	2161	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.79, -0.41]
1.1.1 Alprazolam	6	1139	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-0.96, -0.32]
1.1.2 Lorazepam	4	527	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-1.06, -0.06]
1.1.3 Bromazepam	2	282	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.72, -0.22]
1.1.4 Diazepam	2	213	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-0.98, -0.41]
1.2 Addiction - withdrawal symptoms	1	37	Risk Ratio (IV, Fixed, 95% CI)	8.89 [1.38, 57.34]
1.2.1 Alprazolam	1	37	Risk Ratio (IV, Fixed, 95% CI)	8.89 [1.38, 57.34]
1.3 Addiction withdrawal symptoms	4	463	Std. Mean Difference (IV, Random, 95% CI)	0.37 [0.11, 0.63]
1.3.1 Alprazolam	1	184	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.20, 0.38]
1.3.2 Lorazepam	3	279	Std. Mean Difference (IV, Random, 95% CI)	0.50 [0.26, 0.74]
1.4 Function - Work	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.08, -0.05]
1.4.3 Bromazepam	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.08, -0.05]
1.5 Function - Social	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.10, -0.07]
1.5.3 Bromazepam	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.10, -0.07]
1.6 Function - Family	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.27, -0.22]
1.6.3 Bromazepam	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.27, -0.22]
1.7 Serious adverse eventsrisk ratio	9	2218	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.43, 4.80]
1.7.1 Alprazolam	4	1325	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.31, 5.99]
1.7.2 Lorazepam	3	412	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.20, 12.79]
1.7.3 Bromazepam	1	229	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.7.4 Diazepam	2	252	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.8 Serious adverse events_risk difference	9	2218	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.00]
1.8.1 Alprazolam	4	1325	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.00]
1.8.2 Lorazepam	3	412	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.02, 0.02]
1.8.3 Bromazepam	1	229	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.02, 0.02]
1.8.4 Diazepam	2	252	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.02, 0.02]
1.9 Suicidal thoughts/attempts_risk ratio	2	912	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.92]
1.9.1 Aprazoloam	1	777	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9.6 Lorazepam	1	135	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.92]
1.10 Suicidal thoughts/attempts_risk difference	2	912	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
1.10.1 Aprazoloam	1	777	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
1.10.6 Lorazepam	1	135	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.06, 0.03]
1.11 Daytime drowsiness	10	2138	Risk Ratio (M-H, Random, 95% CI)	2.21 [1.55, 3.16]
1.11.7 Aprazoloam	4	1187	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.07, 2.17]
1.11.10 Diazepam	2	250	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.97, 1.75]
1.11.14 Lorazepam	3	412	Risk Ratio (M-H, Random, 95% CI)	4.45 [2.95, 6.70]
1.11.18 Bromazepam	2	289	Risk Ratio (M-H, Random, 95% CI)	6.70 [2.77, 16.16]

1.12 Fractures_risk ratio	1	207	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.92]
1.12.1 Alprazolam	1	207	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.92]
1.13 Fractures_ risk difference	1	207	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
1.13.1 Alprazolam	1	207	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
1.14 Weight change	2	1089	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.05, 4.62]
1.14.2 Aprazoloam	2	931	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.69, 10.32]
1.14.6 Diazepam	1	158	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.97, 2.70]
1.15 Cardiac side-effects_risk difference	1	184	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
1.15.4 Alprazolam	1	184	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
1.16 Dizziness	7	1672	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.83, 1.76]
1.16.5 Aprazoloam	3	1168	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.66, 1.47]
1.16.10 Lorazepam	3	412	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.10, 3.61]
1.16.27 Diazepam	1	92	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.35, 1.76]

2 Pregabalin vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Anxiety symptoms - HAM-A	4	942	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.68, -0.38]
2.2 Serious adverse events_risk difference	3	772	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.02, 0.01]
2.3 Serious adverse events_risk ratio	3	772	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 1.31]
2.4 Suicidal thoughts/attempts_risk ratio	1	203	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.01]
2.5 Suicidal thoughts/attempts_risk difference	1	203	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.05, 0.02]
2.6 Daytime drowsiness	3	772	Risk Ratio (IV, Random, 95% CI)	2.55 [1.80, 3.60]
2.7 Cardiac side-effects_risk difference	1	361	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
2.8 Addiction - withdrawal symptoms	4	830	Std. Mean Difference (IV, Random, 95% CI)	0.22 [0.06, 0.39]
2.9 Dizziness	3	772	Risk Ratio (IV, Random, 95% CI)	3.79 [2.39, 6.01]

3 Quetiapine vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Anxiety symptoms - HAM-A	3	1050	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.66, -0.41]
3.2 Serious adverse events_risk ratio	3	1069	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.12, 11.32]
3.3 Serious adverse events_risk difference	3	1069	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
3.4 Addiction - Withdrawal symptoms	2	651	Std. Mean Difference (IV, Random, 95% CI)	0.22 [0.04, 0.40]
3.5 Suicidal thoughts/attempts	2	432	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.04]
3.6 Daytime drowsiness	3	1069	Risk Ratio (IV, Random, 95% CI)	1.56 [0.67, 3.64]
3.7 Weight change	1	637	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [0.94, 17.44]
3.8 Extrapyramidal symptoms	1	637	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.73, 3.17]
3.9 Dizziness	3	1069	Risk Ratio (IV, Random, 95% CI)	1.70 [1.16, 2.49]

4 Agomelatine vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Anxiety symptoms - HAM-A	2	529	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.65, 0.21]
4.2 Serious adverse events_risk ratio	2	533	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.39, 8.74]
4.3 Serious adverse events_risk difference	2	533	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.03]
4.4 Daytime drowsiness	1	410	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.25, 6.60]

4.5 Addiction withdrawal symptoms	1	121	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.42, 0.29]
4.6 Dizziness	2	431	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.54, 4.56]

5 Hydroxyzine vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Anxiety symptoms - HAM-A	1	210	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.48, 0.06]
5.2 Serious adverse events_risk ratio	1	218	Risk Ratio (M-H, Fixed, 95% CI)	3.23 [0.13, 78.34]
5.3 Serious adverse events_risk difference	1	218	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.02, 0.04]
5.4 Daytime drowsiness	1	218	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.40, 11.51]

6 Benzodiazepine vs Pregabalin

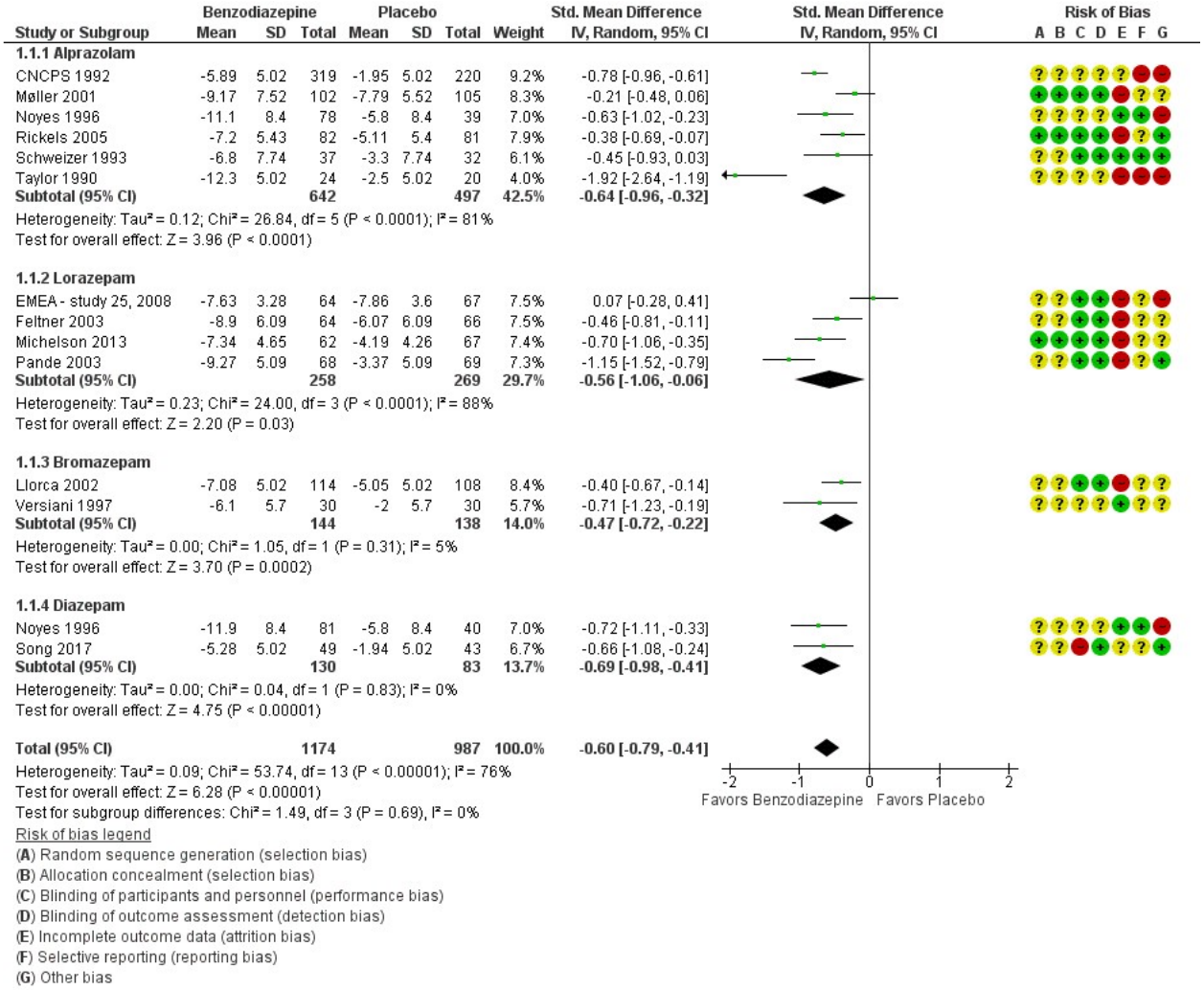
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Anxiety symptoms HAM-A	4	879	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.40, 0.49]
6.1.1 Lorazepam	3	600	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.59, 0.53]
6.1.2 Alprazolam	1	279	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.11, 0.68]
6.2 Serious adverse events	3	774	Risk Ratio (M-H, Random, 95% CI)	6.79 [1.08, 42.82]
6.2.1 Alprazolam	1	363	Risk Ratio (M-H, Random, 95% CI)	8.65 [0.36, 210.49]
6.2.2 Lorazepam	2	411	Risk Ratio (M-H, Random, 95% CI)	6.02 [0.63, 57.35]
6.3 Serious adverse events	3	774	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.03]
6.3.1 Alprazolam	1	363	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
6.3.2 Lorazepam	2	411	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
6.4 Addiction - wihtdrawal symptoms	4	819	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.05, 0.30]
6.4.1 Alprazolam	1	363	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.24, 0.23]
6.4.2 Lorazepam	3	456	Std. Mean Difference (IV, Random, 95% CI)	0.21 [0.01, 0.41]
6.5 Suicidal thoughts/attempts_risk difference	1	204	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
6.5.6 Lorazepam	1	204	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
6.6 Daytime drowsiness	3	774	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.07, 2.18]
6.6.7 Aprazoloam	1	363	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.48]
6.6.14 Lorazepam	2	411	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.29, 2.49]
6.7 Cardiac side-effects_risk difference	1	363	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
6.7.4 Alprazolam	1	363	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.02]
6.8 Dizziness	3	774	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 0.98]
6.8.5 Aprazoloam	1	363	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.25, 0.67]
6.8.10 Lorazepam	2	411	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.29, 1.53]

Figures

Figure 1

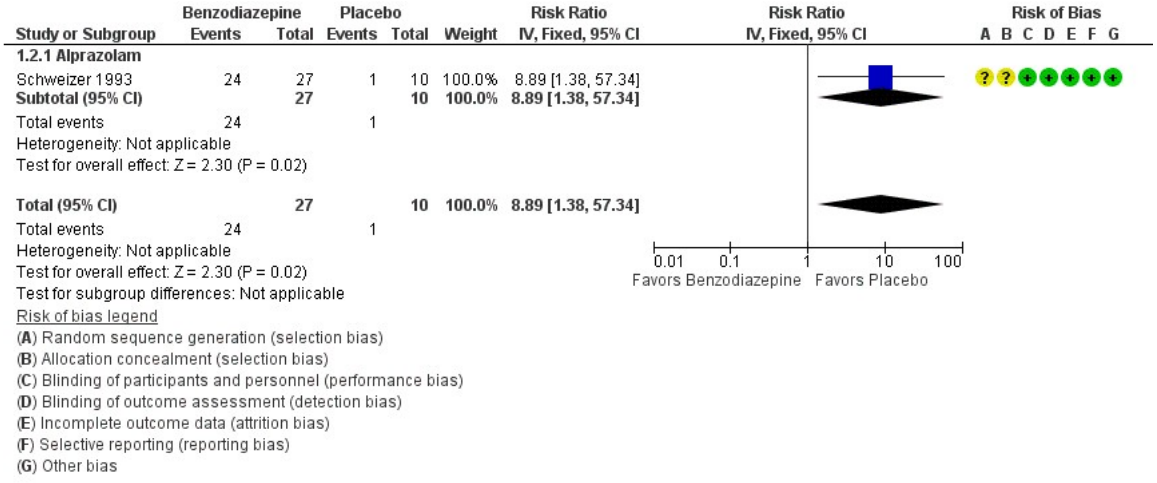
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 1.1)



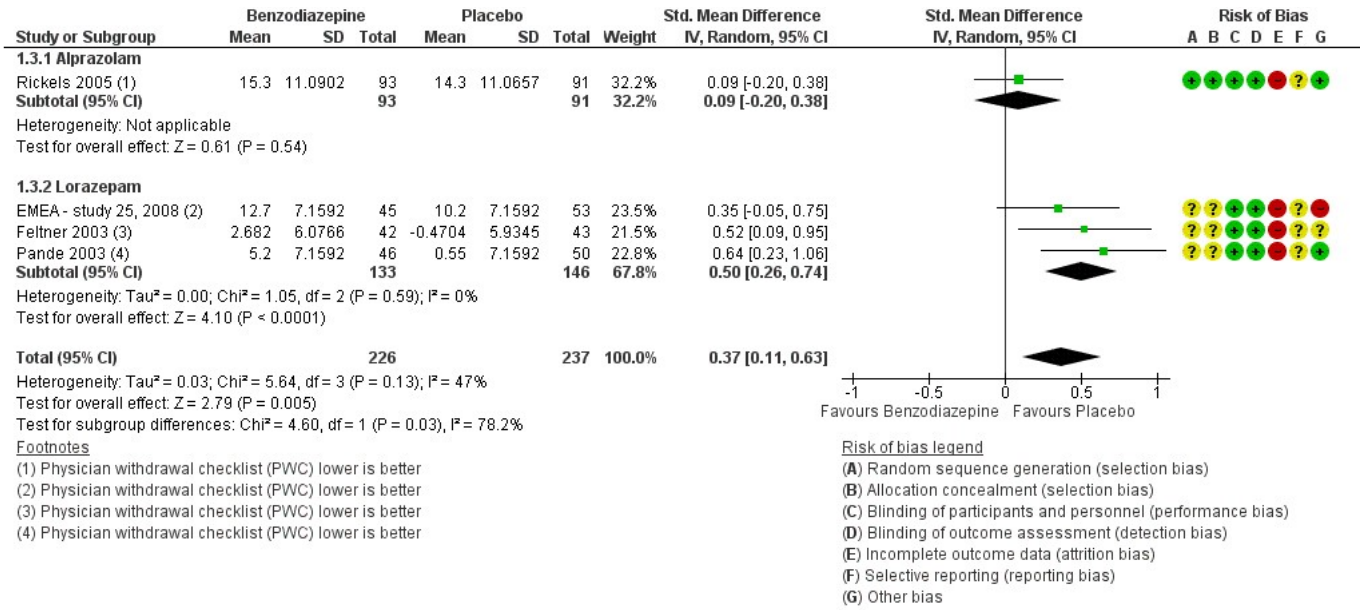
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.1 Anxiety symptoms - HAM-A

Figure 3 (Analysis 1.2)



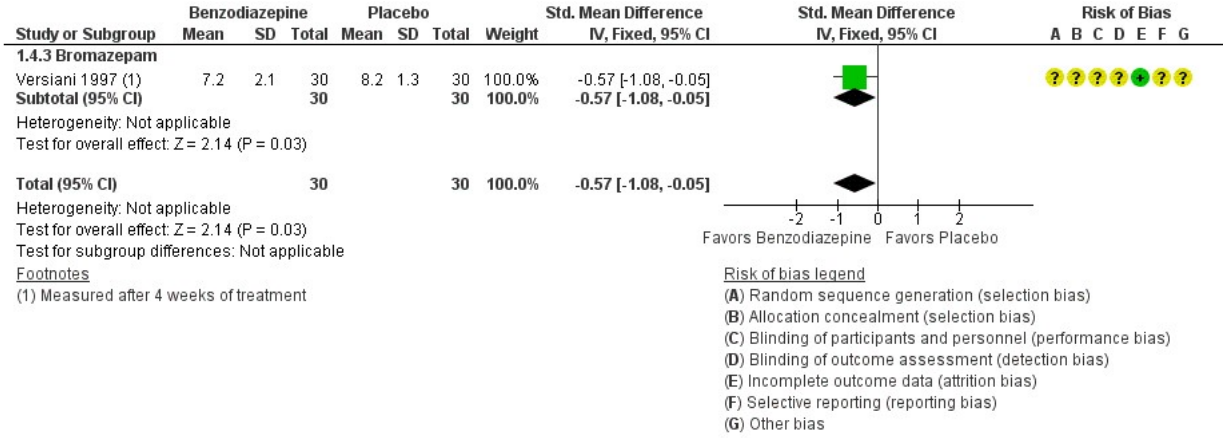
Benzodiazepine vs placebo, outcome: 1.2 Addiction - Withdrawal symptoms

Figure 4 (Analysis 1.3)



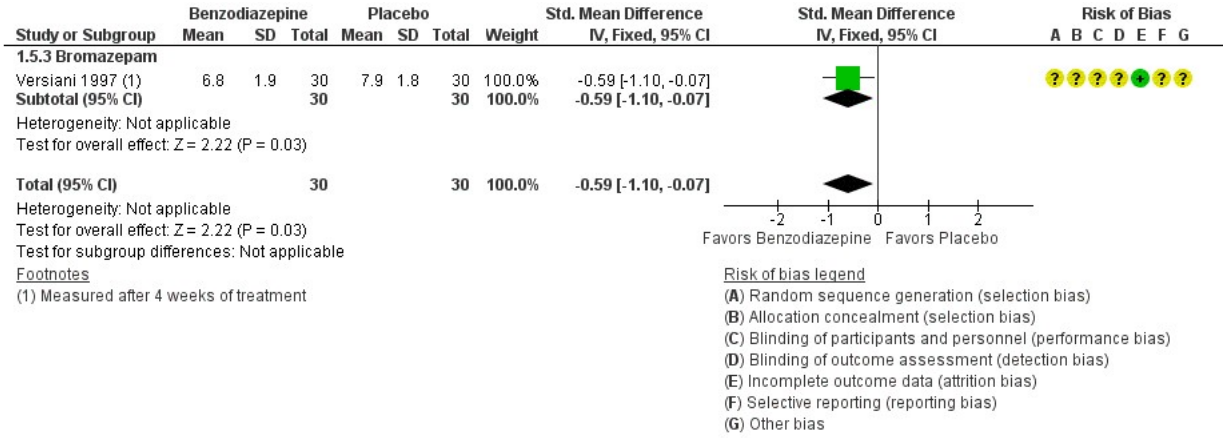
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.3 Addiction withdrawal symptoms.

Figure 5 (Analysis 1.4)



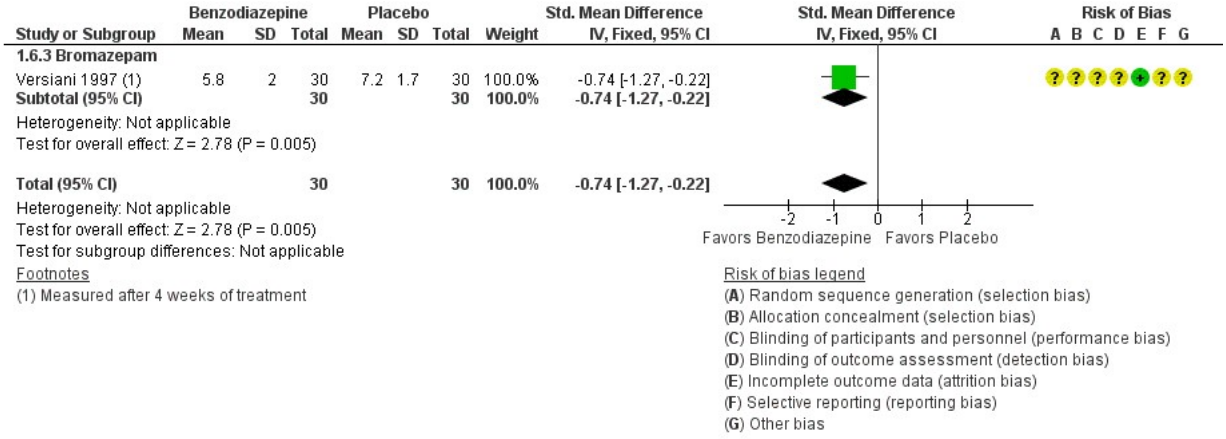
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.4 Function - Work.

Figure 6 (Analysis 1.5)



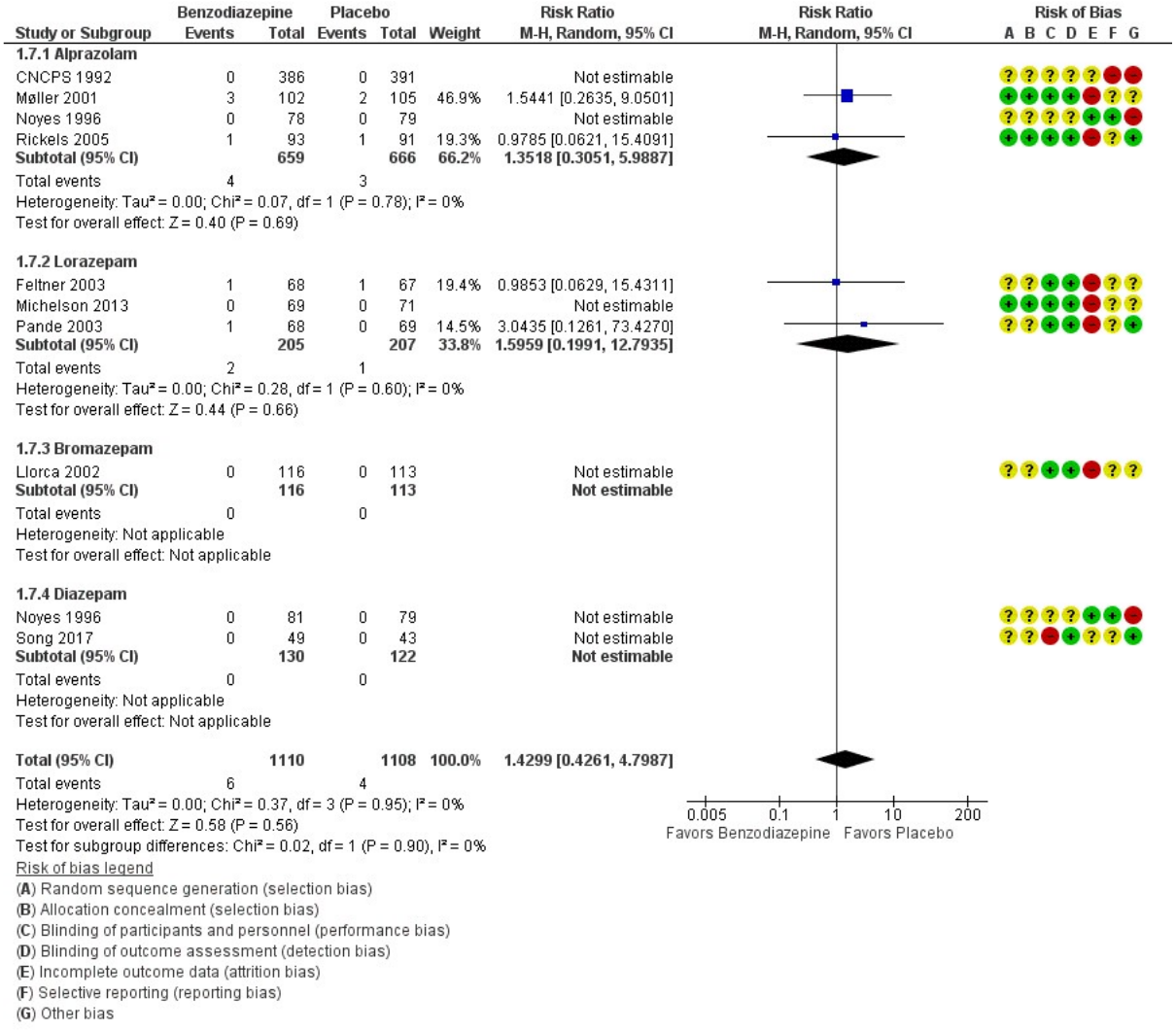
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.5 Function - Social.

Figure 7 (Analysis 1.6)



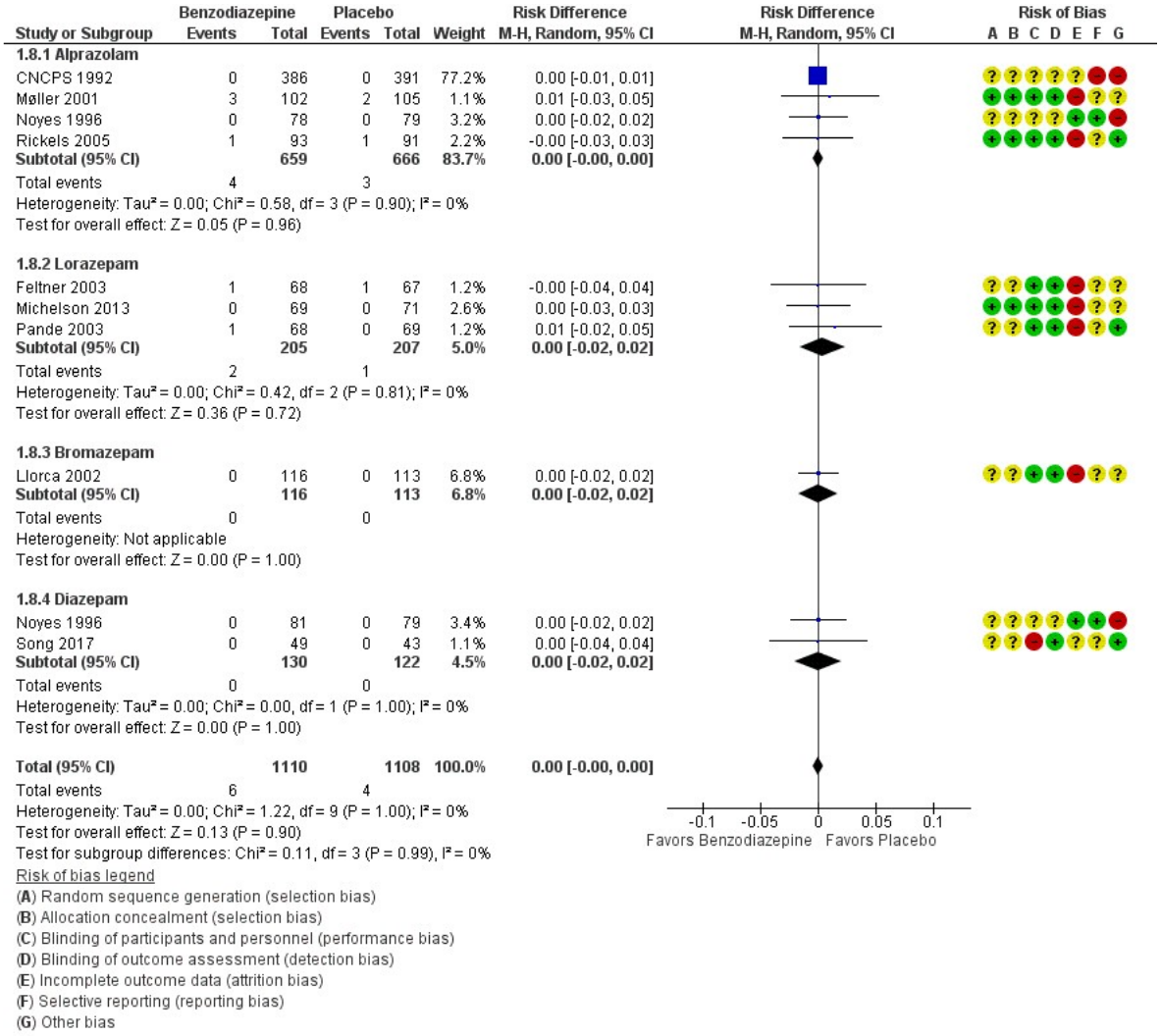
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.6 Function - Family.

Figure 8 (Analysis 1.7)



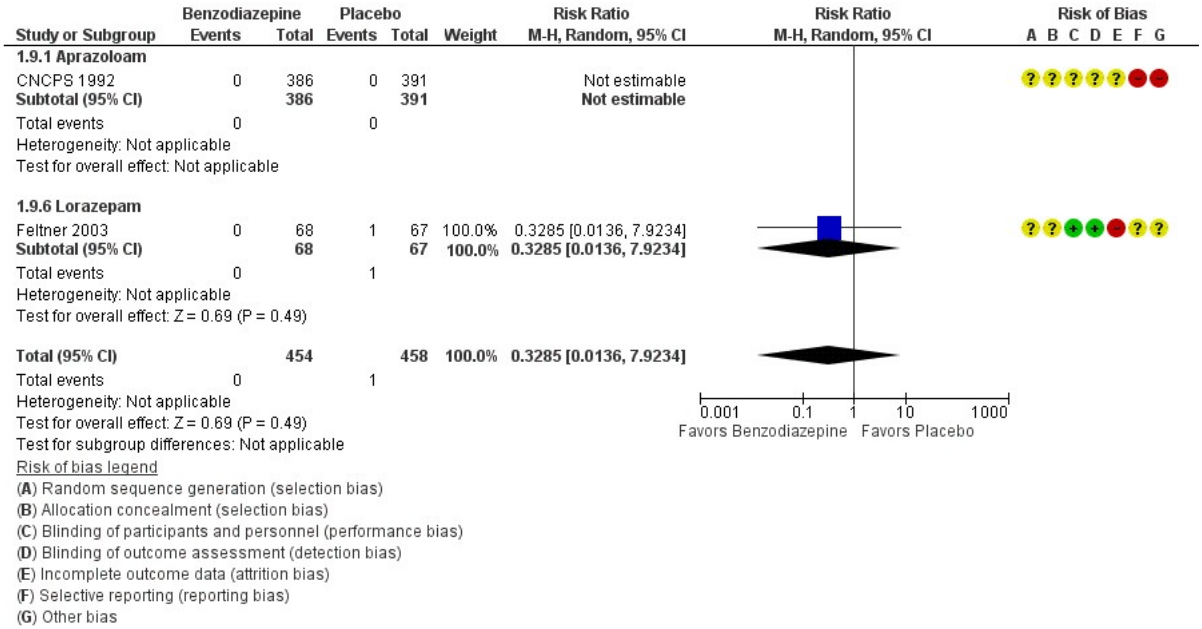
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.7 Serious adverse eventsrisk ratio.

Figure 9 (Analysis 1.8)



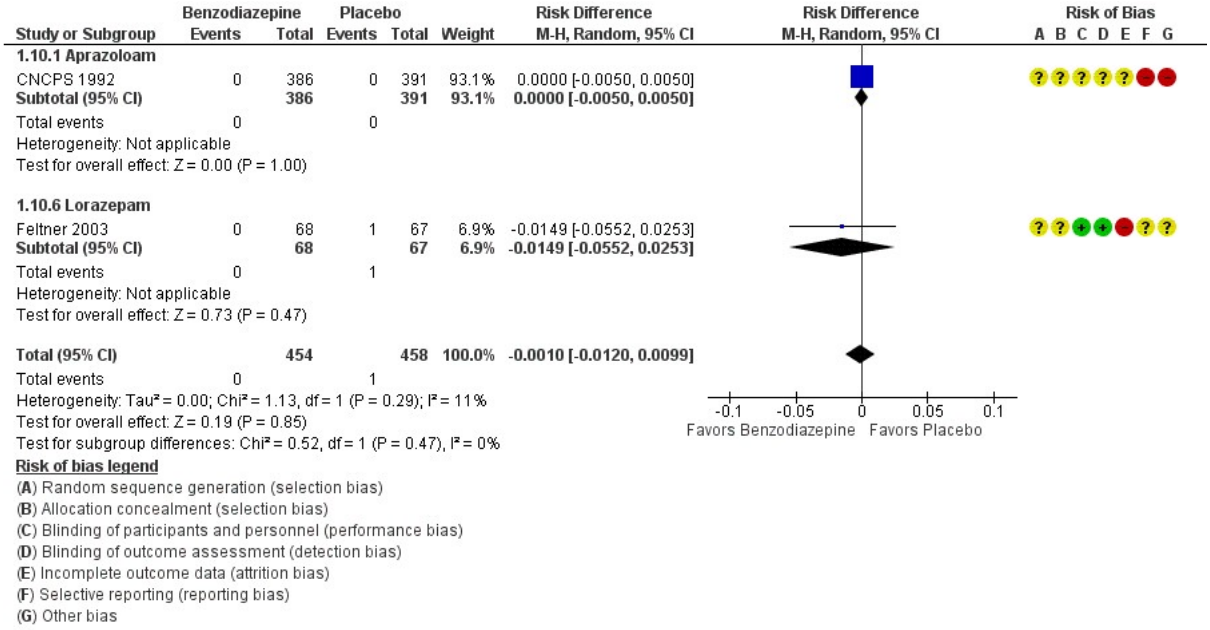
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.8 Serious adverse events_risk difference.

Figure 10 (Analysis 1.9)



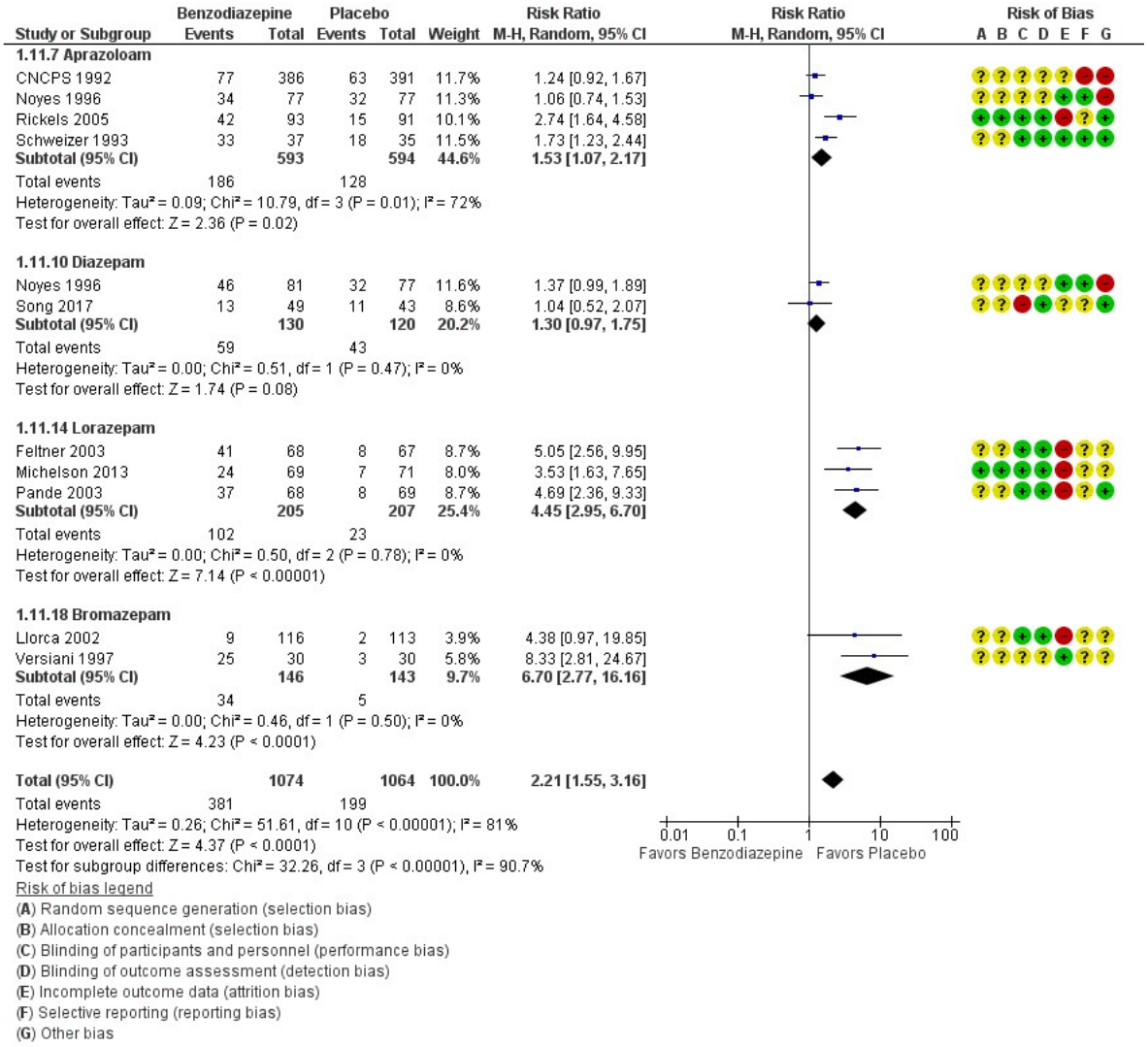
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.9 Suicidal thoughts/attempts_risk ratio.

Figure 11 (Analysis 1.10)



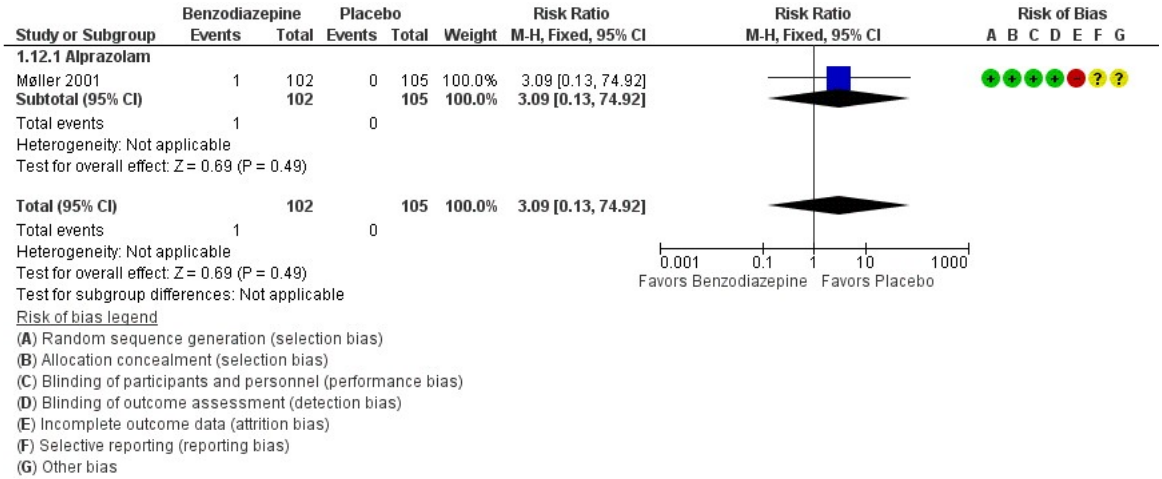
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.10 Suicidal thoughts/attempts_risk difference.

Figure 12 (Analysis 1.11)



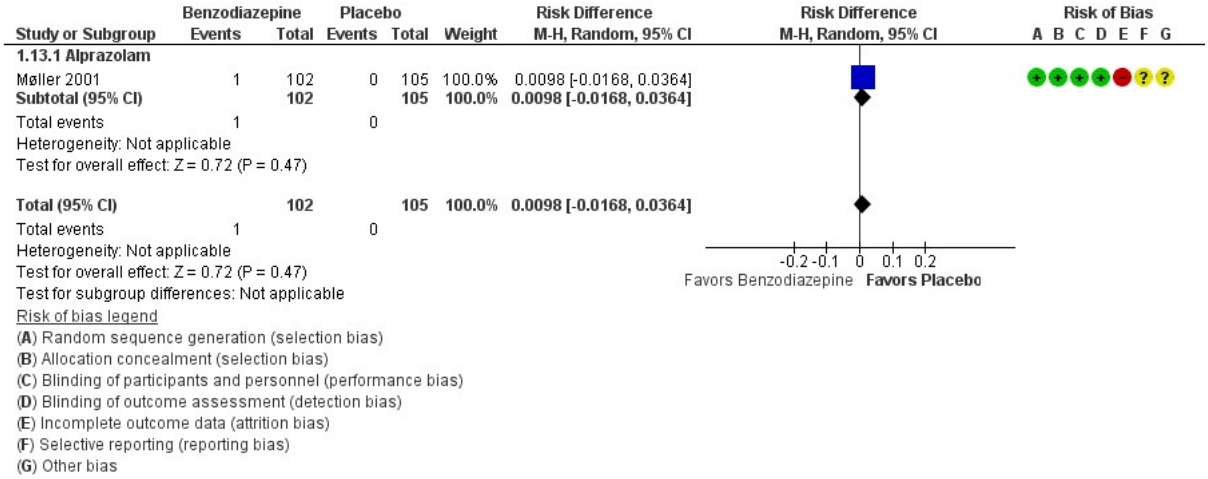
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.11 Daytime drowsiness.

Figure 13 (Analysis 1.12)



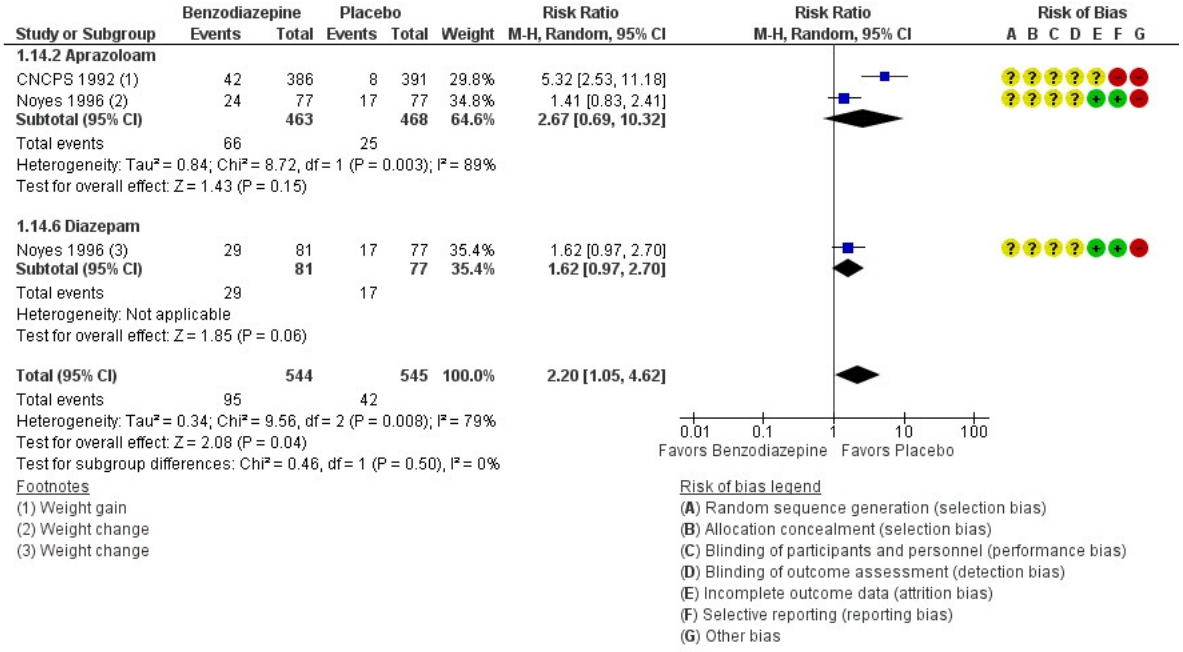
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.12 Fractures_risk ratio

Figure 14 (Analysis 1.13)



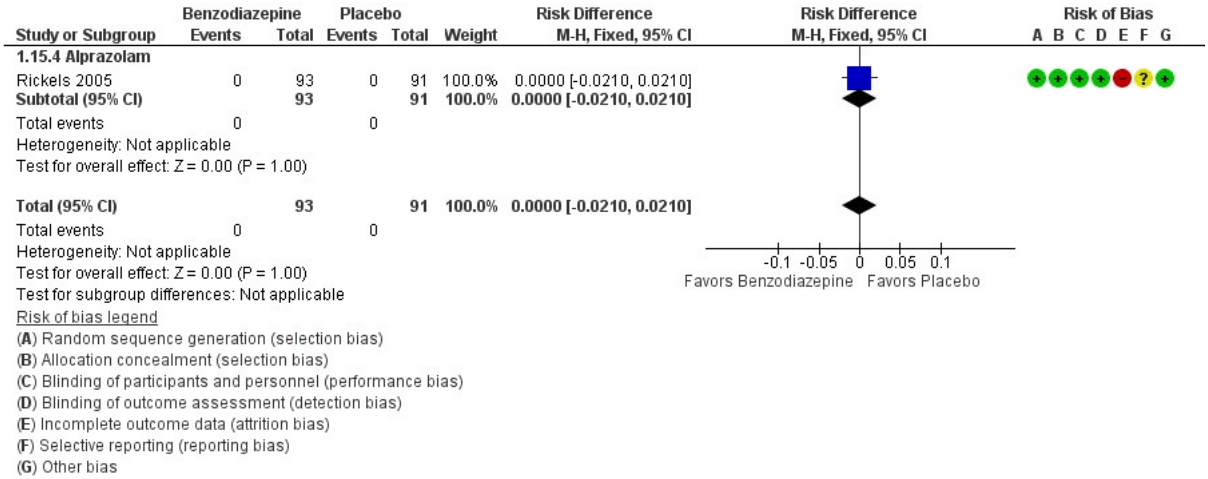
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.13 Fractures_ risk difference.

Figure 15 (Analysis 1.14)



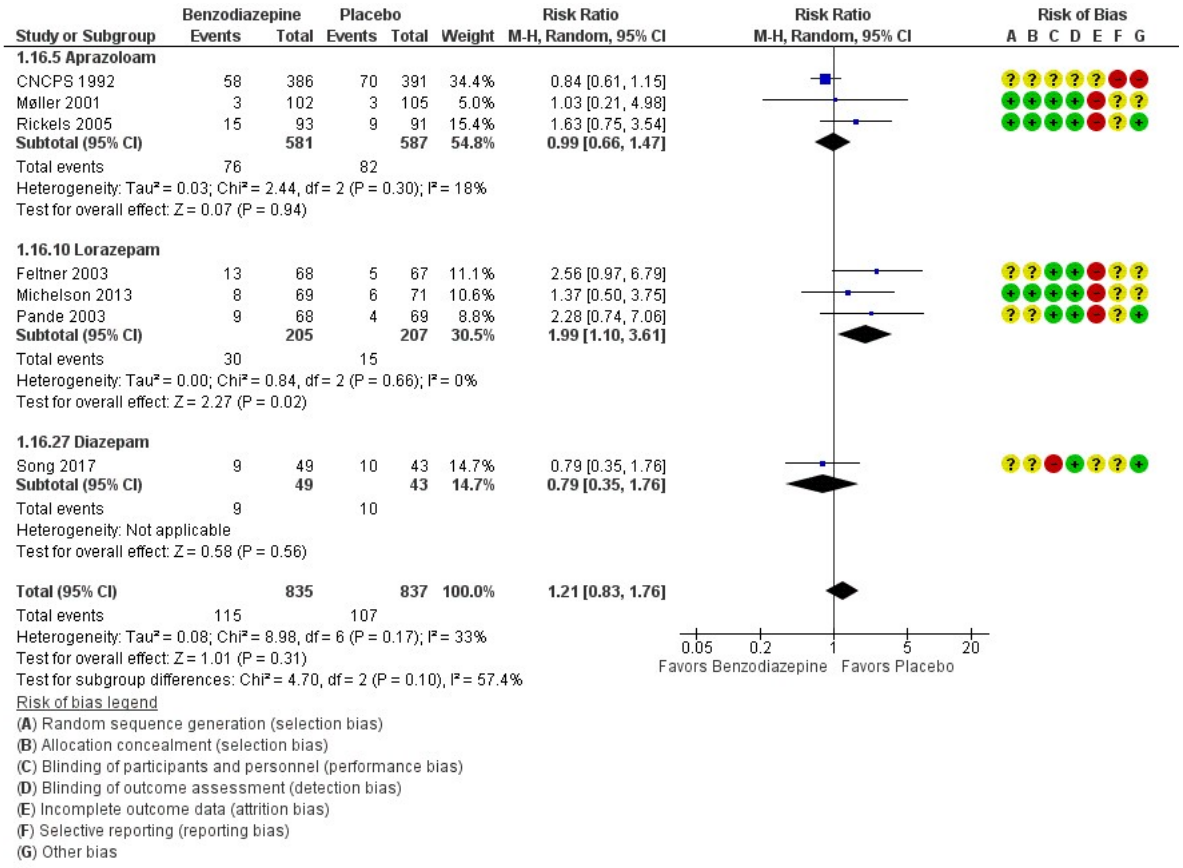
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.14 Weight change.

Figure 16 (Analysis 1.15)



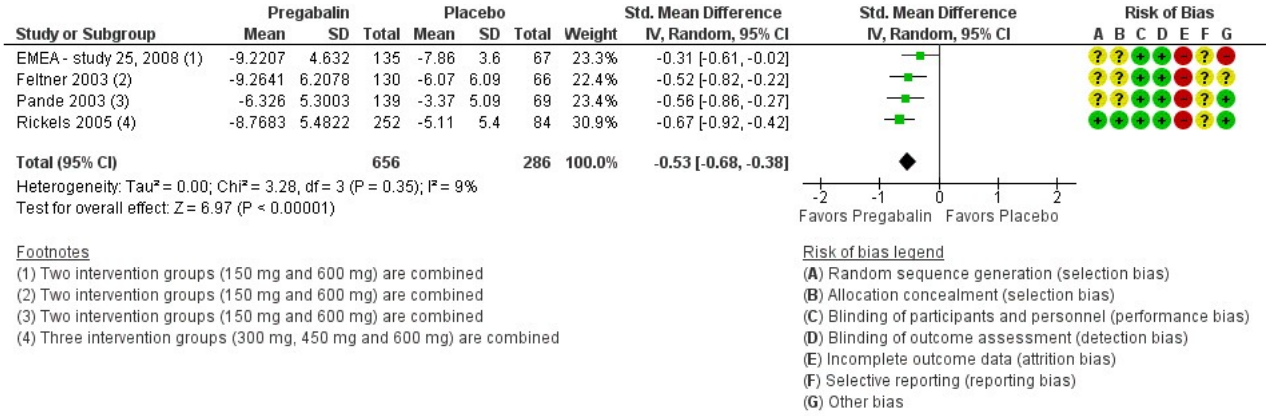
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.15 Cardiac side-effects_risk difference.

Figure 17 (Analysis 1.16)



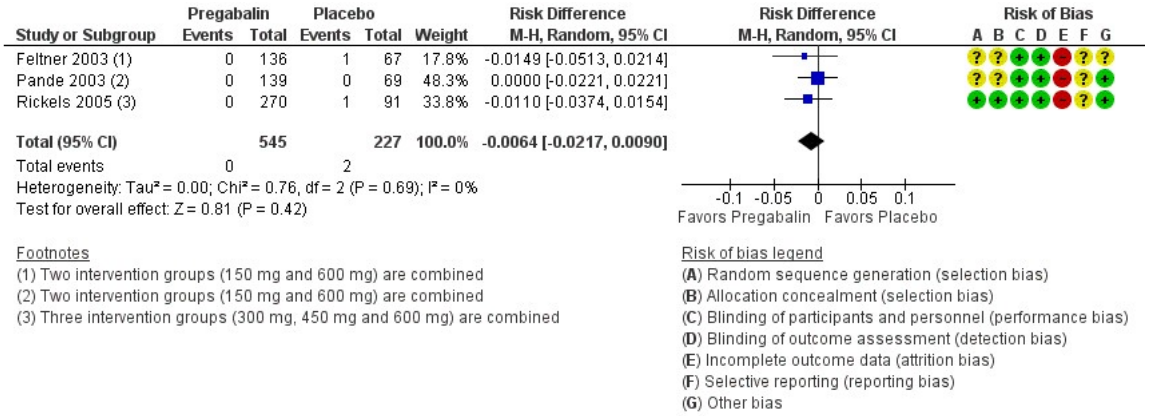
Forest plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.16 Dizziness.

Figure 18 (Analysis 2.1)



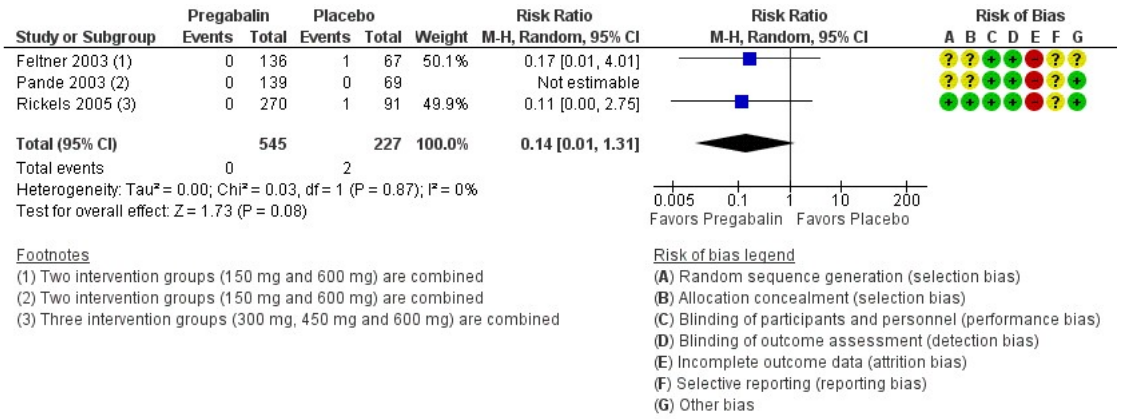
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.1 Anxiety symptoms - HAM-A.

Figure 19 (Analysis 2.2)



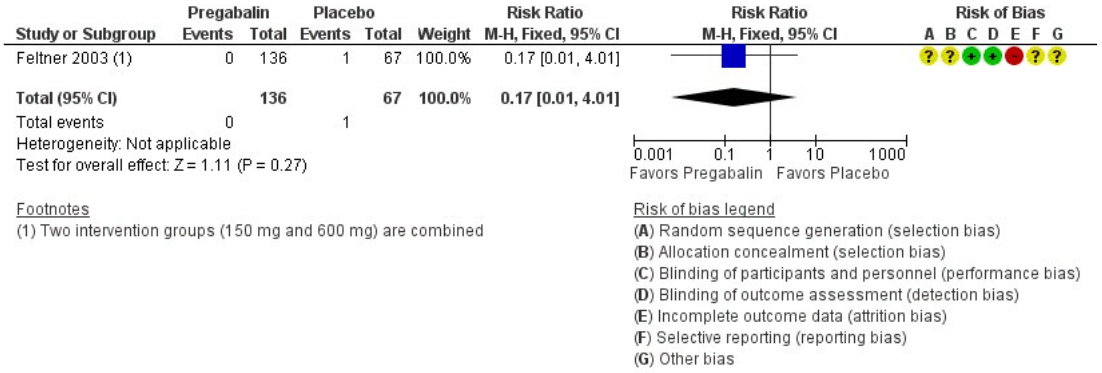
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.2 Serious adverse events_risk difference.

Figure 20 (Analysis 2.3)



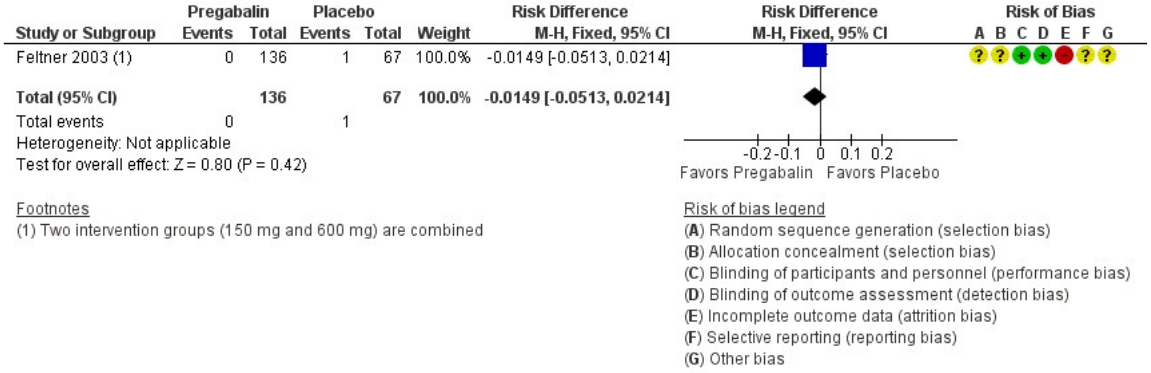
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.3 Serious adverse events_risk ratio.

Figure 21 (Analysis 2.4)



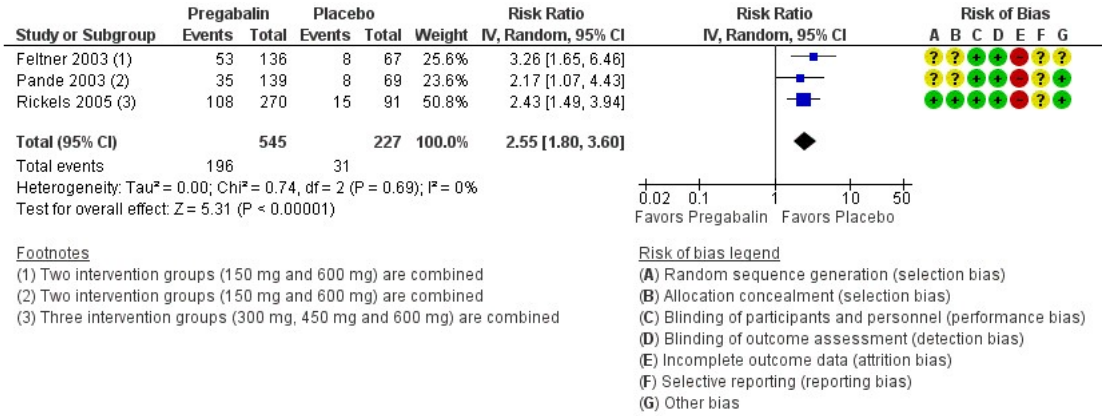
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.4 Suicidal thoughts/attempts_risk ratio

Figure 22 (Analysis 2.5)



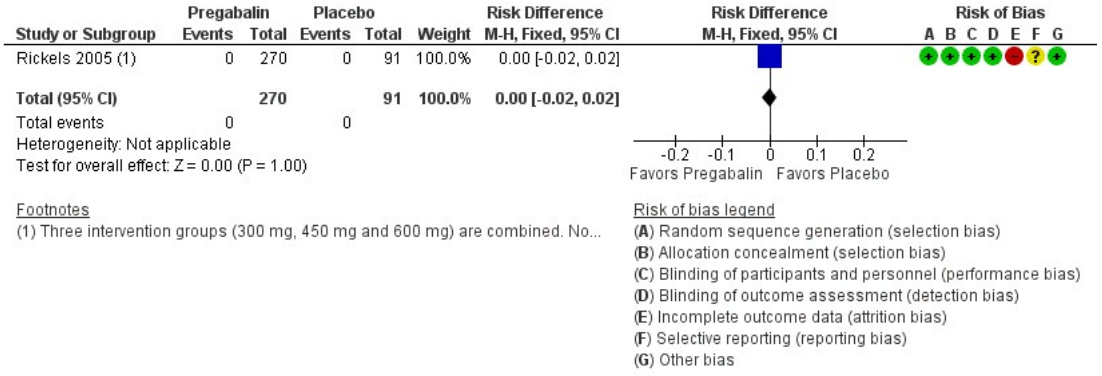
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.5 Suicidal thoughts/attempts_risk difference.

Figure 23 (Analysis 2.6)



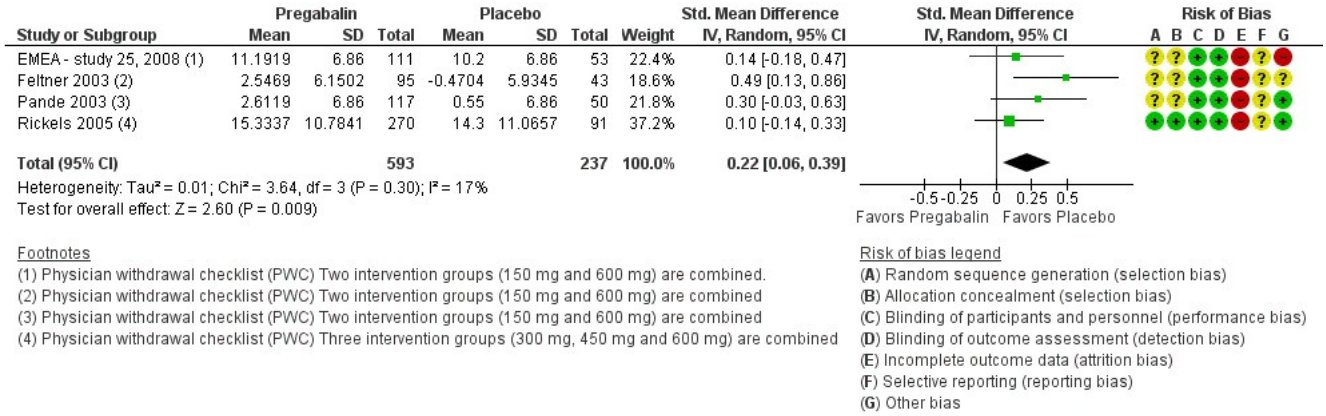
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.6 Daytime drowsiness.

Figure 24 (Analysis 2.7)



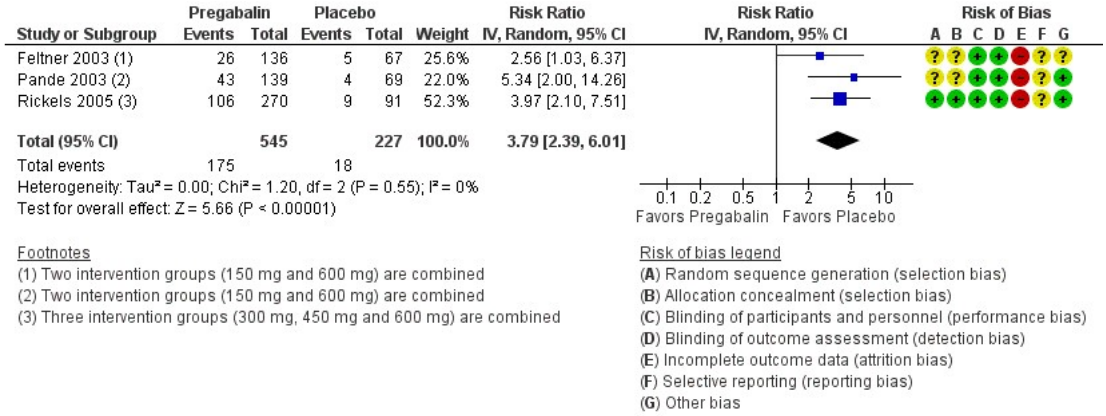
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.7 Cardiac side-effects_risk difference.

Figure 25 (Analysis 2.8)



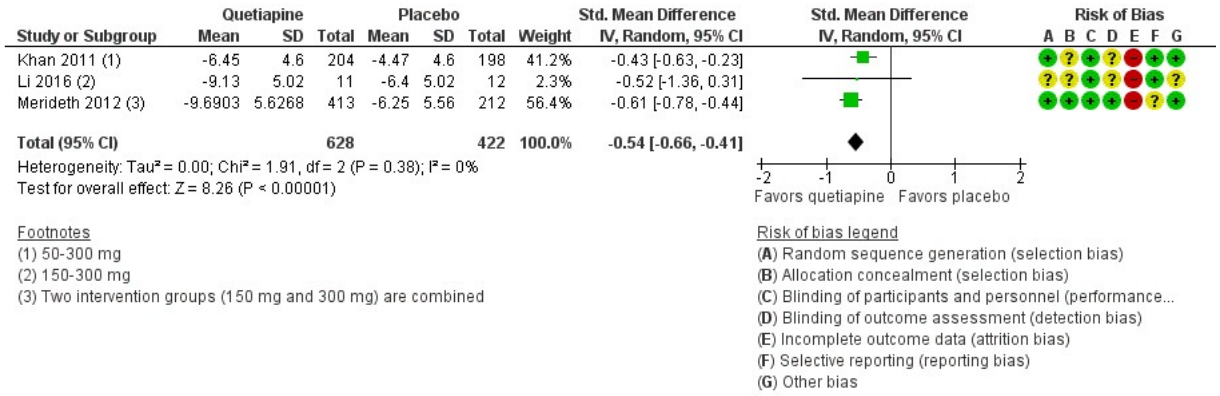
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.8 Addiction - withdrawal symptoms.

Figure 26 (Analysis 2.9)



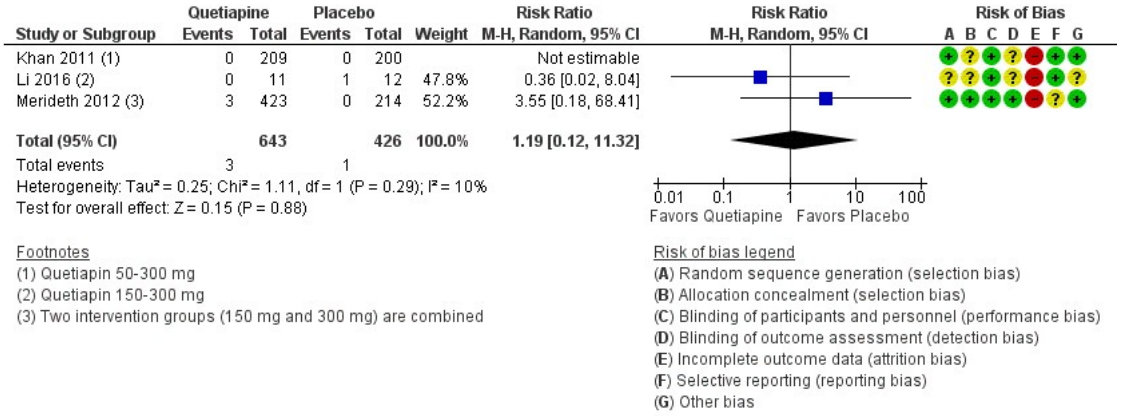
Forest plot of comparison: 2 Pregabalin vs placebo, outcome: 2.9 Dizziness.

Figure 27 (Analysis 3.1)



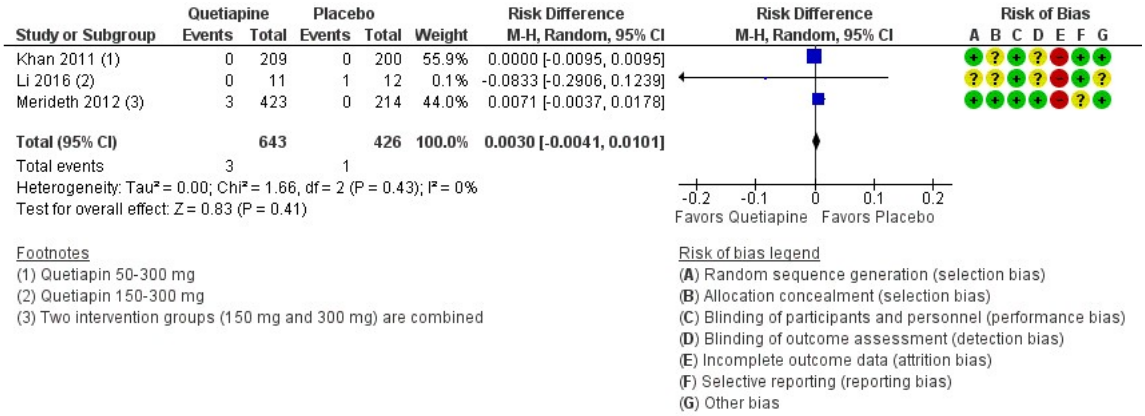
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.1 Anxiety symptoms - HAM-A.

Figure 28 (Analysis 3.2)



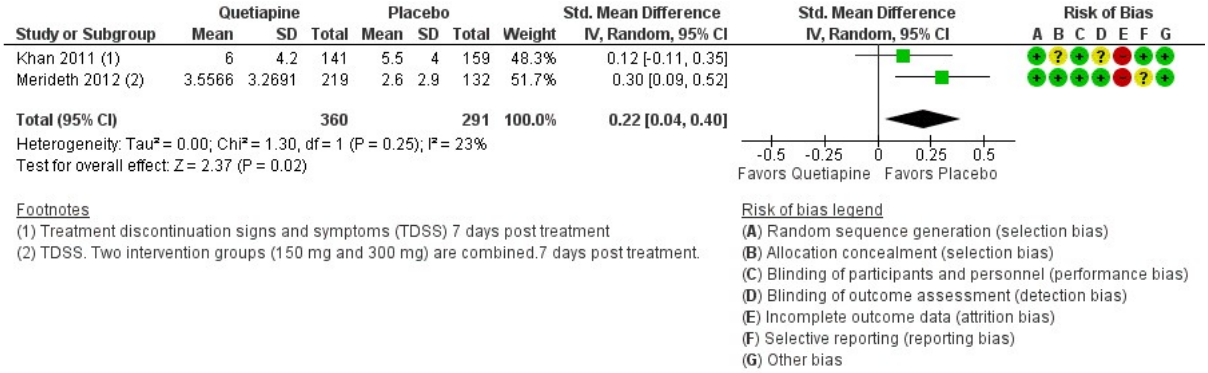
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.2 Serious adverse events_risk ratio.

Figure 29 (Analysis 3.3)



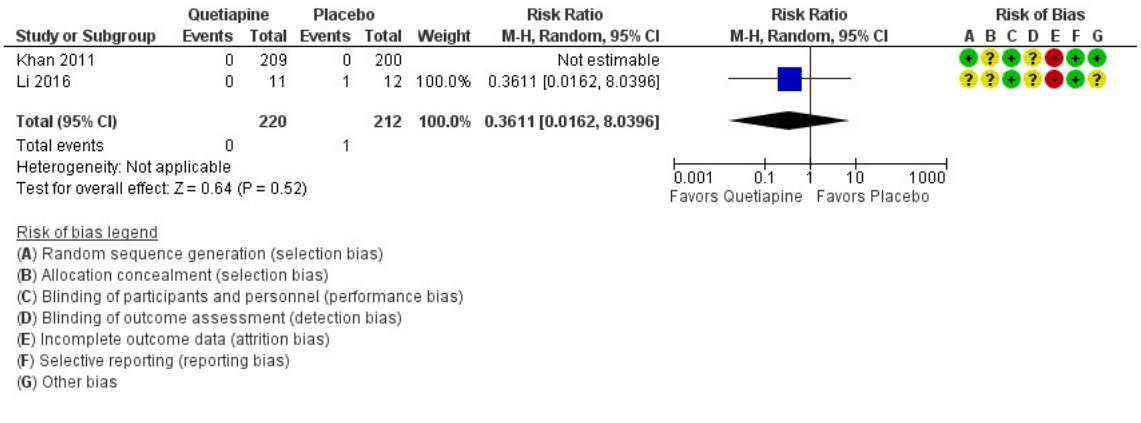
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.3 Serious adverse events_risk difference.

Figure 30 (Analysis 3.4)



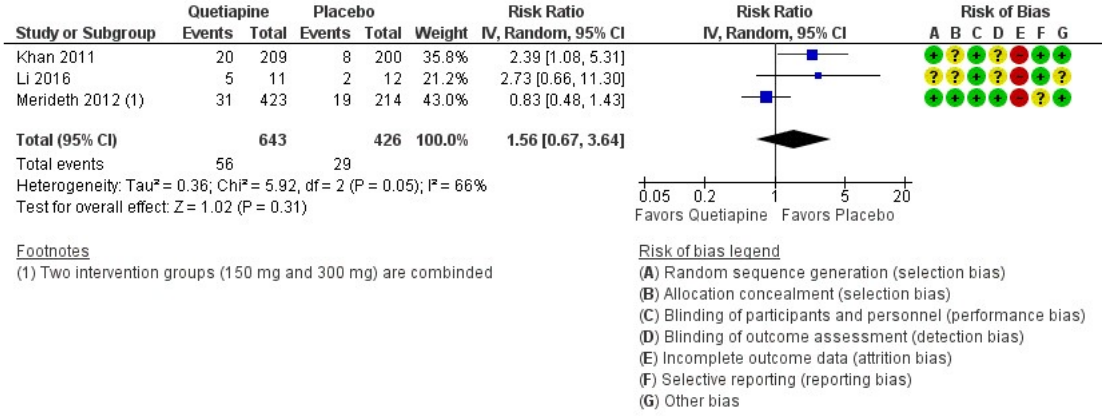
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.4 Addiction - Withdrawal symptoms.

Figure 31 (Analysis 3.5)



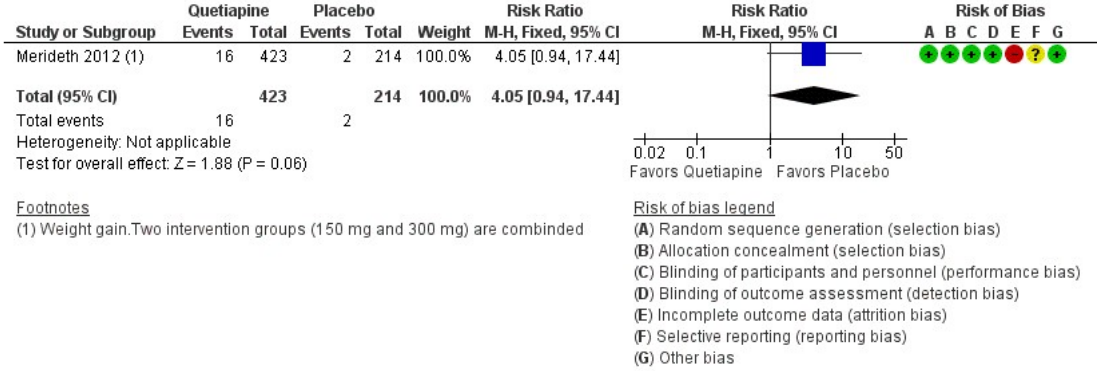
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.5 Suicidal thoughts/attempts.

Figure 32 (Analysis 3.6)



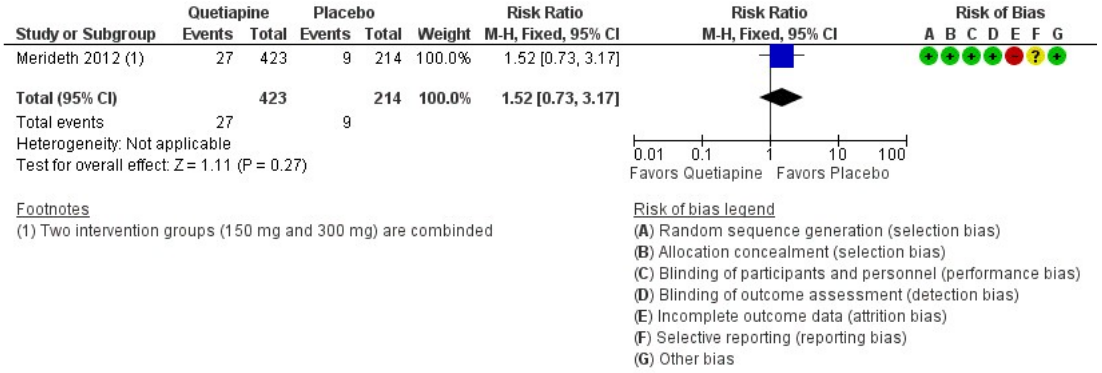
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.6 Daytime drowsiness.

Figure 33 (Analysis 3.7)



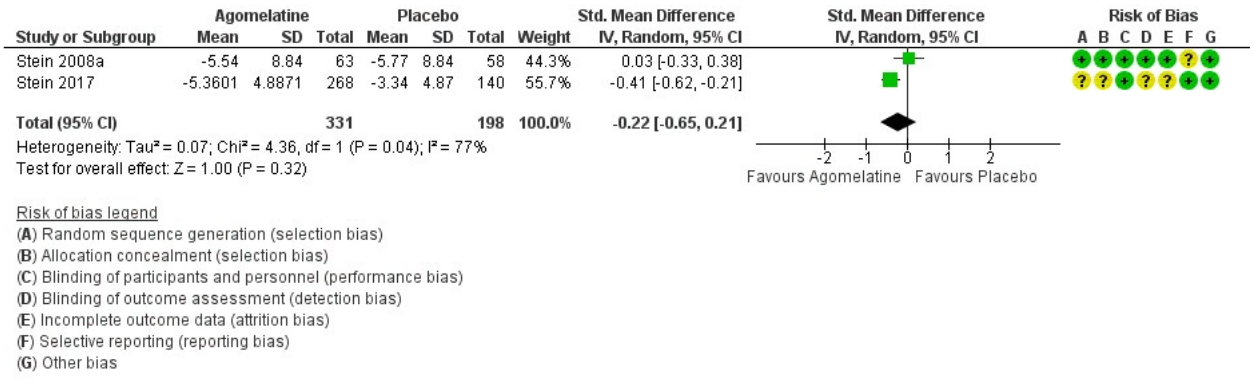
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.7 Weight change.

Figure 34 (Analysis 3.8)



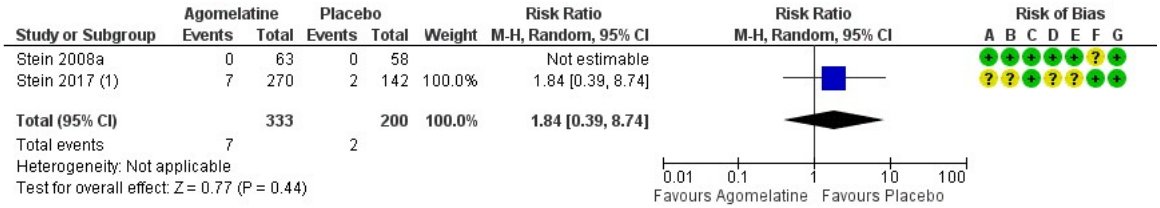
Forest plot of comparison: 3 Quetiapine vs placebo, outcome: 3.8 Extrapyramidal symptoms.

Figure 35 (Analysis 4.1)



Forest plot of comparison: 4 Agomelatine vs placebo, outcome: 4.1 Anxiety symptoms - HAM-A.

Figure 36 (Analysis 4.2)

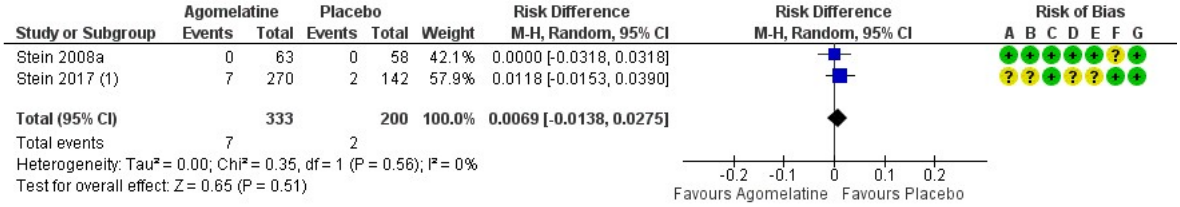


Footnotes
(1) Two intervention groups (10 mg og 25 mg) are combinded

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 4 Agomelatine vs placebo, outcome: 4.2 Serious adverse events_risk ratio.

Figure 37 (Analysis 4.3)

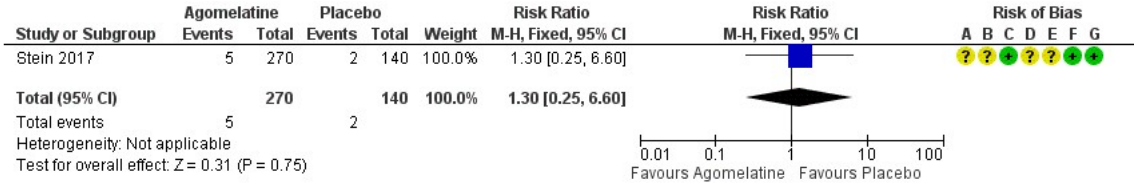


Footnotes
(1) Two intervention groups (10 mg og 25 mg) are combinded

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 4 Agomelatine vs placebo, outcome: 4.3 Serious adverse events_risk difference.

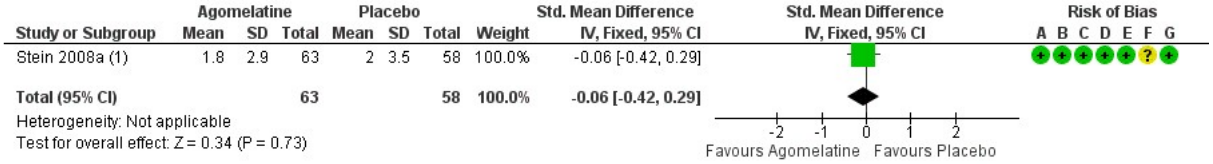
Figure 38 (Analysis 4.4)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 4 Agomelatine vs placebo, outcome: 4.4 Daytime drowsiness.

Figure 39 (Analysis 4.5)

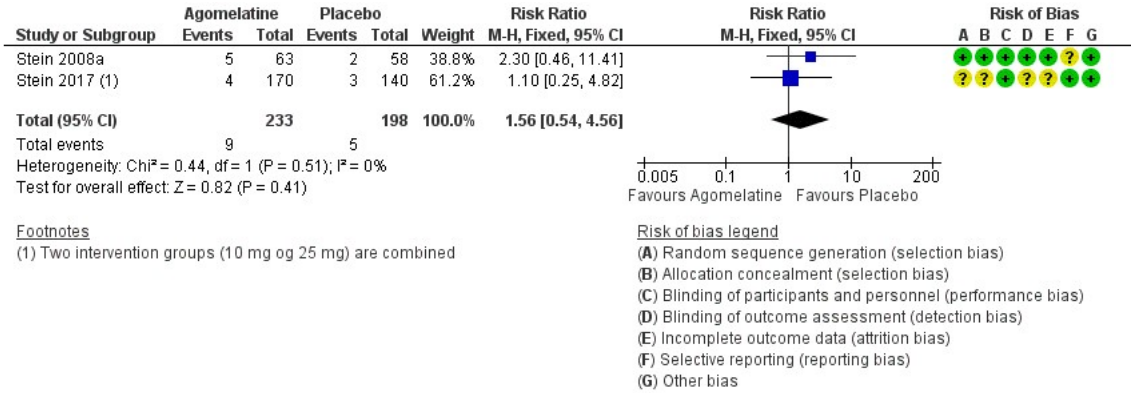


Footnotes
(1) Discontinuation-Emergent Signs and Symptoms (DESS) Scale. post treatment (12 weeks)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

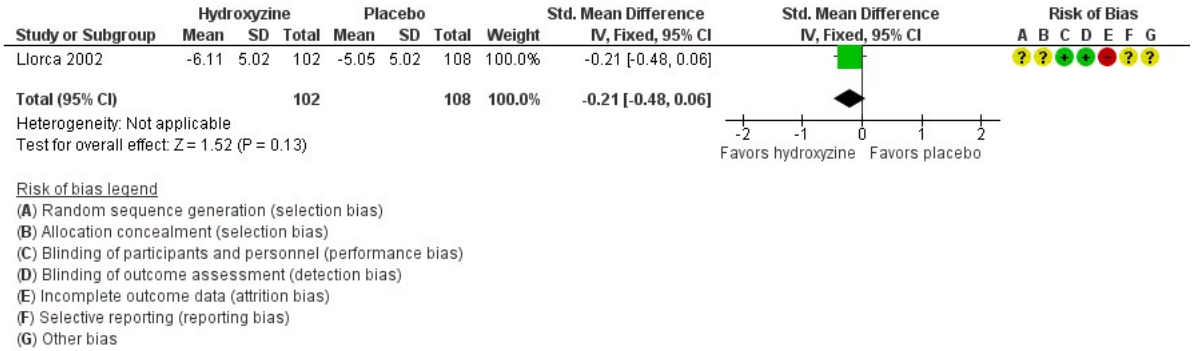
Forest plot of comparison: 4 Agomelatine vs placebo, outcome: 4.5 Addiction withdrawal symptoms.

Figure 40 (Analysis 4.6)



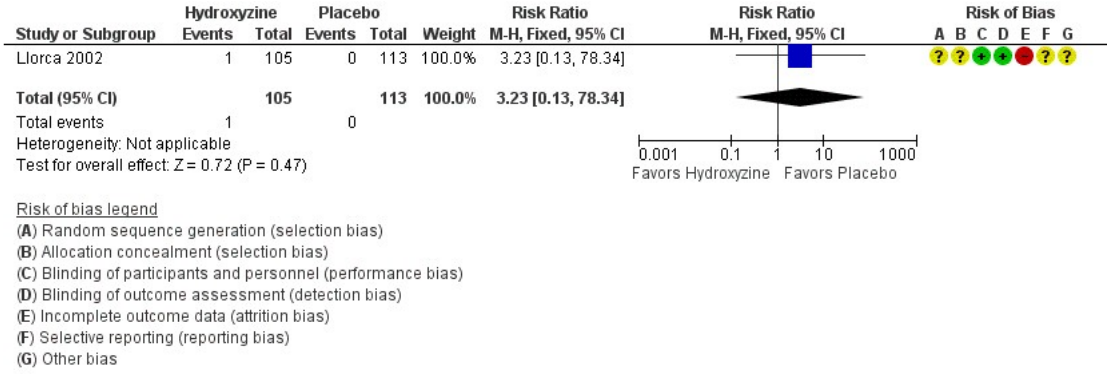
Forest plot of comparison: 4 Agomelatine vs placebo, outcome: 4.6 Dizziness.

Figure 41 (Analysis 5.1)



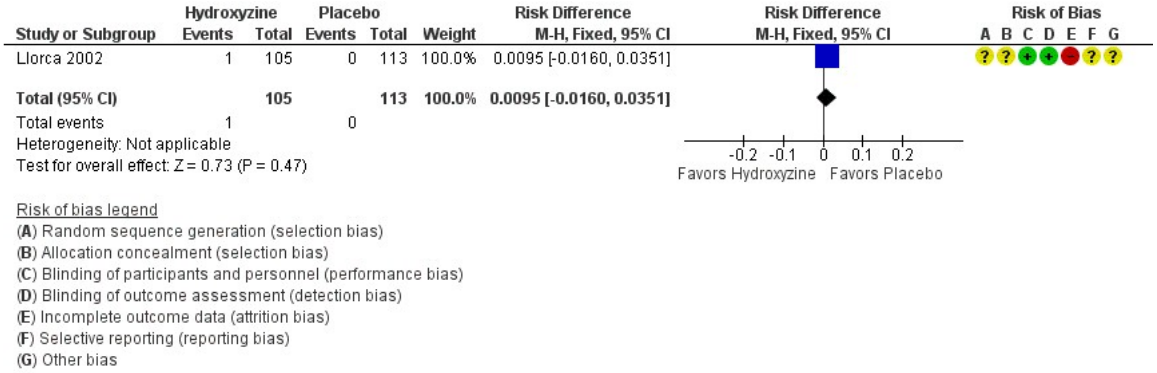
Forest plot of comparison: 5 Hydroxyzine vs placebo, outcome: 5.1 Anxiety symptoms - HAM-A.

Figure 42 (Analysis 5.2)



Forest plot of comparison: 5 Hydroxyzine vs placebo, outcome: 5.2 Serious adverse events_risk ratio.

Figure 43 (Analysis 5.3)



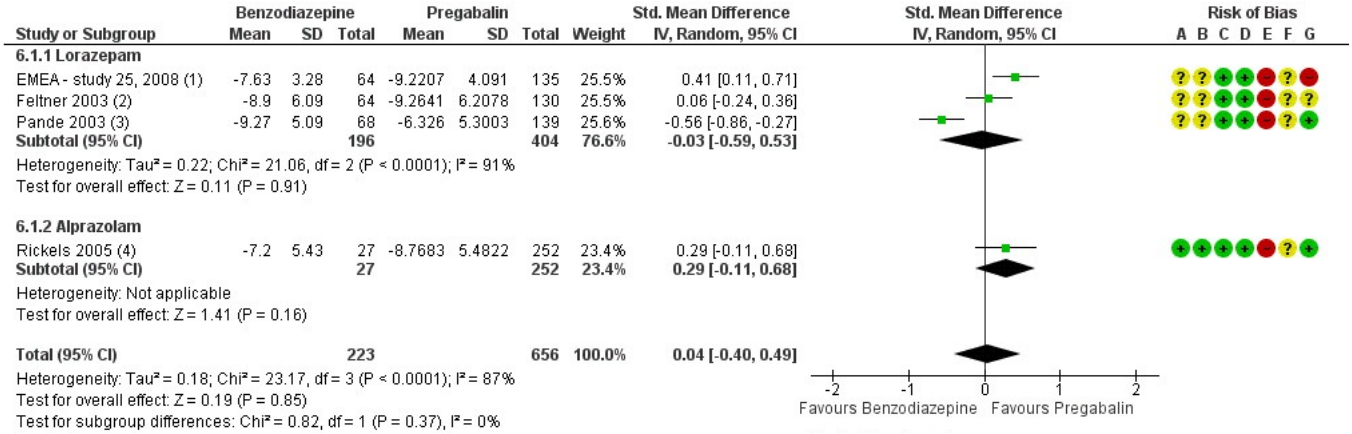
Forest plot of comparison: 5 Hydroxyzine vs placebo, outcome: 5.3 Serious adverse events_risk difference.

Figure 44 (Analysis 5.4)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 5 Hydroxyzine vs placebo, outcome: 5.4 Daytime drowsiness.

Figure 45 (Analysis 6.1)

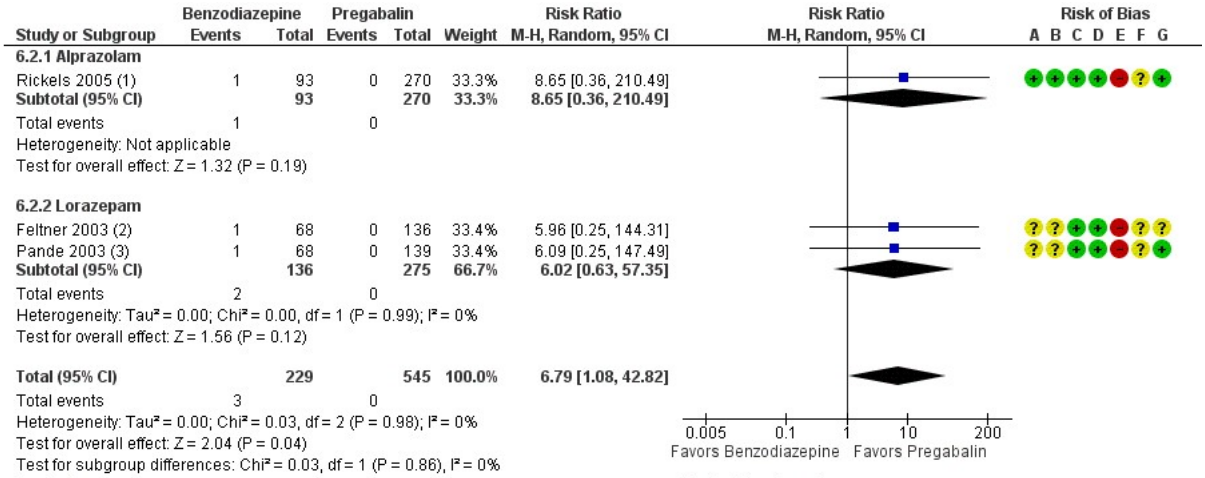


Footnotes
(1) Pregabalin: Two intervention groups (150 mg and 600 mg) are combined
(2) Pregabalin: Two intervention groups (150 mg and 600 mg) are combined
(3) Pregabalin: Two intervention groups (150 mg and 600 mg) are combined
(4) Pregabalin: Three intervention groups (300 mg, 450 mg and 600 mg) are combined

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.1 Anxiety symptoms HAM-A.

Figure 46 (Analysis 6.2)

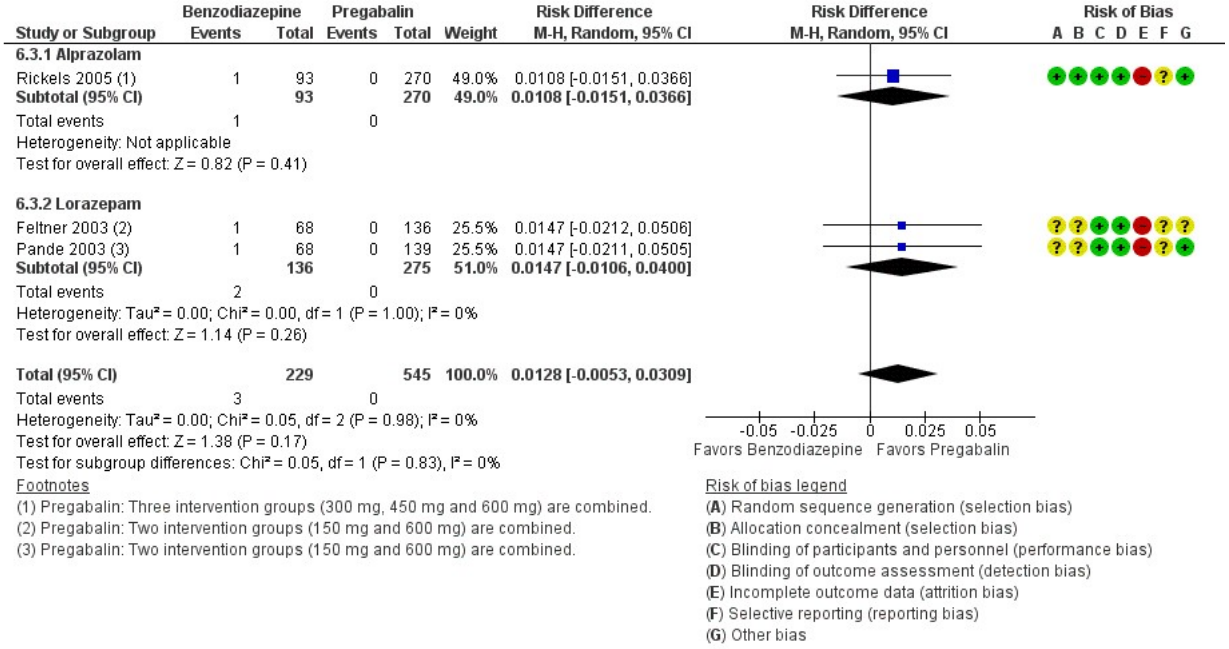


Footnotes
(1) Pregabalin: Three intervention groups (300 mg, 450 mg and 600 mg) are combined.
(2) Pregabalin: Two intervention groups (150 mg and 600 mg) are combined.
(3) Pregabalin: Two intervention groups (150 mg and 600 mg) are combined.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

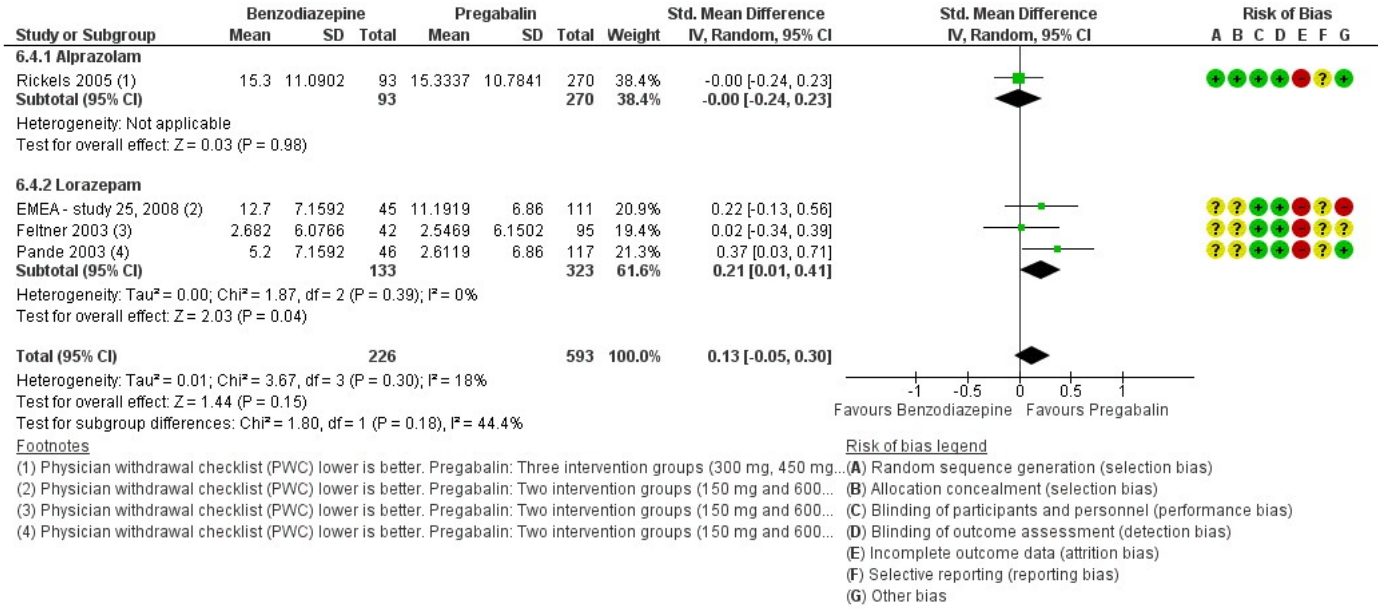
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.2 Serious adverse events.

Figure 47 (Analysis 6.3)



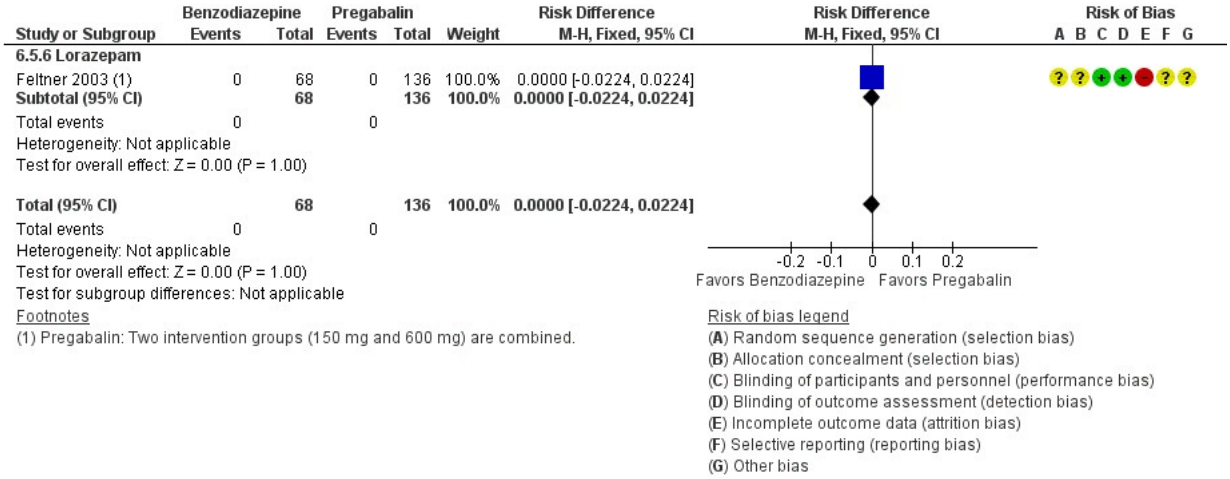
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.3 Serious adverse events.

Figure 48 (Analysis 6.4)



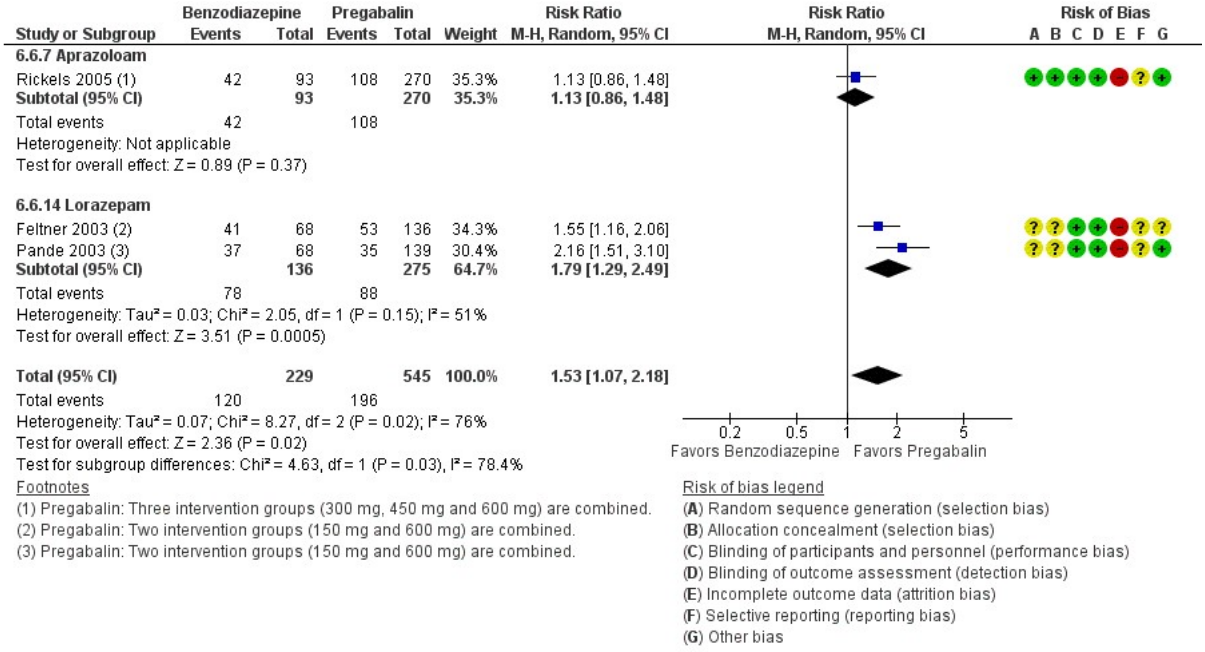
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.4 Addiction - wihtdrawal symptoms.

Figure 49 (Analysis 6.5)



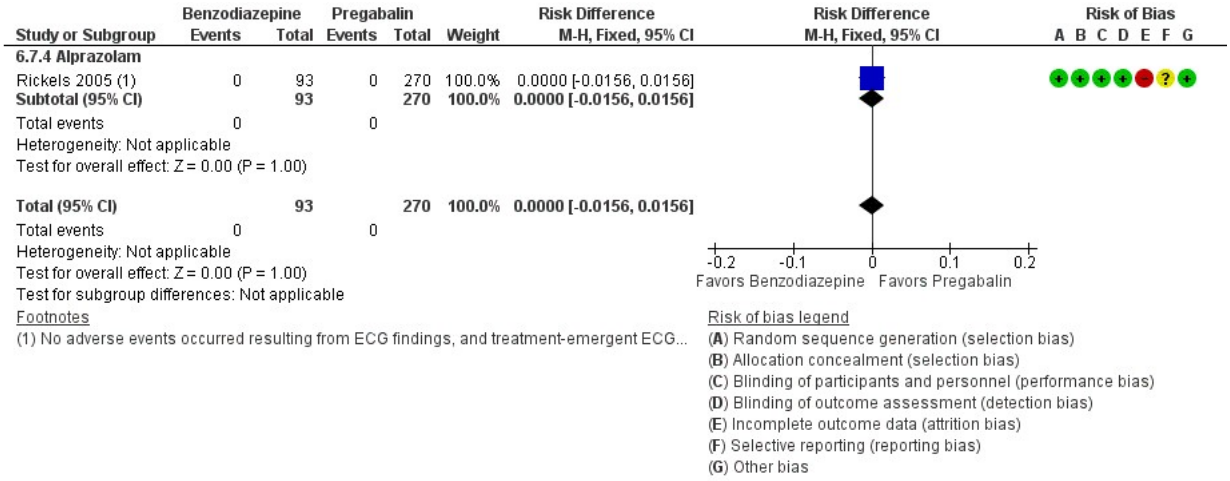
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.5 Suicidal thoughts/attempts_risk difference.

Figure 50 (Analysis 6.6)



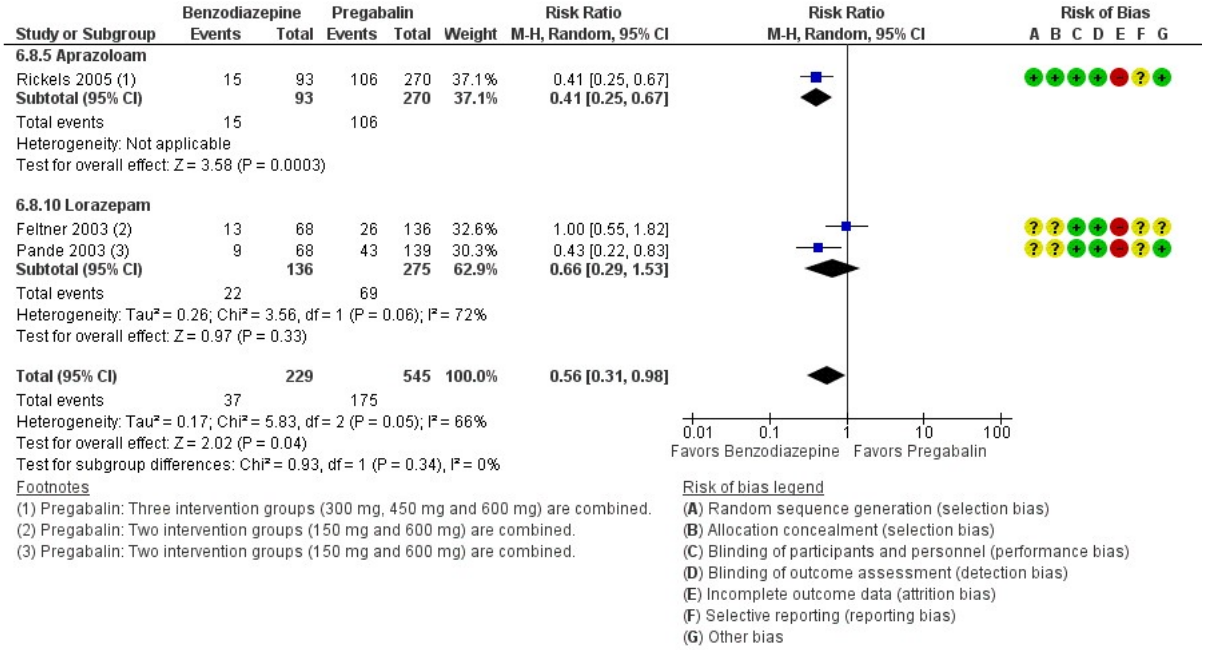
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.6 Daytime drowsiness.

Figure 51 (Analysis 6.7)



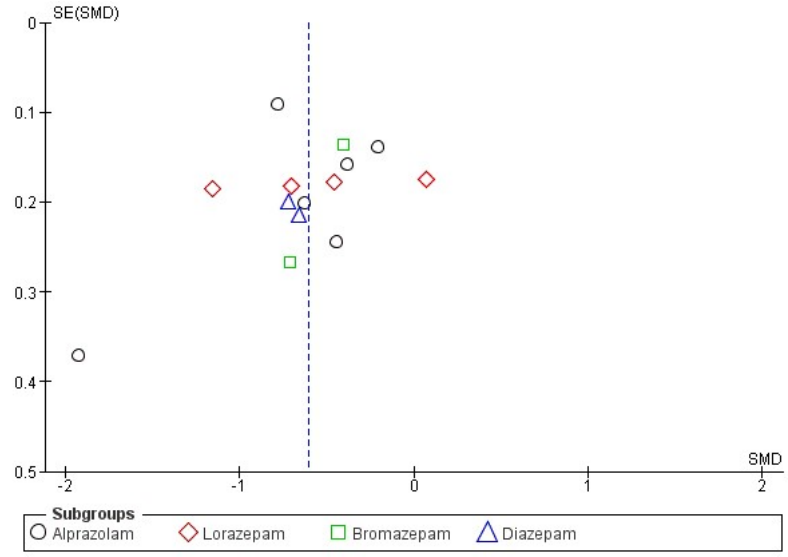
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.7 Cardiac side-effects_risk difference.

Figure 52 (Analysis 6.8)



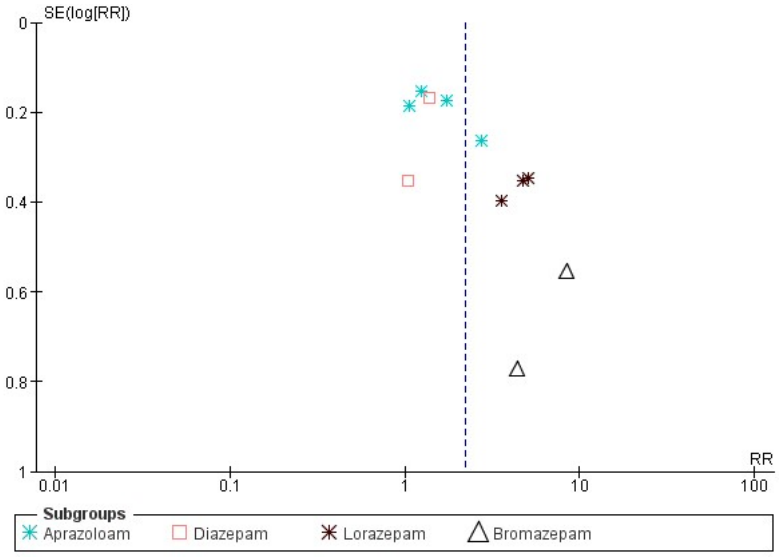
Forest plot of comparison: 6 Benzodiazepine vs Pregabalin, outcome: 6.8 Dizziness.

Figure 53 (Analysis 1.1)



Funnel plot of comparison: 1 Benzodiazepine vs placebo, outcome: 1.1 Anxiety symptoms - HAM-A.

Figure 54 (Analysis 1.11)



Funnel plot of comparison: 1 Benzodiazepin vs placebo, outcome: 1.10 Træthed i dagtiden.