NKR 58 Antidepressiv medicin vs kognitiv adfærdsterapi for angst

Review information

Authors

[Empty name][1]

[1][Empty affiliation]

Citation example: [Empty name]. NKR 58 Antidepressiv medicin vs kognitiv adfærdsterapi for angst. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Azhar 2000

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years (SD)*: 36.36 (7.54) Intervention 2 ● *Mean age, years (SD)*: 31.57 (8.0) Kontrol 1 ● *Mean age, years (SD)*: 31.66 (8.09) **Included criteria:** Subjects selected for the study consisted of male and female patients diagnosed as panic disorder by a psychiatrist based on DSM IV criteria. The subjects were recruited from among the patients attending the USM Hospital psychotherapy clinic. They were on a waiting list.They were divided at random into three groups,i.e.(1) the Fluvoxamine onlyg roup (FVX) group, (2) a group that were treated with both Fluvoxamine and cognitive behaviour therapy (FVX+CBT) and (3) a group that received only Cognitive Behaviour Therapy (CBT). The other inclusion criterias include; age between 18 to 50, ability to communicate well, cooperation to carry ou tsessions in a group for one hour per week. **Excluded criteria:** The exclusion criterias include having other disorders besides panic, egophobias, hypochondriasis, other neuroses. All patients were required to give informed consent to enter the study. They were dropped from the study if they requested to be included in either group.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Fluvoxamine. Thosei nt he FVX group received a starting dose of FVX 50 mg. per day, were seen weekly and the dose increased as necessary to a maximum of 200 mg. per day if no side effects occurred ● *Dose*: 50-200 mg/day ● *Duration*: 9 weeks

	Intervention 2 ● *Description*: Fluvoxamine + Cognitive behavoiral therapy (CBT). Those in the FVX group received a starting dose of FVX 50 mg. per day, were seen weekly and the dose increased as necessary to a maximum of 200 mg. per day if no side effects occurred.Those in the CBT+ FVX group were treated in a similar manner as the previous group with the addition of weekly CBT sessions. ● *Dose*: Fluvoxamine 50-200 mg/day + weekly sessions of CBT ● *Duration*: 9 weeks Kontrol 1 ● *Description*: Cognitive behavoiral therapy (CBT). In the CBT only group, the patients were seen for weekly sessions of CBT but were never given FVX or any other drugs. All patients were seen weekly for 9 weeks and those in the last two groups received weekly sessions of CBT as described by Clark for panic disorder ● *Dose*: weekly sessions of CBT ● *Duration*: 9 weeks
Outcomes	*Grad af angst, HAM-A, mean, SD* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** No information **Country:** Malaysia **Setting:** Outpatient clinic **Authors name:** M Z Azhar **Institution:** Psychotherapy Clinic, Hospital Universiti Sains Malaysia **Address:** Psychotherapy Clinic, Hospital Universiti Sains Malaysia,Kubang Kerian,16150 Kota Bahru, Kelantan
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information of how the allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: No information of blinding of participants and health care professionals. No use of placebo medication described. Blinding of CBT not feasible,

Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "the following tests were done/measured by a research assistant who is blind to the patients' group. The scales are all self-reports and the research assistant only guides the subjects." Judgement Comment: Likely outcome assessor is blinded (HAM-A).Research assistant were blinded but outcomes were stated as self-reported. these scales are normally clinician rated
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "There were 66 patients with 22 patients in each group. However a total of 15 patients defaulted follow-up leaving 51 patients who completed 9 weeks of the study period with 17 patients in each group." Judgement Comment: Moderate attrition (5/22) but balanced between groups however, no investigation of reasons for drop and no intention to treat analyses.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available. The study reports on all the outcomes stated in the methods section.
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Bakker 1999a

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 34.7 (8.9) ● *Number of females (%)*: 19 (59%) ● *Duration/mean years since onset (SD)*: 6.7 (7.5) Intervention 2 ● *mean age, years (SD)*: 35.3 (9.3) ● *Number of females (%)*: 18 (56%) ● *Duration/mean years since onset (SD)*: 7.4 (6.1) Kontrol 1 ● *mean age, years (SD)*: 33.7 (8.1) ● *Number of females (%)*: 23 (66%) ● *Duration/mean years since onset (SD)*: 6.3 (6.3) **Included criteria:** DSM-III-R criteria for panic disorder as a main diagnosis and had a minimum of 3 attacks in the 3-week run-in period. **Excluded criteria:** Pregnant women, and patients with severe somatic deseases were excluded. Patients who used antidepressants, neuroleptics or benzodiazepines could only be included if they were willing and able to stop taking these drugs before the placebo run-in period.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Paroxetine. Medication was administered by residents in psychiatry, with minimum 1 year of experience from a specialized outpatient clinic for anxiety disorders. Treatment started with a daily dose 10 mg/day. Treatment was titrated up to 20 mg/day at the end of the forst week. Thereafter at the end of week 2,3,4,6 the dosage could be adjusted. At all times the patient were unaware of any change in the dosing regime. At week 7-12 the medication continued at a constant level. ● *Duration*: 12 weeks

	● *Dose*: 20-60mg/day Kontrol 1 ● *Description*: Cognitive therapy was provided in 12 wwekly sessions by psychologists and pcychiatrists with broad experience in cognitive-behavoiral treatment of anxiety disorders. Cognitive therapy was based on the cognitive theory of Clark. Patients were challenged to replace their socalled catastrophic misinterpretations of benign bodily sensations by alternative, rational and nondistressing thoughts. Behavioral experiments were introduced to test the empirical basis for the causal catastrophic misinterpretations ● *Duration*: 12 weeks ● *Dose*: 12 weekly sessions of 45 min
Outcomes	*Grad af angst, HAM-A* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint *Funktion, Sheeran Disability Scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Sheeran Disability Scale ● **Range**: 0-30 ● **Direction**: Lower is better ● **Data value**: Endpoint *Grad af undgåelse, Mark Sheran phobia Scale, subscale agoraphobia* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Mark Sheran phobia Scale, subscale agoraphobia ● **Range**: 0-52 ● **Direction**: ● **Data value**: Endpoint *Bedring (free of panic attacts in the last three weeks of the intervention)* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Remitters ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported

	● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** Sponsered by a grant from SmithKline Beecham Pharmaceuticals **Country:** The Netherlands **Setting:** Outpatient clinics **Comments:** **Authors name:** Abraham Bakker **Institution:** Department of Psychiatry and the institute for research in extramural medicine, Vrije University Amsterdam **Email:** bramb@pca-znw.nl **Address:** Valeriusplein 9, 1075 BG Amsterdam
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information of how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Patients were blinded to medication and placebo drug. Blinding of patients receiving CBT and health care providers of CBT not feasible. Quote: "Patients assigned to the medication groups received dobble-blind paroxetine, clomipramine or placebo"
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: No information of blinding of outcome assessors (HAM-A)Patients receiving medication or placebo were blinded regarding self-reported scores(PGE, Sheehan disability score and overall phobia score)Blinding of patients in the CBT-group not feasible Self-reported panic symptoms were recorded in panic diaries and ths scales MSPS, PGE and SDS were self-reported. Other assessors were "experienced residents in psyciatry" however, unclear how they were blinded.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 4 (12.5%) dropped out in the paroxetine group, 3 (9.4 %) in the clomipramine group, 9 (25.7%) in the CBT group.8 dropped out in the CBT due to lact of patient compliance, 1 dropped out in the paroxetine and clomipramine group respectively, due to lack of patient compliance.Imbalance in dropouts both in numbers and reasons. Intention to treatanalyses were performed with last observation carried forward Similar low attrition between groups (<30%) with described reasons for dropout. ITT analysis.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available, the study reports on all the outcome stated in the methods section No protocol however, alle outcomes reported as expected including both completers and ITT.

Other bias	Unclear risk	Judgement Comment: Study supported by a grant from the industry and no statements about conflicts of interest.

Bakker 1999b

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	
Interventions	Intervention 2 ● *Description*: Clomipramine. Medication was administered by residents in psychiatry, with minimum 1 year of experience from a specialized outpatient clinic for anxiety disorders. Treatment started with a daily dose 10 mg/day increasing to 25 mg/day after 3 days. Treatment was titrated up to 50 mg/day at the end of the forst week. At all times the patient were unaware of any change in the dosing regime. At week 7-12 the medication continued at a constant level. ● *Duration*: 12 weeks ● *Dose*: 50-150 mg/day Kontrol 1 ● *Description*: Cognitive therapy was provided in 12 weekly sessions by psychologists and pcychiatrists with broad experience in cognitive-behavoiral treatment of anxiety disorders. Cognitive therapy was based on the cognitive theory of Clark. Patients were challenged to replace their socalled catastrophic misinterpretations of benign bodily sensations by alternative, rational and nondistressing thoughts. Behavioral experiments were introduced to test the empirical basis for the causal catastrophic misinterpretations ● *Duration*: 12 weeks ● *Dose*: 12 weekly sessions of 45 min
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information of how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Patients were blinded to medication and placebo drug. Blinding of patients receiving CBT and health care providers of CBT not feasible. Quote: "Patients assigned to the medication groups received dobble-blind paroxetine, clomipramine or placebo"

Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: No information of blinding of outcome assessors (HAM-A)Patients receiving medication or placebo were blinded regarding self-reported scores(PGE, Sheehan disability score and overall phobia score)Blinding of patients in the CBT-group not feasible Self-reported panic symptoms were recorded in panic diaries and ths scales MSPS, PGE and SDS were self-reported. Other assessors were "experienced residents in psyciatry" however, unclear how they were blinded.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 4 (12.5%) dropped out in the paroxetine group, 3 (9.4 %) in the clomipramine group, 9 (25.7%) in the CBT group.8 dropped out in the CBT due to lact of patient compliance, 1 dropped out in the paroxetine and clomipramine group respectively, due to lack of patient compliance.Imbalance in dropouts both in numbers and reasons. Intention to treat analyses were performed with last observation carried forward Similar low attrition between groups (<30%) with described reasons for dropout. ITT analysis.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available, the study reports on all the outcome stated in the methods section No protocol however, alle outcomes reported as expected including both completers and ITT.
Other bias	Unclear risk	Judgement Comment: Study supported by a grant from the industry and no statements about conflicts of interest.

Barlow 2000

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 35.5 (9.7) ● *Number of females (%)*: 60.2 % ● *Duration/mean years since onset (SD)*: 6.38 (7.54) Intervention 2 ● *mean age, years (SD)*: 34.1 (11.4) ● *Number of females (%)*: 64.1 ● *Duration/mean years since onset (SD)*: 6.60 (8.99) Kontrol 1 ● *mean age, years (SD)*: 37.5 (10.9) ● *Number of females (%)*: 63.2 ● *Duration/mean years since onset (SD)*: 6.61 (8.55) Kontrol 2 ● *mean age, years (SD)*: 37.8 (11.3) ● *Number of females (%)*: 58.1 ● *Duration/mean years since onset (SD)*: 5.50 (8.17) **Included criteria:** All patients passing diagnostic screeing for a principal diagnosis of PD withor without mild agoraphobia (N = 497) were entered in the pretreatment phase. Pretreatment included drug washout for patients taking anxiolytic or antidepressant medication. Patients were permitted up to 10 doses of benzodiazepine (0.5mg of alprazolam-equivalent) in the 2 weeks before the first treatment visit andup to 20 doses during baseline and acutetreatment combined. Diagnosis was confirmed using the Anxiety Disorders Interview Schedule-Revised (ADIS-R). Mild agoraphobia was operationally defined as a score less than or equal to 18 on the ADIS-R avoidance scale. Inaddition, inclusion required at least 1 fullor limited panic

	attack in the 2 weeks before the first treatment visit. **Excluded criteria:** Exclusion criteria were psychotic, bipolar, or significant medical illnesses,suicidality, significant substance abuse,contraindications to either treatment,prior nonresponse to similar treatments, and concurrent competing treatment or pending disability claims. Mordetails are available on request from thauthors. Patients with comorbid unipolar depression were not exclude unless suicidal.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Imipramine alone. ● *Duration*: 6 months ● *Dose*: Starting dosages of imipramine were10 mg/d (or pill placebo equivalent), in-creased every other day by 10 mg until50 mg/d was reached. The dosage was then increased more rapidly, with an effort made to reach 100 mg/d by the endof week 3 and 200 mg/d by week 5, evenif the patient became symptom-free earlier, unless adverse effects became intolerable. If the patient was not symptom-free, the dosage could be increased up to 300 mg/d by week 5. Blood levels of imipramine were assessed at 6 and 12 weeks and benzodiazepine screening of urine samples performed by local commercial laboratories. Intervention 2 ● *Description*: Imipramine + CBT. Cognitive-behavioral therapy for panic disorder developed at the Boston site, combines interoceptive exposure, cognitive restructuring, and breathing retraining. This treatment was describedin a manual containing detailed instructions for the conduct of each session. Therapists providing CBT were doctoral-level clinicians who underwent extensive training and certification supervised by the Boston site prior to treating study patients. Clinicians were not required to have prior training in cognitive-behavioral procedures. Pharmacotherapists were experienced psychiatrists who underwent additional trainingand certification in the study protocol under the direction of the Columbia/Hillside site. All CBT therapists and pharmacotherapists received ongoing supervision of their cases from the responsible site during biweekly telephone calls, and adherence and competence ratings were routinely collected after listening to asample of audiotaped sessions ● *Duration*: 6 months ● *Dose*: Starting dosages of imipramine were 10 mg/d (or pill placebo equivalent), increased every other day by 10 mg until 50 mg/d was reached. The dosage was then increased more rapidly, with an effort made to reach 100 mg/d by the end of week 3 and 200 mg/d by week 5, even if the patient became symptom-free earlier, unless adverse effects became intolerable. If the patient was not symptom-free, the dosage could be increased up to 300 mg/d by week 5. Blood levels of imipramine were assessed at 6 and 12 weeks and benzodiazepine screening ofurine samples performed by local commercial laboratories. Kontrol 1 ● *Description*: CBT alone. Cognitive-behavioral therapy for panic disorders,developed at the Boston site, combines interoceptive exposure, cogni-tive restructuring, and breathing retraining. This treatment was describedin a manual containing detailed instruc-tions for the conduct of each session. Therapists providing CBT were doctoral-level clinicians who underwent extensive training and certification supervised by the Boston site prior to treating study patients. Clinicians were not required to have prior training in cognitive-behavioral procedures. Pharmacotherapists were experienced psychiatrists who underwent additional training and certification in the study protocol under the direction of the Columbia/Hillside site. All CBT therapists and pharmaco therapists received ongoing supervision of their cases from the responsiblesite during biweekly telephone calls, and adherence and competence ratings were routinely collected after listening to a sample of audiotaped sessions ● *Duration*: 6 months Kontrol 2 ● *Description*: CBT + placebo. Cognitive-behavioral therapy for panic disorder,developed at the Boston site, combines interoceptive exposure, cognitive restructuring, and breathing re-training. This treatment was described in a manual containing detailed instructions for the conduct of each session. Therapists providing CBT were doctoral-level clinicians who underwent extensive training and certification supervised by the Boston site

	prior to treating study patients. Clinicians were not required to have prior training in cognitive-behavioral procedures. Pharmacotherapists were experienced psychiatrists who underwent additional trainingand certification in the study protocol under the direction of the Columbia/Hillside site. All CBT therapists and pharmacotherapists received ongoing supervision of their cases from the responsible site during biweekly telephone calls, and adherence and competence ratings werer outinely collected after listening to a sample of audiotaped sessions ● *Duration*: 6 months
Outcomes	*Grad af angst, Panic Disorder Severity Scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Panic Disorder Severity Scale ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Bedring, CGI-I responce rate, Score of 1 or 2* ● **Outcome type**: Dichotomous Outcome ● **Scale**: CGI-I ● **Direction**: Higher is better ● **Data value**: Endpoint *Alvorlige bivirkninger, SAE, antal personer* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Ikke alvorlige bivirkninger, AE, antal personer* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This work was supported by National Institute of Mental Health grant MH45964 (University of Pittsburgh School of Medicine); MH45965(Boston University); MH45966 (Yale University Schoolof Medicine); MH45963 and MH00416 (Senior Scientist Award) (Columbia University). Drs Barlow, Gorman, Shear, and Woods have received research sup-port from the National Institute of Mental Health. Imipramine and matching placebo were provided by Teva Pharmaceuticals USA. **Country:** USA **Setting:** Outpatient clinic **Authors name:** David H. Barlow **Institution:** Center for Anxiety and Related Disorders,Boston University **Address:** David H. Barlow, PhD, Center for Anxiety and Related Disorders,Boston University, 648 Beacon St, Sixth Floor, Boston, MA 02215.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified by site and presence of Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition–defined current major depression and was blocked within stratum. To improve trial efficiency, 30 unequal numbers of patients were randomized to the treatments (6 CBT, 6 imipramine, 5 CBT+ imipramine, 25 CBT+placebo, and 2 pla-cebo per block of 24) based on expected pairwise comparison effect sizes." Judgement Comment: No information of how the allocation sequence was generated. Persume computere generated due to stratification
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The imipramine and placebo interventions were administered in a double-blind, fixed flexible-dose design, accord-ing to a manual developed for this study. Both the imipramine and placebo arms included a medical management com- ponent, specified in the manual." Judgement Comment: Patients were blinded for Imipramine and placebo. Blinding of CBT not feasible.Low risk for PICO 2Unclear risk for PICO 1
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Evaluator assessments occurred at base-line and after acute, maintenance, and follow-up phases, and evaluators were blind to treatment assignment." Judgement Comment: PDSS were clinician rated and outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Quote: "326 patients randomized, 312 are included in the analysis. Thirteen were excluded following uniform screening for loss of eligibility, and 1 was re- moved because of inadvertent unblinding. Proportions of excluded patients were not significantly different among treatment assignments."
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to a protocol, but the protocol is available at ClinicalTrials.gov Identifier: NCT00004834. No outcomes stated in the protocol. The study reports on all the outcomes stated in the methods section. primary and seconday outcomes as expected, were reported as stated for both completer and ITT for all three time points.
Other bias	Low risk	Quote: "Funding/Support: This work was supported by National Institute of Mental Health grant MH45964 (University of Pittsburgh School of Medicine); MH45965 (Boston University); MH45966 (Yale University School of Medicine); MH45963 and MH00416 (Senior Scientist Award) (Columbia University). Drs Barlow, Gorman, Shear, and Woods have received research support from the National Institute of Mental Health. Imipramine and matching placebo were provided by Teva Pharmaceuticals USA." Judgement Comment: The study appears to be free of other sources of bias

Black 1993

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 35.1 (10.4) ● *Number of females (%)*: 60% ● *Duration/mean years since onset (SD)*: 9.8 (9.2) Kontrol 1

	● *mean age, years (SD)*: 38.7 (12.4) ● *Number of females (%)*: 88% ● *Duration/mean years since onset (SD)*: 11.9 (10.9) **Included criteria:** Patients with panic disorder between the age of 18 and 65 years. Structured clinical interview for DSM-III-R criteria for panic disorder. Patients meeting criteria for current or past DSM-III-R major depression were included. At least one panic attack in the final week of the observation period. An average weekly panic attack severity score of 25 based on the following formula: each panic attack was rated for severity on an 11-point scale (0, absent to 10, worst imaginable), and then the individual scores were added. **Excluded criteria:** Patients who were pregnant, lactating, psychotic, suicidal, or demented, or who had significant medical illness, were ineligible. patients were not allowed to undergo additional psychotherapy or behavior therapy. Patients taking psychotropic medication were required to discontinue this medication for four weeks before randomization, or, in the case of tricyclic antidepressants 3 weeks before randomization.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Fluvoxamine. Medication were administered in double-blind fashion. Capsules were administered in divided doses up to three times daily. Medications consisting of one capsule of fluvoxamine 50 mg. The number of capsules were gradually increased according to a standardized, but flexible, schedule until maximum benefits was achieved or dose-limiting side effects developed. Patients began taking one tablet per day (for three days), then increased to two tablets for five days, three for six days, continuing up to a total of six tablets per day in two divided doses. When side effects were reported, medication increases were slowed or the dose was reduced. Every effort was made to achieve a dosage of four capsules per day. The maximum dosage was six capsuels per day corrosponding to 300 mg/day ● *Duration*: 8 weeks ● *Dose*: The maximum dosage was six capsuels per day corrosponding to 300 fluvoxamine mg/day Kontrol 1 ● *Description*: Cognitive therapy. Cognitive therapy was based on reproducing the patients most important symptoms though various procedures (eg, hyperventilation, imagery). After determing that the patient had made a pathologic attribution of certain symptoms, he og she was encouraged to test the validity of his or hers interpretation and to consider a more benign one. patients were provided other tools such a breething exercises, positive affirmation statements, and refocussing techniques. Patients were also encouraged to challence themselfes in phobic situations to apply these newly learned techniques in vivo. Instructions to the patients and homework assignments were reviewed carefully by the therapist each week. ● *Duration*: 8 weeks ● *Dose*: Weekly sessions for 8 weeks
Outcomes	*Grad af angst, Clinical anxiety scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Clinical anxiety scale, clinician rated ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Funktion, Sheeran Disability Scale, subscale work* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported

	● **Scale**: Sheeran Disability Scale, subscale work ● **Range**: ● **Direction**: Lower is better ● **Data value**: Endpoint *Bedring, Free of panic attacks at end of treatment* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Free of panic attacks, numbers ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Alvorlige bivirkninger, SAE, antal personer* ● **Outcome type**: Adverse Events ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This study was sponsered in part though a grant from Reid-Rowell Pharmaceuticals Inc, Atlanta, Ga. **Country:** USA **Setting:** Outpatient clinic **Authors name:** Donald W Black
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Patients were randomly assigned. No informaiton of how the allocation sequence was generated

Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Not possible to blind participants and personel Participants were blinded for Fluoxamine and placebo drug. Blinding of CBT not feasible
Blinding of outcome assessment (detection bias)	High risk	Judgement Comment: The outcomes were clinician rated (Clinical anxiety Scale) and self-rated (sheehan disability scale)The participants in the CBT group were not blinded.The participants in the fluvoxamine group were blinded for medication/placebo.The outcome assessor in the CBT group was not blinded.One of the outcome assessors in the medication group was not blinded, unclear whether the other assessor was.
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: 4 of 25 dropped out in the fluvoxamine group (16%) . 9 of 25 dropped out in the CBT group (36%). reasons for dropout stated.No intention to treat analyses
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available. The study reports on all the outcoems stated in the methods section
Other bias	Unclear risk	Judgement Comment: Not clear if the medical company which gave a grant to the study took part in the analyses and the revision of the manuscript.

Blanco 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 30.66 (7.98) Intervention 2 ● *mean age, years (SD)*: 35.63 (9.84) Kontrol 1 ● *mean age, years (SD)*: 31.71 (9.63) **Included criteria:** Inclusion criteria were: (1) a primary DSM-IV diagnosis of SAD;and (2) age between 18 and 65 years. To increase the comparability with other treatmentstudies of SAD and eliminate the possibility that improvements in SAD could be attributedto the antidepressant effects of phenelzine. **Excluded criteria:** exclusion criteria were: (1) a comorbid anxietydisorder more clinically salient for the patient (2) lifetime history of schizophrenia, bipolardisorder, or mental disorder due to a general medical condition; (3) major depressive disorder or substance use disorder within the last 6 months; (4) prior failure of treatment with phenelzine or CBT defined as non response to 60 mg or more of phenelzine (or the equivalent dose of another MAOI) for at least 4 weeks or to 6 sessions of CBT for SAD; (5) concurrent psychiatric/psychological treatment; and, (6) pregnancy, lactation, or inability or unwillingness to use contraceptive measures for the duration of the study.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Phenelzine. Pharmacotherapy patients began with phenelzine 15 mg/day or matching placebo for 3 days,then 30 mg/day for 4 days, 45 mg/day for the second week, and 60 mg/day for weeks 3 and 4. Depending on clinical progress and side effects, dosage could be raised to 75 mg at week 5 and 90 mg at weeks 6–12. Patients were instructed to expose themselves to anxiety-provoking situations and told that the role of medication was to make such exposure easier. However, no systematic exposure instructions or programmed practice was offered. Noother psychotropic medication was permitted except chloral hydrate 500–1000 mg orzolpidem 5–10 mg prn for sleep. Patients were instructed about the

	dietary restrictions appropriate to phenelzine, symptoms that could occur if the restrictions were violated, and procedures to follow in that event. ● *Duration*: 12 weeks ● *Dose*: Phenelzine: 15-90 mg/day Intervention 2 ● *Description*: Phenelzine and cognitive behavioral group therapy (CBGT). Patients assigned to combined treatment received both CBGT and phenelzine as described above, beginning in the same week. To remove potential bias in the performance of treatments, neither pharmacotherapists nor CBGT therapists were informed as to whether a specific patient was also receiving the other treatment, and they could not consult each other or attempt to integrate their treatment efforts. Patients were also coached to withhold information that would indicate whether they were receiving combined treatment. Although all combined treatment patients actually received phenelzine, they were told, with the approval of the institutional review board at each site, that they might receive either active medication or placebo ● *Duration*: 12 weeks ● *Dose*: Phenelzine: 15-90 mg/day. CBGT: 12 2.5-hour sessions to groups of 4–6 participants. Kontrol 1 ● *Description*: Cognitive behavioral group therapy (CBGT) was administered by 2 therapists in 12 2.5-hour sessions to groups of 4–6 participants. In the first 2 sessions, patients were taught to identify negative cognitions(automatic thoughts [ATs]), to observe the covariation between anxiety and ATs, to challenge logical errors in ATs, and to formulate rational alternatives. Thereafter, they confronted increasingly difficult feared situations, first through role-playing in the session and then in real life, while applying cognitive skills. Patients worked on their personal target situations following a standard sequence: 1) identification of ATs; 2) identification of logical errors in ATs; 3) disputation of ATs and formulation of rational responses; and, 4) establishment of observable behavioral goals. Patients practiced cognitive skills while completing behavioral tasks (e.g., conversing with another group member). Goal attainment and use of cognitive skills were reviewed. Patients were given assignments for exposures between sessions and completed self-administered cognitive restructuring exercises before and after these assignments. ● *Duration*: 12 weeks ● *Dose*: CBGT: 12 2.5-hour sessions to groups of 4–6 participants.
Outcomes	*Grad af angst, LSAS, clinician rated* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: LSAS, clinician rated ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af angst, LSAS (social fear subscale)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: LSAS (fear subscale) ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Funktion, Sheeran Disability Scale* ● **Outcome type**: Continuous Outcome

	● **Reporting**: Fully reported ● **Scale**: Sheeran Disability Scale ● **Range**: 0-30 ● **Direction**: Lower is better ● **Data value**: Endpoint *Grad af undgåelse, social phobia scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: social phobia scale ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Bedring, CGI-I responce rate, Score of 1 or 2* ● **Outcome type**: Dichotomous Outcome ● **Scale**: CGI-I ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** Supported in part by NIH grants DA023200 (Dr. Blanco), MH44119 (Dr. Heimberg) and MH57148 (Dr.Liebowitz), and the New York State Psychiatric Institute (Drs. Blanco, Schneier, Campeas and Liebowitz and Ms.Vermes). This work was also supported in part by GCRC grant RR00349 from the NCRR:NIH to Temple University **Country:** USA **Setting:** Outpatient clinics **Authors name:** Carlos Blanco **Institution:** Department of Psychiatry, New York State Psychiatric Institute, College of Physicians andSurgeons of Columbia University, New York, NY **Email:** cb255@columbia.edu **Address:** Carlos Blanco, M.D., Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, Box 69, New York,NY 10032, Telephone: 212-543-6533, Facsimile: 212-543-6515
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Quote: Patients were randomozed according to a table of pseudorandom numbers by the New York site data manager, who had no patient contact.
Allocation concealment (selection bias)	Low risk	Quote: "Patient allocation was concealed from all other research personnel at both sites prior to randomization and from independent evaluators providing the clinician-administered assessments throughout the study."
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Participants and personel were blinded to placebo/phenelzine. Blinding to CBT not feasible.
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Clinician rated outcomes: LSAS, CGI were performed by blinded outcome assessors elf rated outcoems: Sheehan disability scaleand social phobia scale (patiente were blinded to medication, not to CBT)
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: High number of dropouts in alle three groups, 23/45 (51%) in the pheneline group, 18/40 (45%) in the CBT group and 19/42 (45%) in the Pheneline+ CBT group. Reasons for dropout not stated. No intention to treat analyses, expect for the respons rate, where last observation caried forward was used Even when ITT was used there was an extensive drop out rate in all groups. (almost 50%) Nothing described about imputation methods but even IF they had used a imputation methods statistics cannot save data when 50% drops outs
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available. Reports on all the outcome stated in the methods section
Other bias	Low risk	Quote: "Acknowledgments Financial Support Supported in part by NIH grants DA023200 (Dr. Blanco), MH44119 (Dr. Heimberg) and MH57148 (Dr. Liebowitz), and the New York State Psychiatric Institute (Drs. Blanco, Schneier, Campeas and Liebowitz and Ms. Vermes). This work was also supported in part by GCRC grant RR00349 from the NCRR:NIH to Temple University. Judgement Comment: The study appears to be free of other sources of bias

Clark 1994

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● *mean age, years (SD)*: 34.6 (9.2) ● *Number of females (%)*: 78% ● *Duration/mean years since onset (SD)*: 3.3 (range 0.5-15) **Included criteria:** a) DSM-III-R criteria for panic disorder with no, mild, or moderate agoraphobic avoidance. b) current episode duration at least 6 months. c) a least three panic attacks in the last three weeks. d) Consider panic their main problem. e) age 18 - 60 years. f) willing to accept random allocation. **Excluded criteria:** g) no depressive disorder, sever enough to require immediate psychiatric treatment. h) no cognitive therapy, applied relaxation or imipramine in the current episode. i) no evidence of organic mental disorder, schizophrenia, alcohol or drug dependence, cardiovascular disease, asthma, epilepsy, pregnancy or intention to become pregnant.

Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Imipramine. Patients started on 10 mg. The dose was increased in 10 mg per steps every threes days up to 60 mg, then to 75 mg. and then in 25 mg. steps until either panic ceased or 300 mg. was reached. ● *Duration*: 6 months ● *Dose*: 10 mg/day - 300 mg/day Kontrol 1 ● *Description*: Cognitive therapy based on the cognitive theory of panic. Several cognitive and behavioral therapies were used to help patients identify and change misinterpretations of bodily sensations. Cognitive procedures included: identifying and challenging patients' evidence for their misinterpretations; substituting more realistic interpretations; and restructuring images. behavioral procedures included: inducing feared sensations (by hyperventilation, focusing attention on the body, or reading pairs of words representing feared sensations and catastrophes) in order to demonstrate possible causes of patients' symptoms; and stopping safety behaviors (such as holding unto solid objects when feeling dizzy) in order to help patient disconfirm their predictions about the consequence of their symptoms. Homework assignments also included keeping a daily record of negative thoughts and rational responses, and conducting behavioral experiments to test these thoughts. ● *Duration*: 6 months ● *Dose*: 12 weekly sessions in the first 3 months and up to 3 booster sessions in the next 3 months
Outcomes	Grad af angst, HAM-A ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint *Grad af undgåelse, Fear Questionnaire, social phobia subscale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: FQ (social phobia subscale) ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Bedring, Free of panic attacks* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Free of panic attacks, numbers ● **Direction**: Higher is better ● **Data value**: Endpoint *Tilbagefald, relapse and required further treatment, percentages* ● **Outcome type**: Dichotomous Outcome

	● **Scale**: relapse and required further treatment ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** Medical research council of the united kingdom **Country:** England **Setting:** Outpatient clinic **Authors name:** David M Clark **Institution:** Department of psychiatry, university of Oxford **Address:** Department of psychiatry, university of Oxford, Warneford hospital, Oxford OX3 7JX
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information of how the allocation sequence was geenrated
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: no information of allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: No information of blinding of participants or health care providers, blinding of CBT not feasible
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Number of panic attacks were self-reported.HAM-A and FQ social phobia were clinician rated by blinded outcome assessors
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: No diagram of participant flow. 72 were randomised. 16 in each group completed 3 month. Hereafter 12 patients from the waiting list were randomised to the three intervention groups. resulting in 20 in each group at 6 month follow up. No intention to treat analysis. Dropouts and refuseres after randomisation were replaced and not included in the analyses.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available, the study reports on all the outcomes stated in the methods section
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Dannon 2004

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 45.1 (11.9) ● *Number of females (%)*: 59% ● *Duration/mean years since onset (SD)*: 9.1 (6.4)

	Kontrol 1 ● *mean age, years (SD)*: 44.8 (13.1) ● *Number of females (%)*: 56% ● *Duration/mean years since onset (SD)*: 9.8 (8.7) **Included criteria:** All the completers in thesample met DSM-IV criteria for PD (N = 31) or Panic Disorder with agoraphobia (N = 19) **Excluded criteria:** The exclusion criteria were: 1) age less than 18, 2) comorbid psychiatric diagnosis and substance abuse (including benzodiazepines and alcohol), 3) psychological treatment in the past year, and 4) lack of ability to sign informed consent. The enrolled patients did not have any other Axis I diagnoses.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Paroxatine. The pharmacotherapy condition involved monthly visits. Paroxetine was started at 10 mg per day and was increased up to 40 mg per day according to thepatient's response. Paroxetine was continued throughout the 12 week duration of the study. Efforts were made to ensure that the study patients did not take benzodiazepines on their own to control panic symptoms. Patients made a verbal agreement with the investigators to take only the study medication and not to take benzodiazepines during the study. We also contacted each patient's general practitioner and requested that no benzodiazepines be prescribed during the study protocol. ● *Duration*: 12 weeks ● *Dose*: 10-40 mg/day Kontrol 1 ● *Description*: Cognitive behavioral group therapy. The CBGT patientswere formed into three groups of eight patients, and the groups met weekly for eight weeks. Efforts were made to ensure that the study patients did not take benzodiazepines on their own to control panic symptoms. Patients made a verbal agreement with the investigators to take only the study medication and not to take benzodiazepines during the study. We also contacted each patient's general practitioner and requested that no benzodiazepines be prescribed during the study protocol. The CBGT treatment program used at the Israeli site was largely modeled after the moderate view of CBT forPD as described by Beck and Clark. Patients were taught a variety of techniques aimed at increasing their ability to control panic symptoms. Each treatment session was two hours long, and the outline of material covered in each session was based on material presented by Bourne in his workbook on the step-by-step treatment of panic disorder (9).Material covered in a sequential manner through the eight sessions included: 1) psycho education regarding the causes of PD, 2) coping strategies for controlling panic attacks (such as challenging catastrophic misinterpretations bodily sensations and counteracting panic at an early stage), 3) identification and reframing of negative cognitive schemata (which Bourne refers to as negative "self-talk"), 4) discussion of the role of physical exercise and nutrition in the treatment of PD, 5) relaxation techniques including abdominal breathing, progressive muscle relaxation, and visualisation, and 6) assertiveness training (based on the idea that an effective communication style can reduce tension and frustration and improve interpersonal relationships). The patients were given homework assignments after each session. The group was designed as a closed group for only panic disorder patients with or without agoraphobia. The group met weekly for eight weeks. The principal therapist for the CBGT group was MGO, and AG was the co-therapist. Both therapists were psychiatric nurses. A board certified, senior psychiatrist was in charge of treating the patients in the medication group. A psychiatric nurse (EN) who was blind to treatment administered the psychiatric rating scales at baseline and atweeks four and twelve of the study. ● *Duration*: 8 weeks ● *Dose*: Weekly sessions for eight weeks

Outcomes	Grad af angst, HAM-A ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint *Bedring, Free of panic attacks, no panic attacks per week.* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Free of panic attacks, numbers ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** The study was partially supported by a personal grant from the ministry of health, Israel. **Country:** Israel **Setting:** Outpatient clinic **Authors name:** PINHAS N. DANNON **Institution:** Chaim Sheba Medical Center, Psychiatry Ward Tel Hashomer and the Sackler School of Medicine, Tel Aviv University, Tel Aviv,Israel **Email:** pinhasd@post.tau.ac.il **Address:** Pinhas N Dannon, M.D., Rehovot Community Mental Health and Rehabilitation, Center. Remez Str80, 76449 Rehovot, Israel.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information of how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: No inforrmation of blinding of participants and personel, blinding to CBT not feasible.
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: HAM-A were measured by blinded outcome assessors. Number of panic attacks were self reported and participants were not blinded.
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: Unbalance number of dropouts. 6/33 in the medication group(du to adverse events) 1/24 in the CBT gropu (trip abroad)No intention to treat analyses
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available, the study reports on all the outcoems stated in the methods section
Other bias	Low risk	Judgement Comment: The study apperas to be free of other sources of bias. Note that due to an unexpected staff shortage, an additional group of 8 patients who had been randomized receive CBGT was not able to participate in the study.

Davidson 2004

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 36.3 (11.1) ● *Number of females (%)*: 42.9% Intervention 2 ● *mean age, years (SD)*: 38.2 (10.7) ● *Number of females (%)*: 54.2% Kontrol 1 ● *mean age, years (SD)*: 36.7 (9.1) ● *Number of females (%)*: 53.3% Kontrol 2 ● *mean age, years (SD)*: 37.8 (10.2) ● *Number of females (%)*: 36.6% **Included criteria:** Inclusion criteria were: (1)DSM-IV diagnosis of GSP; (2) age between 18 and 65 years; (3) fluency in English; and (4) provisionof written informed consent. **Excluded criteria:** Exclusion criteria were: (1) a primary co-morbid anxiety disorder (defined by which disorder was the more debilitating and clinically salient); (2) lifetime history of schizophrenia, bipolar disorder, or organic brain syndrome; (3)major depression within the last 6 months; (4) substance

	abuse or dependence within the past year; (5) mental retardation or pervasive developmental disability; (6) unstable medical condition;(7) prior failure of response to fluoxetine at 60 mg/d for at least4 weeks or to 12 weekly sessions of CCBT for GSP; (8) concurrent psychiatric treatment or other psychoactive medications; (9) positive urine drug screen results; (10) inability to maintain 2 weeks' psychotropic drug-free washout; and (11) pregnancy or lactation.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Fluoxetine. Fluoxtine was started at 10 mg/d, increasing on day 8 to 20mg/d, on day 15 to 30 mg/d, and on day 29 to 40 mg/d. Unlessadverse effects became problematic, the goal was for subjectsto reach 40 mg/d. At days 43 and 57, the dose could be raisedto 50 mg/d and 60 mg/d, respectively, if subjects failed to achieve a Clinical Global Impressions (CGI) Improvement score of 1or 2 and were tolerating medication. Compliance was monitored by reviewing daily medication logs and pill counts at each visit. Normally, the dose was given in the morning Intervention 2 ● *Description*: Combination treatment with Fluoxetine and Cognitive behavioral therapy. Kontrol 1 ● *Description*: Comprehensive cognitive behavioral therapy is a 14-week group treatment that combines in vivo exposure, cognitive re-structuring, and social skills training. Derived in part from a treatment developed by Heimberg et al. CCBT differs from Heimberg group CBT in that CCBT includes specific social skills training (eg, how to begin a conversation with a stranger) and improves specific behaviors (eg, eye contact), the role-plays are much shorter, and CCBT is 2 sessions longer than group CBT. Two therapists (1 male, 1 female) who received extensive training prior to this study conducted the treatment; each group consisted of 5 to 6 subjects. The first 2 sessions were educational,with therapists presenting a cognitive behavioral model of social anxiety and explaining treatment techniques. Sessions 3 and 4 were devoted to social skills training; patients received instruction and role-played short (30-60 second), repeated (5-7times) scenarios devoted to initiating, maintaining, and ending conversations, as well as compromise/negotiation. In sessions 5 through 13, patients participated in longer (3-4 minute)role-plays tailored to their specific social concerns. Prior to eachrole-play, subjects identified a core dysfunctional thought associated with that situation and a relevant rational response to replace it. Next, social skills training instructions were provided before the role-play, and specific aspects of each role-play were repeated to facilitate skills acquisition. Between sessions, subjects completed homework assignments designed tohelp them confront fearful social situations using the techniques learned in therapy. Session 14 included a discussion oftreatment gains and recommendations for future practices ● *Duration*: 14 weeks
Outcomes	*Grad af angst, Social phobia and anxiety inventory* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Social phobia and anxiety inventory ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af undgåelse, Brief social phobia scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Brief social phobia scale ● **Range**:

	● **Direction**: ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Alvorlige bivirkninger, SAE, antal personer* ● **Outcome type**: Adverse Events ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This study was supported by grant R10-MH49339-05A1 from the National Institute of MentalHealth, Bethesda, Md (Drs Davidson and Foa) **Country:** USA **Setting:** Outpatient clinic **Authors name:** Jonathan R. T. Davidson **Institution:** Department of Psychiatry andBehavioral Sciences, DukeUniversity Medical Center,Durham,
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were assigned to treatment by block randomization, which was generated by computer program at Duke University Medical Center, in groups of 10, with 2 subjects assigned to each of the 5 conditions." Judgement Comment: Computer generated allocation sequence
Allocation concealment (selection bias)	Low risk	Quote: "The study coordinator at each site enrolled and allocated subjects to their treatment groups. This individual was blind to the sequence prior to assignment."
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Participants were blinded to medication/placebo drug. Blinding to CBT not feasible.

Blinding of outcome assessment (detection bias)	Low risk	Quote: "Primary outcome assessments by the blinded independent evaluator (IE) were as follows: (1) CGI Improvement scale, a 7-point rating measured improvement wherein response is defined as hav- ing a CGI Improvement score of 1 (very much improvement) or 2 (much improvement), and the 7-point CGI Severity scale 12 and (2) the Brief Social Phobia Scale (BSPS), an 18-item scale com- prised of fear, avoidance, and physiological symptoms. 14 Inde- pendent evaluator ratings were conducted at baseline and at weeks 4, 8, and 14. Success of the blinding procedure was not evalu- ated." Judgement Comment: All outcomes were clinician rated, outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Numbers and reasons for dropout stated. 18/57 dropped out in the medication group.12/60 dropped out in the CBT group.17/59 dropped out in the medication + CBT group.13/59 dropped out in the CBT+ placebo group. Intention to treatanalyses performed
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to a protocol. The study reports on all outcomes stated in the methods section
Other bias	Low risk	Quote: "This study was supported by grant R10- MH49339-05A1 from the National Institute of Mental Health, Bethesda, Md (Drs Davidson and Foa). Additional Information: Medication and matching placebo were provided by Eli Lilly, Indianapolis, Ind, who have reviewed the manuscript. They were uninvolved in study design, data analysis, or manuscript preparation."

Heimberg 1998

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 32.1 (8.4) ● *Number of females (%)*: 45.2 % ● *Duration/mean years since onset (SD)*: 21.1 (11.7) Kontrol 1 ● *mean age, years (SD)*: 37 (9.7) ● *Number of females (%)*: 55.6% ● *Duration/mean years since onset (SD)*: 20.8 (14.2) **Included criteria:** For study inclusion, prospective patients had to meet criteria for social phobia and had to be between 18 and 65 years old, fluent in English, willing to provide written informed consent, and able to participate responsibly in treatment. **Excluded criteria:** Exclusions included schizophrenia, major depression, prominent risk of self-harm, organic mental disorder,history of bipolar I disorder, alcohol or substance abuse(within the past 6 months), a previous adequate trial of cognitive behavioral therapy (over or equal to 6 sessions) or MAOI treatment (phenelzine sulfate over or equal to 45 mg/d, or the equivalent dosage of another MAOI for 4 weeks) for social phobia, or any serious medical condition that would increase the patient's chances of being harmed by study participation.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Phenelzine. A psychiatrist monitored patients' clinical state and offered support according to a manual adapted from the National Institute of Mental Health Treatment of Depression Collaborative Research Program.Visits lasted 30 minutes, except for a 45-minute initial visit. No systematic ex- posure instructions were offered. Patients received 15-mg phenelzine sulfate tablets (n = 31) or matching placebo tablets (n = 33) in 1 morning dose; dosages of 60 mg/d (4 pills) and greater were split between morning and noontime. Dosages started at 15 mg/d and increased

	to 30 mg/d on day 4, to 45 mg/d on day 8,and to 60 mg/d on day 15. After 4 weeks, depending on symptoms and adverse effects, dosages could be raised to75 mg/d. After 5 weeks, dosages could be raised to 90 mg/d.No other psychotropic medications were permitted, and patients followed MAOI dietary restrictions ● *Duration*: 12 weeks ● *Dose*: 15-60 mg/day Kontrol 1 ● *Description*: Cognitive Behavioral Group Therapy Cognitive behavioral group therapy was administered in 12 sessions of 2.5 hours each to groups of 5 to 7 patients (n = 36).In the first 2 sessions, patients were taught to identify negative cognitions (“automatic thoughts” [ATs]), to observe the covariation between anxiety and ATs, to challenge logical errors in ATs, and to formulate rational alternatives. Thereafter, they confronted increasingly difficult feared situations (first in the session and then in real life) while applying cognitive skills. When patients worked on their personal target situations, a standard sequence was followed: (1) identification of ATs, (2) identification of logical errors in ATs, (3) disputation of ATs and formulation of rational responses, and (4) establishment of behavioral goals. Patients practiced cognitive skills while completing behavioral tasks (eg, conversing with another group member or giving a speech). Goal attainment and use of cognitive skills were reviewed. Behavioral experiments were used to confront specific reactions to the exposure. Patients were given assignments for exposure to real-life situations between sessionsand were instructed to complete self-administered cognitive restructuring exercises before and after. ● *Duration*: 12 weeks ● *Dose*: 12 sessions of 2.5 hours
Outcomes	*Grad af angst, LSAS (social fear subscale)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: LSAS (fear subscale) ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af undgåelse, LSAS (avoidance subscale)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: LSAS (avoidance subscale) ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Bedring, Social Phobic Disorder severity (a score 1or 2 of 7)* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Social Phobic Disorder severity (a score 1or 2 of 7) ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event

	● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Alvorlige bivirkninger, SAE, antal personer* ● **Outcome type**: Adverse Events ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** Supported by grants MH44 119 (Dr Heimberg) and MH40 121 (Dr Liebowitz) from the National Institute of Mental Health, Bethesda, Md, and grant PO5 MH30906 from theNew York State Psychiatric Institute Mental Health ClinicalResearch Center, New York. Parke-Davis Pharmaceuticals,Morris Plains, NJ, supplied Nardil and matching placebo. **Country:** USA **Setting:** Outpatient clinic **Authors name:** Richard G. Heimberg, **Institution:** Center for Stress and Anxiety Disorders, StateUniversity of New York at Albany **Email:** e-mail: rheimber@nimbus.ocis.temple.edu **Address:** Richard G. Heimberg, PhD,Adult Anxiety Clinic of Temple, Department of Psychology, Temple University, Weiss Hall, 1701 N 13th St, Philadelphia, PA 19122-6085
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Pretreatment assessment included an independent assessor inter- view, self-report questionnaires, and a behavioral test. Groups of 5 to 7 patients, stratified by social phobia subtype, were then randomly assigned to 12 weekly sessions of 1 of the 4 treatments." Judgement Comment: No information of how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Patients were blinded for medication/placebo drug. Blinding for CBT not feasible.

Blinding of outcome assessment (detection bias)	Low risk	Quote: "The independent as- sessor (IA), unaware of treatment condition, completed the 7-point rating of change from the Social Phobic Disorders Severity and Change Form. This rating was used to categorize treatment response. Patients rated 1 or 2 (markedly or moderately improved) were classified as respond- ers and patients rated 3 or higher were classified as nonresponders. Other IA Measures. The IA also administered the Liebowitz Social Anxiety Scale (LSAS)," Judgement Comment: Clinician rated outcomes rated by blinded assessor
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: dropouts were balanced in numbers, reasons for dropout not stated per groupIntention to treat analysis for treatment responce, but not for the other outcomes
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to a protocol, the study reports on all the outcomes stated in the method ssection.
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias. Parke-Davis Pharmaceuticals,Morris Plains, NJ, supplied Nardil and matching placebo.

Hendriks 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 68.8 (4.3) ● *Number of females (%)*: 58.8% ● *Duration/mean years since onset (SD)*: 12.3 (17.5) Kontrol 1 ● *mean age, years (SD)*: 69.9 (5.0) ● *Number of females (%)*: 55% ● *Duration/mean years since onset (SD)*: 12.3 (14.2) **Included criteria:** Eligible were all adults aged over 60 years with a principal diagnosis of panic disorder (PD) or PD with agoraphobia (PDA) treatment in our out-patient clinic specialized in the yreatment of anxiety disorders. All patients were referred by their primary care physician. **Excluded criteria:** Exclusion criteria were the presence of severe psychiatric disorders (e.g. psychotic disorder, bipolar disorder), a severe somatic condition that would hinder appropriate application of CBT (e.g. severe cardiovascular disease), a contraindication for paroxetine, current use of an antidepressant in an adequate dose, current and adequate psychological treatment, failure of paroxetine or CBT in the past,abuse of or dependency on alcohol or psychoactive substances, dementia and a score of 23 or less on the Mini-Mental State Examination. Co-morbidity with other anxiety disorders, depression or dysthymia was allowed as long as PD(A) was the principal diagnosis. Participants using benzodiazepines were asked to adhere to a fixed daily dose for the duration of the study (also see the Procedure and Treatment sections).
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Patients in the paroxetine condition were treated according to a fixed-dose schedule. The daily 10 mg starting dose in week 1 was increased with10 mg a week to 40 mg/day in week 4, during which period patients were seen during 30-min weekly consultations. To control for any adverse events and to encourage patients to adhere to the treatment protocol, from week 5 to week 14, all patients attended five 30 min medical consultations once every 2 weeks during which their queries were addressed and information about the expected (side) effects of the

	treatment was provided. Paroxetine was maintained in a 40 mg/day dosage during weeks 14–26 ● *Duration*: 14 weeks ● *Dose*: 10-40 mg/day Kontrol 1 ● *Description*: Individual CBT consisted of 14 weekly sessions of 50 min each consistent with Craske and Barlow. The standardized programme comprised thefollowing five components: (1) education aboutpanic and anxiety, (2) relaxation techniques, (3) interoceptive exposure, (4) cognitive therapy and(5) exposurein vivo. After the 14th session, CBTwas tapered off within a maximum of six sessions during the 12-week follow-up period ● *Duration*: 14 weeks ● *Dose*: 14 weekly sessions of 50 minutes
Outcomes	*Funktion, SCL-90* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: SCL-90 ● **Range**: ● **Direction**: Lower is better ● **Data value**: Endpoint *Grad af undgåelse, Mobility Inventory Avoidance Scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Mobility inventory avoidance scale ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Bedring, Free of panic attacks, numbers* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Free of panic attacks, numbers ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better

	● **Data value**: Endpoint
Identification	**Sponsorship source:** No information **Country:** The Netherlands **Setting:** Outpatient clinic **Authors name:** Hendriks G-J **Institution:** Forum GGz Nijmegen, Department for Anxiety Disorders ``Overwaal'', Nijmegen, **Email:** ghendriks@overwaal.nl **Address:** Gert-Jan Hendriks, Forum GGz Nijmegen, Department for Anxiety Disorders Overwaal, Pastoor vanLaakstraat 48, 6663 CB Lent, the Netherlands.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " patients were randomly assigned to one of the three study conditions according to a 2: 2: 1 schedule. To this end, a sealed envelop was randomly selected from an initial total of 75 envelopes containing the treatment assignments, with 30 being labelled as "CBT", 30 as "paroxetine" and 15 as "waiting list".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: No information of blinding, blinding of CBT not feasible.
Blinding of outcome assessment (detection bias)	High risk	Quote: "All assessments were administered by trained, independent psychologists who were blind to the study and treatments delivered." Judgement Comment: outcomes were self-reported and participants were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 3/17 dropped out in the paroxetine group. 1/20 dropped out int he CBT group. Reasons stated. No intention to treat analyses
Selective reporting (reporting bias)	High risk	Judgement Comment: Trial registration: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC = 1144. Beck Depression Inventory (BDI) was stated in the protocol but not reported in the publication. No reporting of anxiety severity in the study.
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Koszycki 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years (SD)*: 36.40 (10) ● *Number of females %*: 53.2 %

	● *Duration of symptoms/mean years since onset (SD)*: 10.63 (9.5) Intervention 2 ● *Mean age, years (SD)*: 36.22 (10.9) ● *Number of females %*: 74.6 % ● *Duration of symptoms/mean years since onset (SD)*: 9.74 (10.5) Kontrol 2 ● *Mean age, years (SD)*: 36.80 (12.2) ● *Number of females %*: 73.4 % ● *Duration of symptoms/mean years since onset (SD)*: 8.95 (8.0) **Included criteria:** To minimize placebo response and select patients with at least moderately severe PD, participants had to have a minimum ofsix full panic attacks in the 4-week period prior to the screen visit, and two full panic attacks a week in the 2-week lead-in period before the baseline visit. Co-morbid depression, generalized anxiety disorder, social phobia, somatization disorder and specificphobia were allowed as long as these conditions were secondary to and not clinically more prominent than the PD AG. To prevent the inclusion of severely depressed patients, subjects were eligible if their score on the 21-item Hamilton Depression Rating Scale was under 17 (Hamilton, 1960). **Excluded criteria:** Patients were excluded if they had other Axis I psychiatric disorders; electroconvulsive therapy in the past 6 months; a history of psycho surgery; significant medical conditions; abnormal laboratory findings; a hypersensitivity to serotonergic agents; a history of non-response to sertraline; lactose intolerance; significant suicide risk; and use of any psychotropics within 14 days of the baseline visit (6 weeks for fluoxetine) or treatment with CBT in the past 12 months. Oxazepam was allowed during the study if needed, with a maximum daily dose of 15 mg and a weekly total dose of 60 mg. Women who werepregnant, lactating or not using reliable contraception were excluded. **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Sertraline and placebo were provided within the context of clinical management sessions as described byFawcett et al. (1987). Study drugs were initiated at25 mg/day and increased to 50 mg/day after 1 week.In the presence of dose-limiting side-effects, patients were maintained at 25 mg/day for an additional week.If side-effects persisted and the dose could not be increased, the patient was withdrawn from the study.The dose was maintained at 50 mg/day until week 4.Thereafter, the dose was increased by 50 mg every 2 weeks or more until maximum improvement onthe Clinical Global Impression scale (Guy, 1976) wasobtained. The targeted maximal dose for acute treatment was 200 mg/day. During extension treatment,patients were maintained at the dose achieved byweek 12. However, if side-effects occurred at any time, the dose was decreased to the next lower level. Compliance with study medication was monitored by pillcount. A returned capsule count for trial medication was recorded at each visit to monitor compliance.*Dose*: 25-200 mg/day ● *Duration*: 12 weeks Intervention 2 ● *Description*: Combination of sertraline and Self-administered Cognitive behavioral therapy (SCBT) ● *Dose*: Sertraline 25-200 mg/day + 12 audiotapes and a workbook for CBT ● *Duration*: 12 weeks Kontrol 2 ● *Description*: Self-administered Cognitive behavioral therapy (SCBT) + Placebo drug. SCBT consisted of 12 audiotapes and a work book that contained monitoring forms for homework. The tapes and workbook were developed for this study by psychologists with expertise in CBT. Each tape described the principles of treatment and provided detailed instructions and home work.Treatment components included extensive

	psychoeducation about anxiety and the cognitive model of PD, breathing retraining and relaxation skills, cognitive restructuring that addressed misappraisal of panic symptoms, interoceptive and situational exposure, and relapse prevention. Tapes were distributed weekly during acute treatment by a research coordinator and a standard format was adopted for instructions to be given to patients. Compliance was assessed at each visit by asking patients how much time they spent listening to the tape, whether they attempted the suggested home work and whether they recorded their homework in the work book. Patients who entered the 12-week extension phase were given the CBT package to use at their own discretion and no particular instructions were given ● *Dose*: 12 audiotapes and a work book ● *Duration*: 12 weeks
Outcomes	*Funktion, Sheehan Disability Scale, subscale work* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: *Sheehan Disability Scale, subscale work* ● **Direction**: Lower is better ● **Data value**: Endpoint *Grad af undgåelse,Mobility Inventory Avoidance Scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: *Mobility Inventory Avoidance Scale* ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** The canadian Institutes of Health Research (POP-15247) and Pfizer Canada **Country:** Canada **Setting:** Outpatient clinic **Authors name:** Koszycki **Institution:** Faculty of education, university of Ottawa, ON, Canada **Email:** dkoszyck@uottawa.ca **Address:** Faculty of education, university of Ottawa, ON, Canada, 145 Jean-Jacques Lussier, Ottawa, Ontario, KIN 6N5, Canada

Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Computer generated allocation sequence
Allocation concealment (selection bias)	Low risk	Judgement Comment: Placebo and sertraline were provided as matching capsules and administered double-blind. Investigators at each site were provided with a sealed envelope that contained the identification of the study drug being administered to the patient. In a medical emergency, the investigator was authorized to break the code for that subject only
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Sertraline and placebo double-blinded. Patients obviously aware of SCBT allocation but were instructed not to divulge assignmement to investigators. Paitents and personel were blinded for medication/placebo. Blinding for CBT not feasible.
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Double-blinded design. Patients obviously aware of SCBT allocation but were instructed not to divulge assignmement to investigators. Outcome assessments were made by investigators who were blind to allocation of the drug and who were not told whether the patient was assigned to SCBT. Patients were instructed not to divulge their SCBT assignment to the investigators.Outcomes of interests were clinician rated.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Moderate but balanced attrition with reasons reported. ITT analysis. About 25-30% dropped out in each group. Numbers and reasons for dropout are balanced across groupsIntention to treat analyses.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No protocol available. The study reports on all the outcomes stated in the methods section
Other bias	Low risk	Judgement Comment: This work was supported by the Canadian Institutes of Health Research (POP-15247) and Pfizer Canada. We thank Dr V. Hadrava of Pfizer Canada for his generous support during the study.

Nordahl 2016

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 31 ● *Number of females (%)*: 65% Intervention 2 ● *mean age, years (SD)*: 34.5 ● *Number of females (%)*: 54% Kontrol 1 ● *mean age, years (SD)*: 27 ● *Number of females (%)*: 46%

	Included criteria: Inclusion criteria were as follows: age of 18–65 years, fulfillment of DSM-IV criteria for SAD, and symptoms present for at least 6 months. **Excluded criteria:** Exclusion criteria were any form of physical disease, psychotic illness, acute suicidality, a primary diagnosis of major depressive disorder, diagnosis of body dysmorphic disorder, drug or alcohol dependence, and cluster A or cluster B personality disorders. Subjects not willing to accept random allocation were also excluded. We excluded patients who had been exposed to CT or to SSRIs previously in order to eliminate any bias of negative expectations to the treatment offered. Participants who were pregnant or were planning to become pregnant during the next 6 months were excluded due to the drug condition. **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Paroxetine. The medication used was paroxetine (paroxetine hydrochloride). It was administered as capsules manufactured by the phar-maceutical laboratory at St. Olav's University Hospital to make them identical to the placebo. The placebo capsules contained lac-tose. The paroxetine and the placebo were identical in size, color, smell, taste, and appearance. The pharmaceutical laboratory at St. Olav's University Hospital provided the medication to the psy Paroxetine, Cognitive Therapy and Their Combination in SAD Psychother Psychosom 2016;85:346–356 DOI: 10.1159/000447013349chiatrists. In addition to the medication they received clinical management. All patients were educated by the psychiatrists, and they provided information about the drugs and the management of it. All patients were asked for self-exposure during the psycho-pharmacological treatment and were able to discuss any problems related to drugs or side effects with their psychiatrist. Following the clinical guideline by Stein et al. [25] , drug treatment was administered over 26 weeks, and tapering of medications/placebo commenced at week 23, tapering 10 mg per week or alternatively 25% of dosage per week. Medication was administered adhering to best prescribing practices for social phobia as suggested by the manufacturer. The recommended initial dosage was 20 mg per day, and minimum–maximum dosage was 20–60 mg/day. The target range of paroxetine in the blood serum was set between 80 and 450 μmol/l. After 4 and 12 weeks of medication, blood serum was tested in all patients receiving paroxetine or pill placebo to monitor treatment compliance and ensure the target range of the drug was achieved. If needed, medication could be titrated upwards by 20 mg/day in steps until reaching the defined target level. The laboratory communicated serum levels outside the targeted range to the psychiatrist, and medications were added. Changes of medications were always counterbalanced in a 1: 1 format so that changes in dosage were done simultaneously in both the active and the placebo arms in order to maintain the blinding of the treatment. ● *Dose*: 20-60 mg/day ● *Duration*: 26 weeks Intervention 2 ● *Description*: Combination treatment with paroxetine and Ccgnitive therapy ● *Dose*: 20-60 mg/day ● *Duration*: 26 weeks Kontrol 1 ● *Description*: Cognitive therapy (CT) The CT protocol for SAD followed the manual based on the model of Clark and Wells [10] but included specific enhancements based on metacognitive therapy [13] . Thus, there was greater systematic work on changing attention in social situations, more work on eliminating worry and rumination, and metacognitive experiments were used in each session, i.e. testing social performance while changing attention. Compared to the original version of the treatment, there was no work on reality testing underlying assumptions and beliefs about the self and social situations, limited work on imagery, and no work on memories of social situations. We replaced this with a greater focus on regulating attention and reducing threat monitoring. The main treatment elements in the manual were (a) developing and sharing a cognitive formulation of the problem, (b) reducing safety behaviors, (c) modifying the inner image of self as a social object (video feedback), (d) practicing

	external focus of attention in social situations, (e) carrying out behavioral experiments to test alternative mental strategies in social encounters and (f) using strategies for reducing worry, rumination, and threat monitoring associated with social situations ● *Duration*: 26 weeks
Outcomes	*Grad af angst, Beck anxiety inventory, mean, SD* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Beck anxiety inventory ● **Range**: 0-63 ● **Direction**: Lower is better ● **Data value**: Endpoint *Bedring, recovered or improved at the Fear of negative evaluation questionnaire* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: the Fear of negative evaluation questionnaire ● **Direction**: Higher is better ● **Data value**: Endpoint *Tilbagefald, deteoriated at the the Fear of negative evaluation questionnaire* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: the Fear of negative evaluation questionnaire ● **Direction**: Lower is better ● **Data value**: Endpoint *Alvorlige bivirkninger, SAE, antal personer* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** No external sponsors were involved. **Country:** Norway **Setting:** Outpatient clinic **Authors name:** Hans M. Nordahl **Institution:** Departments of Psychology and Neuroscience, Norwegian University of Science and Technology, St. Olav's University Hospital, Trondheim , Norway **Email:** hans.nordahl @ svt.ntnu.no **Address:** Department of Psychology University Outpatient Clinic, NTNU, Dragvoll NO−7491 Trondheim (Norway)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomly assigned to 1 of 4 conditions. The randomization used gender and diagnosis of APD as stratification variables in blocks of 10 to ensure equal distribution." Judgement Comment: Presume the allocation sequence was computed generated
Allocation concealment (selection bias)	Low risk	Quote: "The randomization lists were kept independently of the principle investigator, the psychiatrists, and the therapists. Blinding"
Blinding of participants and personnel (performance bias)	High risk	Quote: "In the groups receiving pills, we applied triple masking, and the patient, the psychiatrists, and the principle investigator were blinded to which treatment (drug or placebo) was administered." Quote: "Blinding was conducted for the treatment conditions using medication or placebo and achieved for the primary outcome measures by using independent evaluators who were blinded to the treatment assignment" Judgement Comment: Patients and personel was blinded for medication/placebo. Blinding of CT not feasible
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The participants, independent diagnosticians, psychiatrists, and the principal investigator remained blinded to the paroxetine alone and pill placebo conditions. In addition, specific instructions were given to all participants to avoid disclosing information about their treatment to the evaluators." Quote: "In the groups receiving pills, we applied triple masking, and the patient, the psychiatrists, and the principle investigator were blinded to which treat- ment (drug or placebo) was administered." Quote: "Blinding was conducted for the treatment conditions using medication or placebo and achieved for the primary outcome measures by using independent evaluators who were blinded to the treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	Quote: "All data were analyzed based on an intention-to-treat approach, and missing data were treated using last observation carried forward on the primary measure." Judgement Comment: Numbers and reasons for dropout stated in all groups. Intention to treat analyses with last observation carried forward.
Selective reporting (reporting bias)	High risk	Quote: "The study protocol was approved by the Regional Committee for Medical and Health Research Ethics of Central Norway (No. REK-018-03), the Norwegian Medicines Agency (SN 04-01998) and the Norwegian Data Inspectorate (ClinicalTrials.gov identifier: NCT00184106)." Judgement Comment: The protocol is available at clinicaltrials.gov. Only the primary outcome stated in the protocol and the outcome is reported in an other way than stated in the protocol. No secondary outcomes stated in the protocol, but the study repoerts on all the secondary outocmes stated in the method section. The study protocol and reported outcomes do not match. The study reports on outcomes that is not prespecified
Other bias	Low risk	Quote: "The study was financially supported by the Departments of Psychology and Neuroscience at the Norwegian University of Science and Tech- nology (NTNU), Trondheim. No external sponsors were involved." Judgement Comment: The study appears to be free of other sources of bias

Sharp 1996

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 36.62 ● *Number of females (%)*: 79% ● *Duration/mean years since onset (SD)*: 7.32 Intervention 2 ● *mean age, years (SD)*: 37.27 ● *Number of females (%)*: 72% ● *Duration/mean years since onset (SD)*: 7.00 Kontrol 1 ● *mean age, years (SD)*: 33.23 ● *Number of females (%)*: 73% ● *Duration/mean years since onset (SD)*: 5.11 Kontrol 2 ● *mean age, years (SD)*: 38.81 ● *Number of females (%)*: 82% ● *Duration/mean years since onset (SD)*: 9.93 **Included criteria:** (a) Patients presented with panic disorder with or without agoraphobia that conformed to the Diagnostic and Statistical Manual of Mental Disorders (third edition, revised) criteria (DSM-III-R, American Psychiatric Association [APA], ; (b) patients scored a minimum of 15 on the Hamilton Anxiety Scale (HAM-A) at both entry (Day -7) and after one week wash-in (Day 0); (c) duration of the problem was greater than or equal to 3 months; (d) patients were aged between 18 and 70 years inclusive; (e) patients were willing and able to provide informed written consent to participation. **Excluded criteria:** a) Patients were required to undergo a 4-week wash-out from concurrent psychotropic medication prior to entry, if required; (b) patients suffering from a major depressive disorder as defined by a score of 21 or greater on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg. 1979) were excluded; (c) patients suffering from obsessive-compulsive disorder, paranoid personality disorder, schizophrenia, schizo-affective disorder, manic disorder, or other unspecified psychosis were excluded; (d) patients with severe concurrent somatic disease, particularly impairment of hepatic/renal function, or heart disease of significant clinical importance were excluded; (e) patients with evidence of epilepsy, organic brain disease, or other serious neurological deficit were excluded; (f) patients who were alcohol dependent or drug dependent or showed a risk of dependency were excluded; (g) patients considered a high suicide risk were excluded; (h) female patients who were pregnant, breast feeding, or who were not taking adequate contraceptive precautions were excluded; (i) patients who suffered from a physical disability that severely restricted mobility were excluded; (j) patients who had received psychological treatment for panic disorder and agoraphobia within the 6 months prior to entry were excluded; (k) patients who attended other therapists, whether lay or professional, were excluded.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Fluvoxamine. Following 1 week of single-blind placebo, patients in the FL and PL groups received 12 weeks of either Fluvoxamine or placebo. Patients receiving Fluvoxamine received an initial dose of 50mg/day Fhrvoxarnine at Day 0; this was increased by 50mg to lOO mg/day at Day 7 and by a further 50mg to 150mg/day at Day 14. Thereafter the dose was maintained at 15Omg/day for the remaining 10 weeks of the

study period. Medication was discontinued without taper at Day 84. Medication was supplied in 50-mg tablets, patients receiving placebo were given the equivalent number of tablets at each appoint- ment, thus maintaining the double-blind status. The dosage for patients who were unable to tolerate the maximum dose of medication was reduced from three to two tablets/day (i.e., 150 mg/day to 100 mg/day for the Fluvoxamine groups).

- *Duration*: 12 weeks
- *Dose*: Fluvoaxmine 50-150 mg/day

Intervention 2

- *Description*: Fluvoxamie + cognitive behavioral therapy. Patients receiving either fluvoxamine + cognitive behaviour therapy (PL+CBT) or placebo + cognitive behaviour therapy (PL+CBT) received medication to the identical protocol and cognitive behaviour therapy to the identical protocol to those detailed above. The medication was emphasised as adjunctive or complementary to the cognitive behaviour therapy in the combined treatment groups in an attempt to engage an equal commitment to the cognitive behaviour therapy in these groups.
- *Duration*: 12 weeks
- *Dose*: Fluvoxamine 50-150 mg/day +7 sessions distributed over a period of 12 weeks. Sessions of 30-60 minutes

Kontrol 1

- *Description*: cognitive behavioral therapy. A cognitive behaviour therapy was employed that emphasised both gross exposure techniques and cognitive and behavioural panic management techniques as contributing factors to emotional processing (Foa & Kozak, 1986) and thus fear reduction. Areas targeted in treatment were those outlined by Barlow and co-workers (Barlow, 1988; Zinbarg, Barlow, Brown, & Hertz, 1992) and included (a) the action tendencies associated with panic, (b) the sense of lack of control, and (c) hypervigilant and avoidant information processing strategies. The first two sessions of treatment (Day -7 and Day 0) were given over to assessment. Patients detailed both gross avoidances, (e.g., of situations, and more subtle control and avoidance behaviors employed in an attempt to control panic attacks, such as holding on to supports or cognitive and behavioral distraction techniques). Patient's personal understanding of their panic attacks, including any fears of catastrophic outcome, were also investigated. At Day 0 patients were informed of the basic nature of panic attacks and informed that full explanation of their disorder would be given at their next appointment (Day 7). This educational component of treatment has previously been emphasized as important (Shear & Francis, 1988). Patients were informed that their spouse, partner, or other relative could attend this appointment, if desired. At Day 7 a full explanation of the likely causes, course, and nature of patient's panic disorder was given. Treatment instructions were given in keeping with the above sug- gested essential targets of change. Treatment emphasized the importance of patients' confronting their panic attacks and attempting to replace avoidance responses, both behavioral and cognitive, with more approach-centerd actions. In this way patients were enabled to appreciate that their worst fears were not realized and that if unsupported by avoidant actions, their panic attacks dissipated and gradually settled over time. Treatment, therefore, attempted to follow the principles of emotional processing. Traditional exposure requiring a return to avoided situations was presented as a useful and ecologically valid means to encounter the panic attacks and thus present a forum for change. Artificial methods of panic provocation or simulation such as interoceptive exposure (Barlow, 1988) were not employed. All patients received a standardized treatment manual at the Day 7 appointment. All further sessions (Days 14-84) were devoted to a review of progress, discussion of any possible problems in treatment, and identification of future targets for exposure and change. Treatment was presented as a profoundly patient-led endeavour with efforts between sessions seen as an essential component of change. This being the case, targets were decided by patients with therapist dictated "homework" being kept to a minimum wherever possible. Patients in the cognitive behaviour therapy group (CBT) received no medication throughout treatment.
- *Duration*: 12 weeks
- *Dose*: 7 sessions distributed over a period of 12 weeks. Sessions of 30-60 minutes

Kontrol 2

- *Description*: cognitive behavioral therapy and placebo medication.

Outcomes	*Grad af angst, HAM-A* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint *Bedring, Free of panic attacks* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Free of panic attacks, numbers ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This research was supported in part by Duphar laboratories Ltd. (Grant No. H114.928) who also supplied and packaged the Fluvoxamine and placebo medications. **Country:** Scotland **Setting:** Outpatient Clinic **Authors name:** DONALD M. SHARP **Institution:** Anxiety and Stress Research Cents, Department of Psychnlogy, University of Stirling, Scotland **Address:** department of Psychology, University of Stirling, Stirling, FK9 4LA, Scotland
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information of how the allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: No inforamtion of blinding.Participants were blinding for medication/placebo, blinidng of CBT not feasible.PICO 1: Unclear riskPICO 2: Low risk No inforamtion of blinding.Participants were blinding for medication/placebo, blinidng of CBT not feasible.PICO 1: Unclear riskPICO 2: Low risk
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Medication was supplied in 50-mg tablets, patients receiving placebo were given the equivalent number of tablets at each appointment, thus maintaining the double-blind status." Judgement Comment: No information of blinding of outcome assessors.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Numbers and reasons for dropout stated. A higher dropout rate in the CBT group.
Selective reporting (reporting bias)	High risk	Judgement Comment: The study reports only the main measures. stated that a variety of measures were colloected
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

vanApeldoorn 2008

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 38.5 (10.5) ● *Number of females (%)*: 26 (54.2%) ● *Duration/mean years since onset (SD)*: 10.2 (10.4) Intervention 2 ● *mean age, years (SD)*: 34.4 (10.6) ● *Number of females (%)*: 23 (46.9%) ● *Duration/mean years since onset (SD)*: 7.2 (7.6) Kontrol 1 ● *mean age, years (SD)*: 39.4 (10.2) ● *Number of females (%)*: 33 (62.3%) ● *Duration/mean years since onset (SD)*: 8.1 (8.4) **Included criteria:** Inclusion was restricted to patients between 18 and 65 years of age. **Excluded criteria:** Patients who were pregnant, lactating, suicidal, psychotic, or severely depressed were ineligible to participate in the study. Further exclusion criteria comprised contraindications to either treatment or a concurrent competing treatment. Patients were not allowed to use psychotropic drugs except small doses of benzodiazepines (maximum the equivalent of 20 mg of oxazepamper day).

Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: SSRI. SSRI. Patients receiving an SSRI visited theirtherapist nine times, with weekly sessions duringthe first month and the remaining sessions distributed evenly over the treatment period. Each visitlasted approximately 20 min. SSRI prescriptionswere in conformance with the pharmacotherapeutical guidelines as formulated by the Dutch Psychiatry Association (26). Pharmacotherapists couldchoose between five SSRIs currently prescribed inthe Netherlands: fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram. During the firstSSRI session, patients received some general information on the role of serotonergic pathways in thebrain involved in anxiety disorders and the workingof SSRIs in PD. Patients were administered aminimum dosage which was titrated upwards up tothe effective range in the first month, and adjustedaccording to clinical response and tolerability. Pharmacotherapists were instructed to withhold from therapeutical interventions to avoid hidden exposure. Initiatives for exposing oneself to avoided situations were left to the patient. ● *Duration*: 9 months ● *Dose*: nine times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. Each visit lasted approximately 20 min. SSRI prescriptions were in conformance with the pharmacotherapeutical guidelines as formulated by the Dutch Psychiatry Association Intervention 2 ● *Description*: SSRI + Cognitive behavioral therapy (CBT). CBT + SSRI. This treatment was administered according to the CBT and SSRI manuals. Thetwo treatments started simultaneously and were delivered parallel. The CBT was delivered by the CBT therapist and the SSRI treatment was delivered by the pharmacotherapist. ● *Duration*: 9 months ● *Dose*: SSRI: nine times, with weekly sessions duringthe first month and the remaining sessions distributed evenly over the treatment period. Each visit lasted approximately 20 min. SSRI prescriptions were in conformance with the pharmacotherapeutical guidelines as formulated by the Dutch Psychiatry Association CBT: up to 18 CBT sessions each lasting approximately 50 min. Kontrol 1 ● *Description*: Cognitive behavioral therapy (CBT). The CBT protocol is based on the work of Clark and Craske and Barlow. Patients inthe CBT group received up to 18 CBT sessionseach lasting approximately 50 min. To preventreturn of fear, interval between sessions were extended in the course of treatment (from once aweek to twice a week, and from session 16 onwardwith 5 week intermissions) (25). During the firstsession, the treatment rationale was provided which was based on the cognitive model of panicas developed by Clark (23). In the second session,interoceptive exposure was introduced and exercises were performed (throughout sessions two tosix) to provoke relevant bodily sensations. By performing those exercises patients were taught that bodily sensations can indeed be provoked,that these sensations spontaneously subside, and that these sensations are not dangerous and are not followed by any harmful consequences. From session 6 onward, patients received CT. During CT, patients were first taught about the role of thoughts in generating emotions. Detailed discussion of emotions and associated cognitions led tothe identification of specific beliefs, appraisals and assumptions. Patients were encouraged to examinethe validity of their cognitions by considering all the available evidence and actively collecting new evidence. Both automatic appraisals (such as if Ipanic, I will faint) and core-level beliefs orschemata (such as I am weak) were examined in this manner. Based on this hypothesis testing, alternative hypotheses were generated that were evidence based. In the 10 th session, exposure in vivo was introduced. When starting exposurein vivo, an individualized fear hierarchy was constructed. In between sessions, patients conducted self-guided exposure in vivo. Each exposure assignment was carefully designed and written down jointly by a therapist and the patient. Patients were instructed to stay in the feared situation until their anxiety level had dropped significantly. Safety-seeking behaviors were prohibited during the exposure exercises. From session 10 onwards, both CT and exposurein vivo were offered. The emphasis on one of the two was left to the clinical judgment of the therapist. Homework assignments were given throughout the treatment and were thoroughly discussed at the beginning of each session. Each new treatment component was introduced with aseparate treatment rationale.

	These rationales were handed out to patients on paper so they could read them at home. A treatment manual, which contained detailed information about each session, was provided to all CBT therapists. Following each treatment session, all therapists (including pharmacotherapists) completed a detailed form regarding the content of that session. These forms were evaluated by the research team to check treatment adherence. ● *Duration*: 9 months ● *Dose*: CBT: up to 18 CBT sessions each lasting approximately 50 min.
Outcomes	Grad af angst, HAM-A ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint *Grad af angst, Panic Disorder Severity Scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Panic Disorder Severity Scale ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af angst, Clinical anxiety scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Clinical anxiety scale, clinician rated ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af angst, LSAS, clinician rated* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: LSAS, clinician rated ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af angst, LSAS (social fear subscale)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: LSAS (fear subscale) ● **Range**:

- **Direction**:
- **Data value**: Endpoint

Grad af angts, Beck Anxiety Inventory

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Beck Anxiety Inventory
- **Range**: 0-63
- **Direction**: Lower is better
- **Data value**: Endpoint

Grad af angst, Social phobia and anxiety inventory

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Social phobia and anxiety inventory
- **Range**:
- **Direction**:
- **Data value**: Endpoint

Funktion, Sheeran Disability Scale

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Sheeran Disability Scale
- **Range**: 0-30
- **Direction**: Lower is better
- **Data value**: Endpoint

Funktion, Sheeran Disability Scale, subscale work

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Sheeran Disability Scale, subscale work
- **Range**:
- **Direction**: Lower is better
- **Data value**: Endpoint

Grad af undgåelse, Mark Sheran phobia Scale, subscale agoraphobia

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Mark Sheran phobia Scale, subscale agoraphobia
- **Range**: 0-52
- **Direction**:
- **Data value**: Endpoint

Grad af undgåelse, social phobia scale

- **Outcome type**: Continuous Outcome

- **Reporting**: Fully reported
- **Scale**: social phobia scale
- **Range**:
- **Direction**:
- **Data value**: Endpoint

Grad af undgåelse, Fear Questionnaire, social phobia subscale

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: FQ (social phobia subscale)
- **Range**:
- **Direction**:
- **Data value**: Endpoint

Grad af undgåelse, Brief social phobia scale

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Brief social phobia scale
- **Range**:
- **Direction**:
- **Data value**: Endpoint

Grad af undgåelse, Mobility Inventory Avoidance Scale

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: Mobility inventory avoidance scale
- **Range**:
- **Direction**:
- **Data value**: Endpoint

Grad af undgåelse, LSAS (avoidance subscale)

- **Outcome type**: Continuous Outcome
- **Reporting**: Fully reported
- **Scale**: LSAS (avoidance subscale)
- **Range**:
- **Direction**:
- **Data value**: Endpoint

Bedring, Remitters % (free of panic attacts, minimal anxiety and minimal agoraphobia)

- **Outcome type**: Dichotomous Outcome
- **Reporting**: Fully reported
- **Scale**: Remitters
- **Direction**: Higher is better
- **Data value**: Endpoint

	Bedring, responders at 3 of four at the following CGI-I, CGI-S, PGE-I or PGE-S. ● **Outcome type**: Dichotomous Outcome ● **Scale**: *score of 1,2, or 3 at the CGI-I or CGI-S and a score f 1 or 2 at the PGE-I and PGE-SCGI-I, CGI-S, PGE-I, PGE-S* ● **Direction**: Higher is better ● **Data value**: Endpoint *Bedring, Free of panic attacks* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: Free of panic attacks, numbers ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, adverse events* ● **Outcome type**: Adverse Event ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** Grant number OG00-029 from the Dutch Health Insurance Board **Country:** The Netherlands **Setting:** Outpatient clinics **Comments:** **Authors name:** Franske J. van Apeldoorn **Institution:** University Medical Center Groningen **Email:** f.j.van.apeldoorn@psy.umcg.nl **Address:** Franske J. van Apeldoorn, MSc, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to treatment via a blind draw of a raffle ticket. Equal proportions of tickets for each treatment modality were present and the total number of tickets equaled the expected number of patients per site."

Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was stratified by site. Patients were randomly allocated to treatment via a blind draw of a raffle ticket. Equal proportions of tickets for each treatment modality were present and the total number of tickets equaled the expected number of patients per site." Judgement Comment: No information of how the allocation sequence was generated
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: No blinding of participants and health care providers, blinding not feasible for CBT.
Blinding of outcome assessment (detection bias)	High risk	Quote: "The Hamilton Anxiety Rat- ing Scale (HARS) 23 assesses general aspects of anxiety and was administered by trained research assistants." Judgement Comment: No information of blinding of outcome assessors (HAM-A and remitter status)Quality of life scores and number of panic attacts were self-reported and participants were not blinded.PICO 1+2: High risk
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 15/49 (31%) dropped out in the CBT+ SSRI group21/53 (40%) dropped out in the CBT group17/48 (35%) dropped out in the SSRI group Reasons for dropout stated. Missing outcome data are balanced in numbers and reasons. Reasons for dropouts reported. Non-significant dropout rates between groups.
Selective reporting (reporting bias)	Low risk	Quote: "Trial Registration: Netherlands Trial Register (www.trialregister.nl) Identifier: ISRCTN8156869" Judgement Comment: Reference to a protocol, the protocol not available. The study reports on all the outcome stated in the methods section. No reasons to suspect selective outcome reporting.
Other bias	Low risk	Quote: "The authors have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article. Funding/support: Grant number OG00-029 from the Dutch Health Insurance Board" Judgement Comment: The study appears to be free of other sources of bias

Footnotes

Characteristics of excluded studies

Ataoglu 2000

Reason for exclusion	Wrong intervention

Bakhshani 2007

Reason for exclusion	Wrong comparator

Barlow 2016

Reason for exclusion	genoptryk af gammelt studie

Black 1993a

Reason for exclusion	Wrong study design

Blanco 2010a

Reason for exclusion	Duplicate

Blomhoff 2001

Reason for exclusion	Wrong intervention

Clark 2003

Reason for exclusion	Wrong intervention

Davidson 2004a

Reason for exclusion	Wrong comparator

Gelernter 1991

Reason for exclusion	Wrong intervention

Habecker 2018

Reason for exclusion	genoptryk af gammelt studie

Hendriks 2010a

Reason for exclusion	Duplicate

Klosko 1990

Reason for exclusion	Wrong comparator

Lindsay 1987

Reason for exclusion	Wrong comparator

Loerch 1999

Reason for exclusion	Wrong intervention

Marks 1993

Reason for exclusion	Wrong intervention

Otto 2000

Reason for exclusion	Wrong intervention

Payne 2016

Reason for exclusion	Wrong patient population

Prasko 2006

Reason for exclusion	Wrong intervention

Spinhoven 1996

Reason for exclusion	Wrong intervention

Zoellner 2019

Reason for exclusion	Wrong patient population

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

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Data and analyses

1 Antidepressiv medicin vs.kognitiv adfærdsterapi

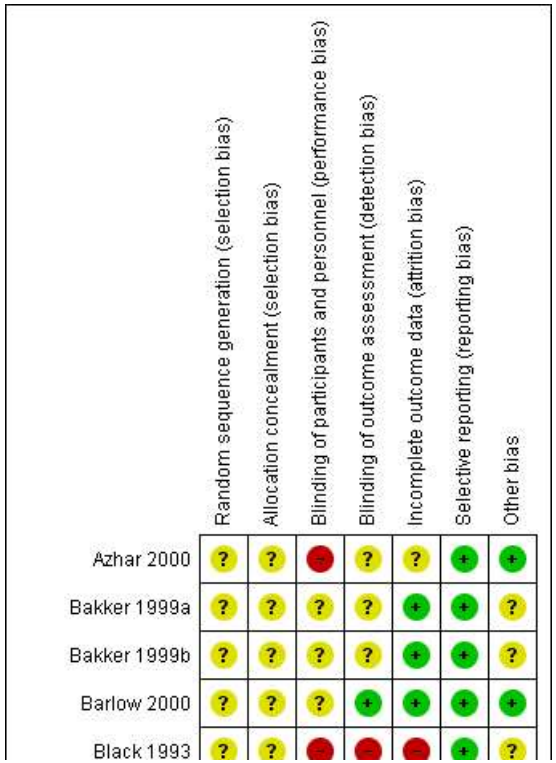
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Grad af angst (severity of anxiety)	12	871	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.45, 0.24]
1.1.1 SSRI	7	460	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.47, 0.66]
1.1.2 TCA	4	367	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.78, 0.19]
1.1.3 MAO	1	44	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-1.18, 0.03]

1.2 Funktion (disability)	7	412	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.68, -0.08]
1.2.1 SSRI	5	318	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.74, 0.03]
1.2.2 TCA	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.34, -0.15]
1.2.3 MAO	1	44	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.79, 0.40]
1.3 Grad af undgåelse (avoidance)	9	645	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.38, 0.12]
1.3.1 SSRI	5	457	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.31, 0.15]
1.3.2 TCA	2	90	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-0.23, 0.68]
1.3.3 MAO	2	98	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.33, 0.16]
1.4 Bedring (Respons)	13	1042	Risk Ratio (IV, Random, 95% CI)	0.96 [0.84, 1.10]
1.4.1 SSRI	8	593	Risk Ratio (IV, Random, 95% CI)	0.95 [0.77, 1.16]
1.4.2 TCA	3	313	Risk Ratio (IV, Random, 95% CI)	0.90 [0.73, 1.11]
1.4.3 MAO	2	136	Risk Ratio (IV, Random, 95% CI)	1.12 [0.84, 1.51]
1.5 Frafald, alle årsager (dropouts, all cauces)	14	1232	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.83, 1.31]
1.5.1 SSRI	10	807	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.75, 1.36]
1.5.2 TCA	2	273	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.20, 3.08]
1.5.3 MAO	2	152	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.59]
1.6 Frafald, grundet bivirkninger (dropouts, adverse events)	10	986	Risk Ratio (M-H, Random, 95% CI)	5.73 [2.51, 13.08]
1.6.1 SSRI	8	713	Risk Ratio (M-H, Random, 95% CI)	5.02 [2.04, 12.37]
1.6.2 TCA	2	273	Risk Ratio (M-H, Random, 95% CI)	11.02 [0.79, 153.55]
1.6.3 MAO	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.7 Tilbagefald (relapse) Risk ratio	1	40	Risk Ratio (IV, Fixed, 95% CI)	8.00 [1.10, 58.19]
1.7.2 TCA	1	40	Risk Ratio (IV, Fixed, 95% CI)	8.00 [1.10, 58.19]
1.8 Tilbagefald (relapse) Risk difference	1	40	Risk Difference (IV, Random, 95% CI)	0.35 [0.12, 0.58]
1.8.2 TCA	1	40	Risk Difference (IV, Random, 95% CI)	0.35 [0.12, 0.58]
1.9 Alvorlige bivirkninger (serious adverse events), antal personer	2	117	Risk Difference (IV, Random, 95% CI)	0.00 [-0.05, 0.05]
1.9.1 SSRI	1	50	Risk Difference (IV, Random, 95% CI)	0.00 [-0.07, 0.07]
1.9.2 MAO	1	67	Risk Difference (IV, Random, 95% CI)	0.00 [-0.06, 0.06]

1.10 Alvorlige bivirkninger (serious adverse events), antal personer	2	117	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.11 Subgruppeanalyser Grad af angst (severity of anxiety)	11	807	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.44, 0.31]
1.11.1 Socialfobi	4	324	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.81, 0.68]
1.11.2 Panikangst	7	483	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.55, 0.41]
1.11.3 Panikangst og socialfobi	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
1.12 Subgruppeanalser Funktion (disability)	7	412	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.68, -0.08]
1.12.2 Panikangst	6	368	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.76, -0.07]
1.12.3 Socialfobi	1	44	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.79, 0.40]

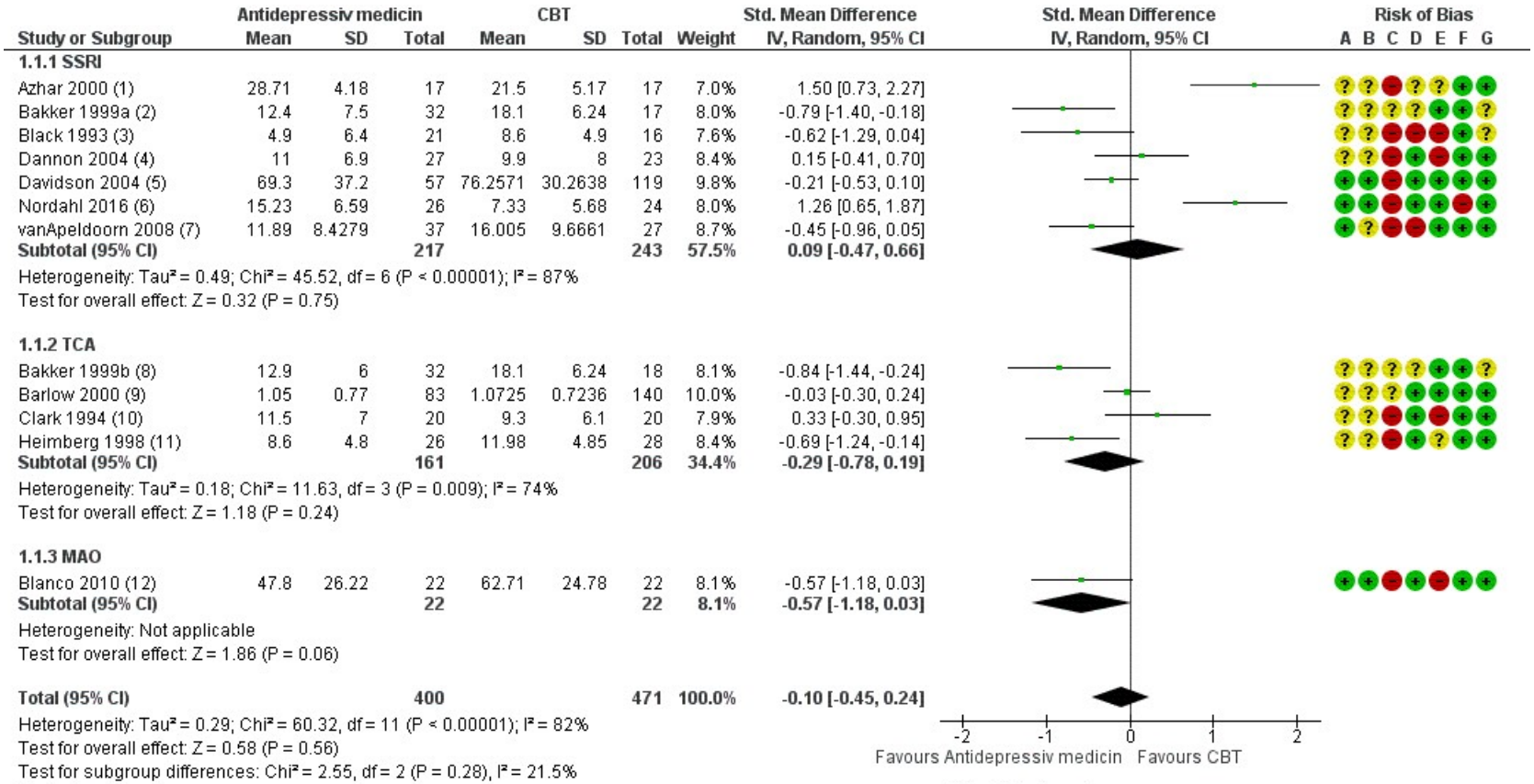
Figures

Figure 1



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

Figure 2 (Analysis 1.1)



Footnotes

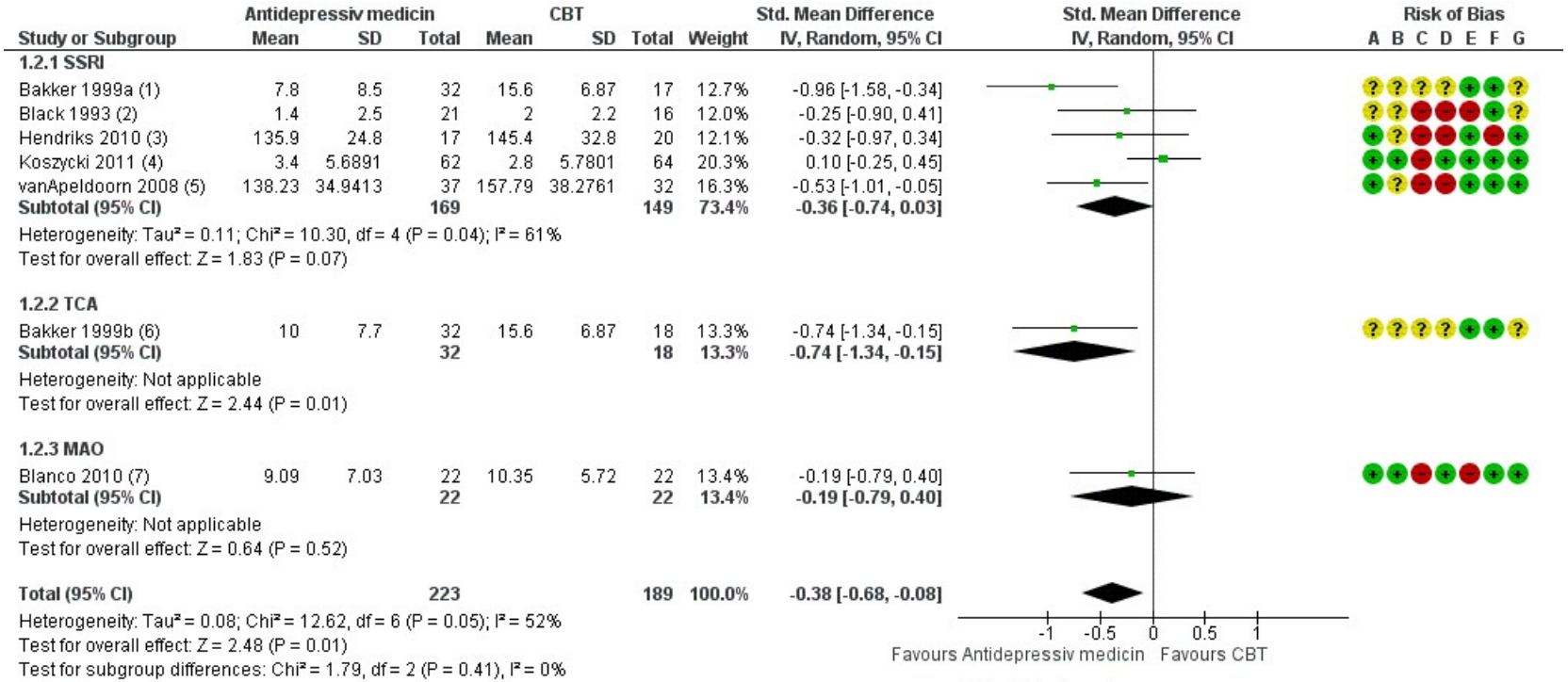
(1) Fluvoxamine (SSRI), panikangst, gruppe/indviduelt fremgår ikke klart
(2) Paroxetine (SSRI), panikangst, gruppe/indviduelt fremgår ikke klart
(3) Fluvoxamine (SSRI), panikangst, gruppe/indviduelt fremgår ikke klart
(4) Paraxotine (SSRI), panikangst, gruppe/indviduelt fremgår ikke klart
(5) Fluvoxamine (SSRI), socialfobi, gruppeterapi
(6) Paxoretine (SSRI), socialfobi, gruppe/indviduelt fremgår ikke klart
(7) SSRI
(8) Clomipramine (TCA), panikangst, gruppe/indviduelt fremgår ikke klart
(9) Imipramine (TCA), panikangst, gruppe/indviduelt fremgår ikke klart
(10) Imipramine (TCA), panikangst, gruppe/indviduelt fremgår ikke klart
(11) Phenelzine (MAO), socialfobi, gruppeterapi
(12) Phenelzine (MAO), socialfobi, gruppeterapi

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: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.1 Grad af angst (severity of anxiety).

Figure 3 (Analysis 1.2)

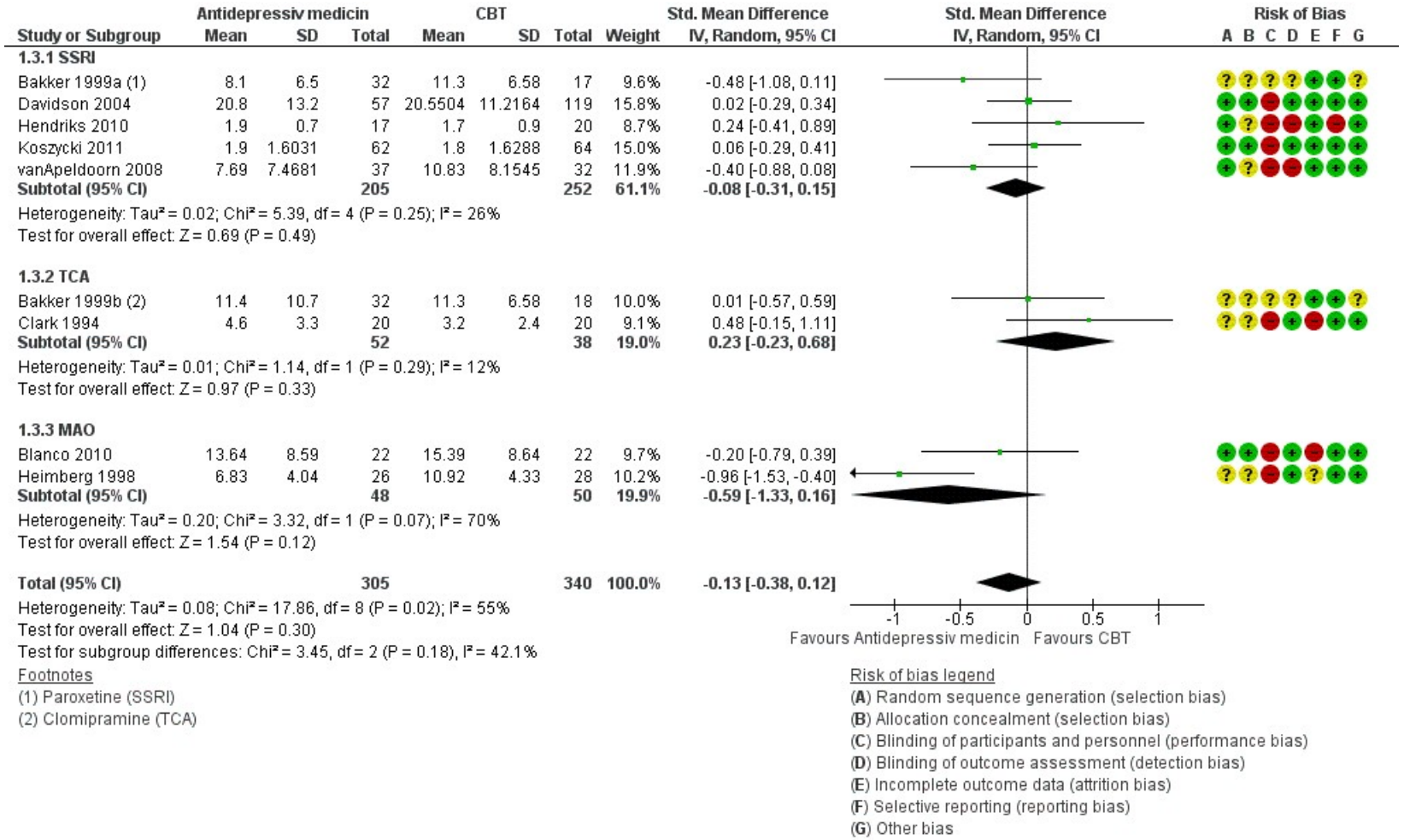


Footnotes
(1) Paroxetine (SSRI), panikangst, gruppe/indviduelt fremgår ikke klart
(2) Fluvoxamine (SSRI), panikangst, gruppe/indviduelt fremgår ikke klart
(3) Paroxetine, panikangst, gruppe/indviduelt fremgår ikke klart
(4) Sertraline, panikangst, gruppe/indviduelt fremgår ikke klart
(5) SSRI (fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram), panikangst med eller uden agorafobi,...
(6) Clomipramine (TCA), panikangst, gruppe/indviduelt fremgår ikke klart
(7) Phenelzine, socialfobi, gruppeterapi

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

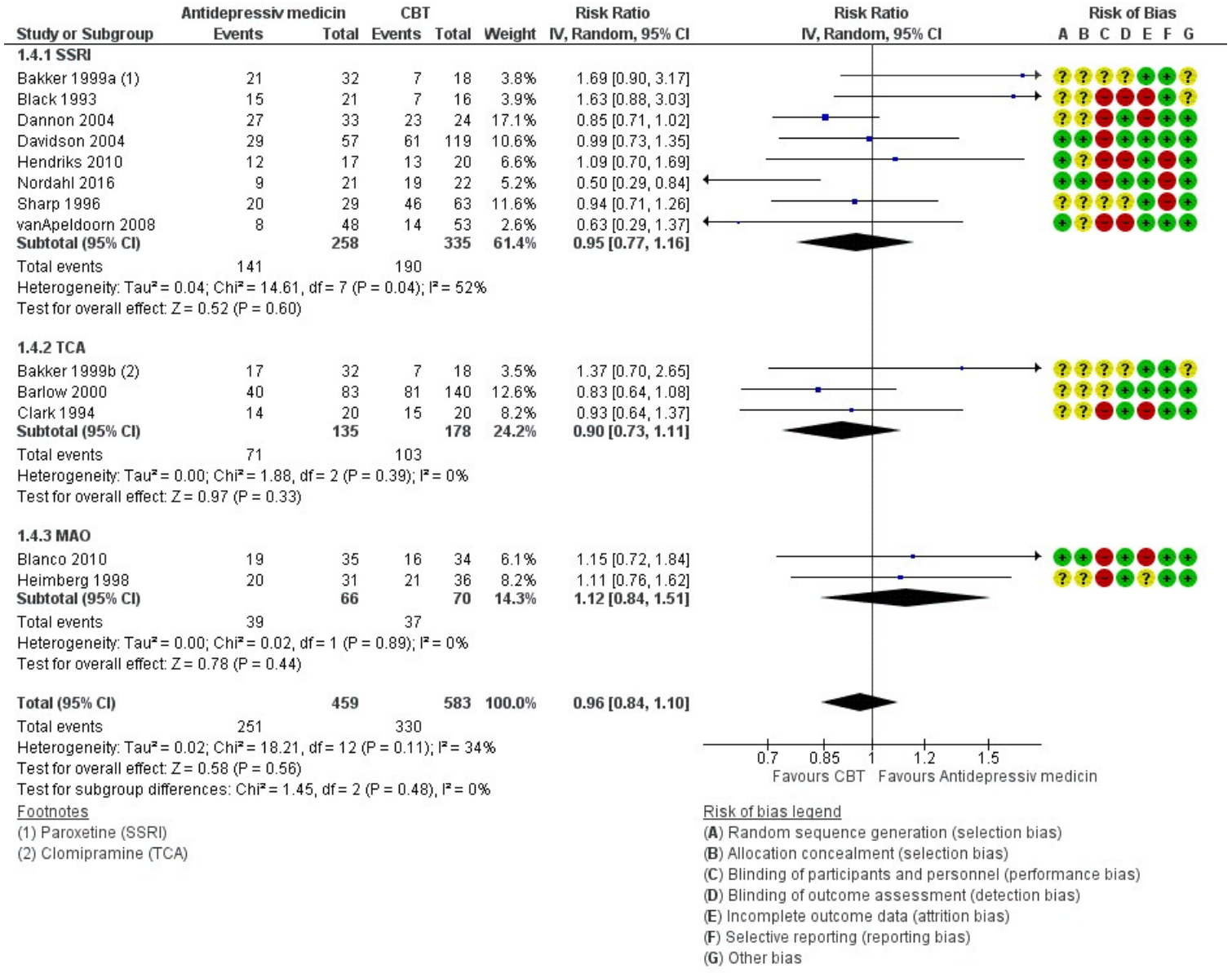
Forest plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.2 Funktion (disability).

Figure 4 (Analysis 1.3)



Forest plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.3 Grad af undgåelse (avoidance).

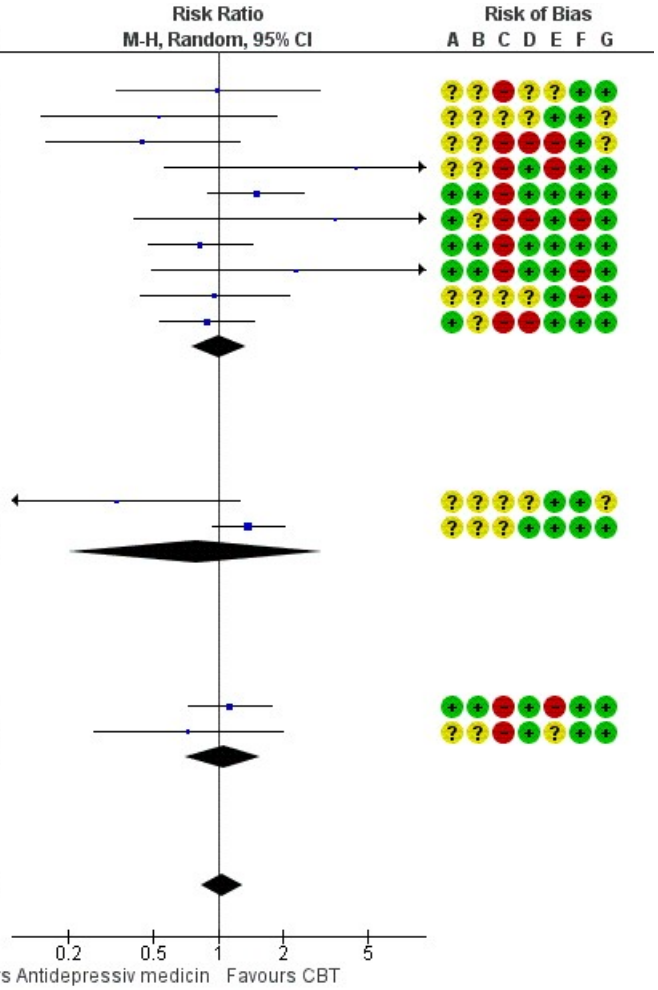
Figure 5 (Analysis 1.4)



Forest plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.4 Bedring (Respons).

Figure 6 (Analysis 1.5)

Study or Subgroup	Antidepressiv medicin Events	Total	CBT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 SSRI						
Azhar 2000	5	22	5	22	3.8%	1.00 [0.34, 2.97]
Bakker 1999a (1)	4	32	4	17	3.0%	0.53 [0.15, 1.86]
Black 1993	4	25	9	25	4.2%	0.44 [0.16, 1.26]
Dannon 2004	6	33	1	24	1.2%	4.36 [0.56, 33.92]
Davidson 2004	18	57	25	119	12.7%	1.50 [0.90, 2.52]
Hendriks 2010	3	17	1	20	1.0%	3.53 [0.40, 30.88]
Koszycki 2011	16	63	20	65	11.4%	0.83 [0.47, 1.44]
Nordahl 2016	5	26	2	24	2.0%	2.31 [0.49, 10.80]
Sharp 1996	7	36	16	79	6.6%	0.96 [0.43, 2.13]
vanApeldoorn 2008	17	48	21	53	13.1%	0.89 [0.54, 1.48]
Subtotal (95% CI)		**359**		**448**	**59.1%**	**1.01 [0.75, 1.36]**
Total events	85		104			
Heterogeneity: Tau² = 0.04; Chi² = 10.79, df = 9 (P = 0.29); I² = 17%						
Test for overall effect: Z = 0.08 (P = 0.94)						
1.5.2 TCA						
Bakker 1999b (2)	3	32	5	18	2.7%	0.34 [0.09, 1.25]
Barlow 2000	32	83	39	140	18.4%	1.38 [0.95, 2.02]
Subtotal (95% CI)		**115**		**158**	**21.1%**	**0.79 [0.20, 3.08]**
Total events	35		44			
Heterogeneity: Tau² = 0.76; Chi² = 4.15, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.5.3 MAO						
Blanco 2010	23	45	18	40	15.4%	1.14 [0.73, 1.77]
Heimberg 1998	5	31	8	36	4.4%	0.73 [0.26, 1.99]
Subtotal (95% CI)		**76**		**76**	**19.8%**	**1.06 [0.70, 1.59]**
Total events	28		26			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Total (95% CI)		**550**		**682**	**100.0%**	**1.04 [0.83, 1.31]**
Total events	148		174			
Heterogeneity: Tau² = 0.03; Chi² = 16.29, df = 13 (P = 0.23); I² = 20%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 0.17, df = 2 (P = 0.92), I² = 0%						

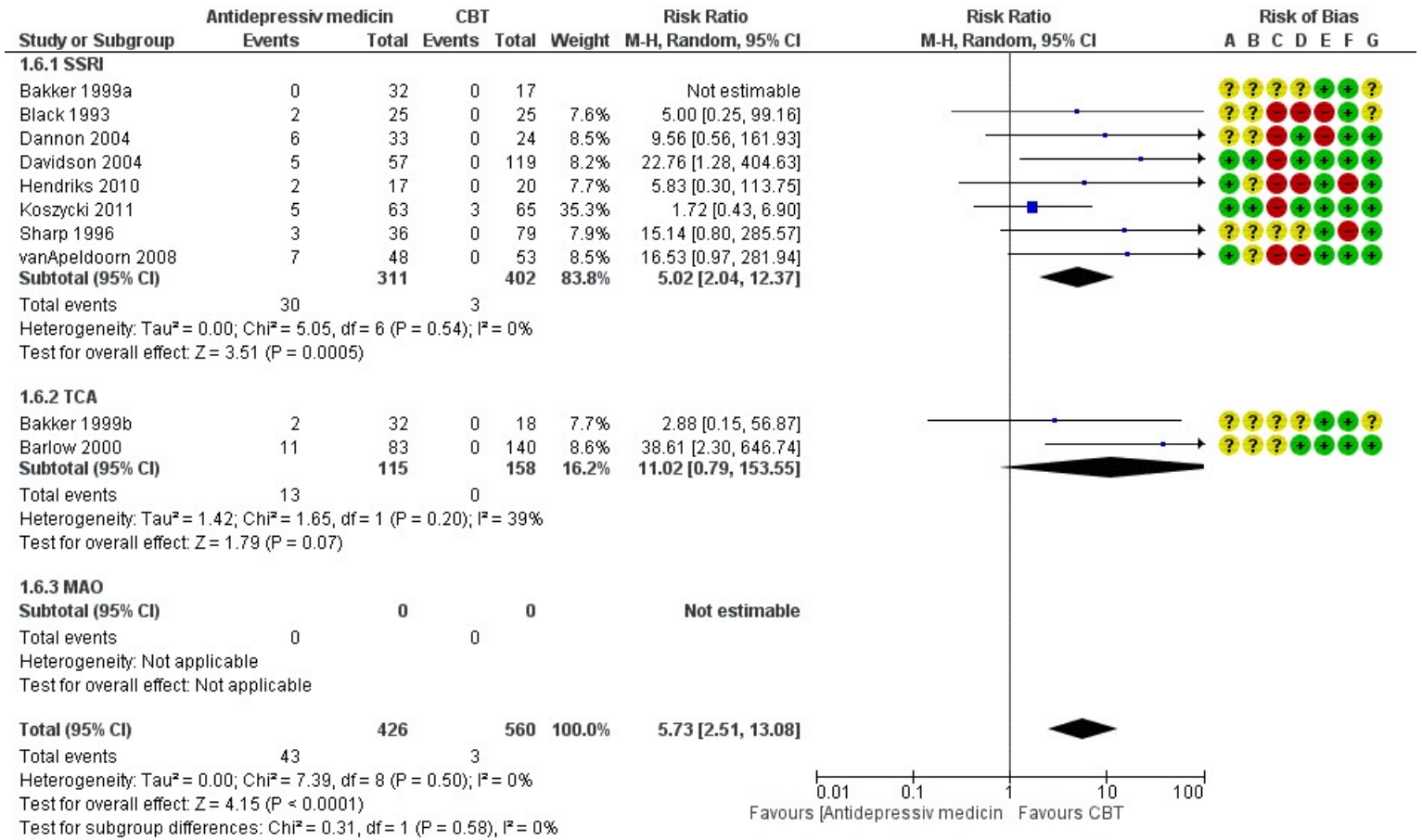


Footnotes
(1) Paroxetine (SSRI)
(2) Clomipramine (TCA

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: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.5 Frafald, alle årsager (dropouts, all cauces).

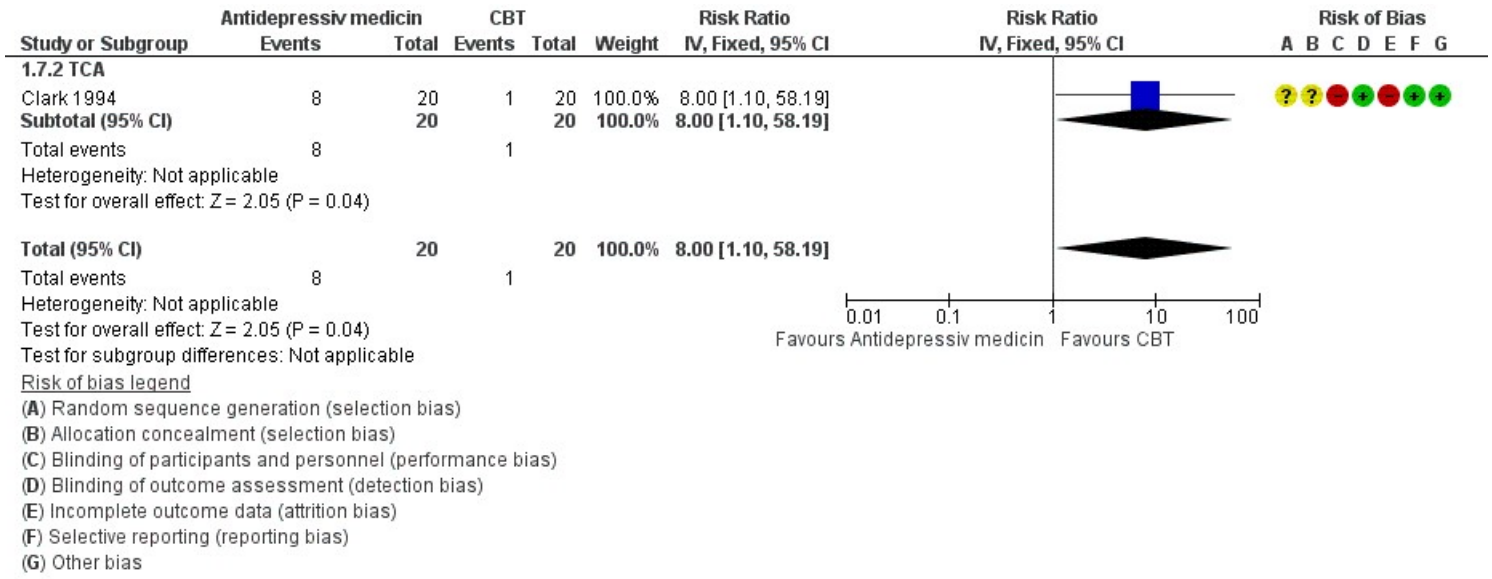
Figure 7 (Analysis 1.6)



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

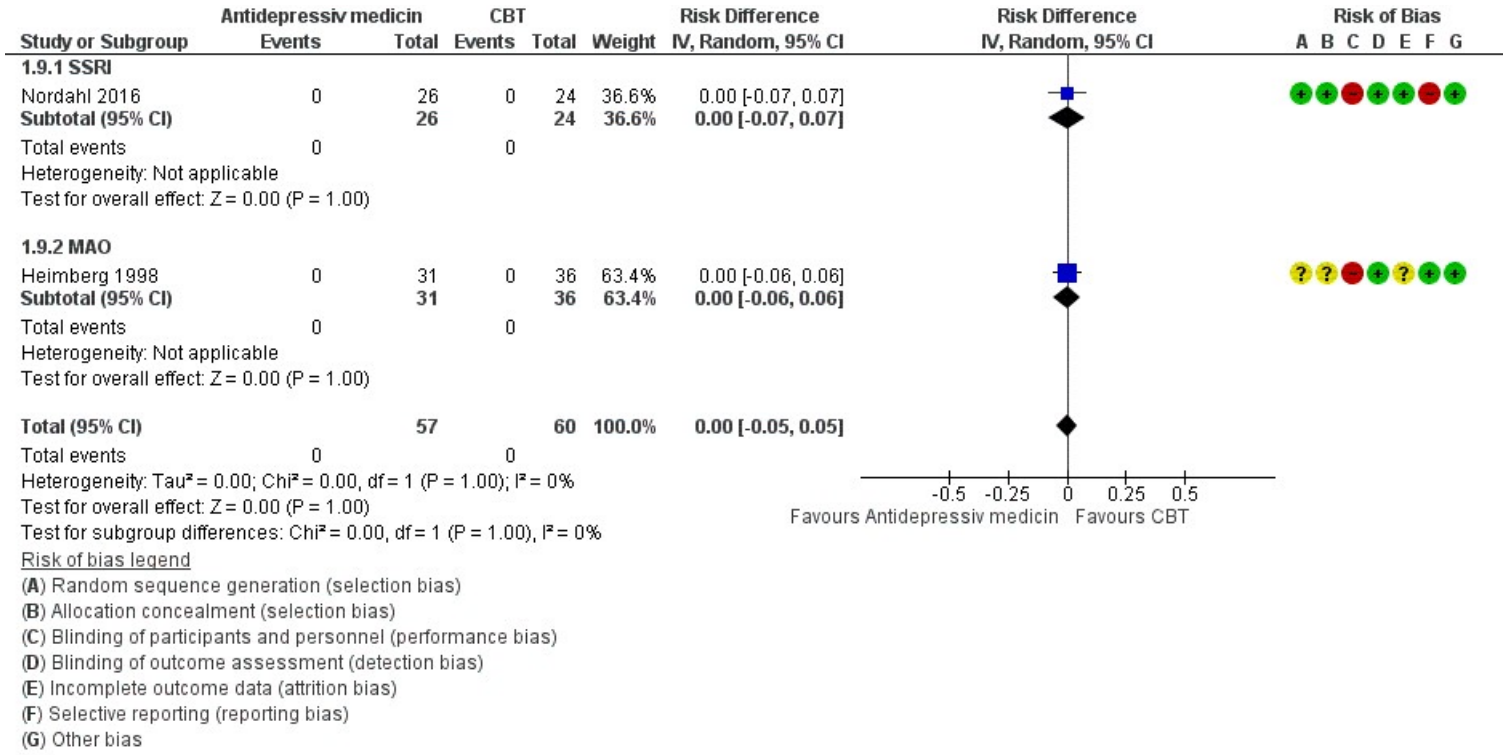
Forest plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.6 Frafald, grundet bivirkninger (dropouts, adverse events).

Figure 8 (Analysis 1.7)



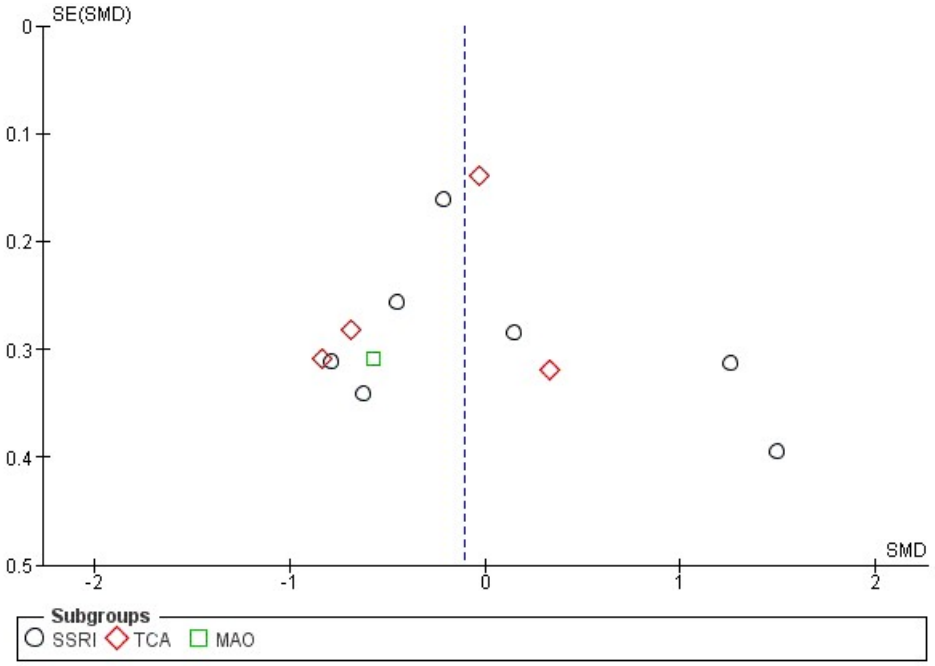
Forest plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.7 Tilbagefald (relapse) Risk ratio.

Figure 9 (Analysis 1.9)



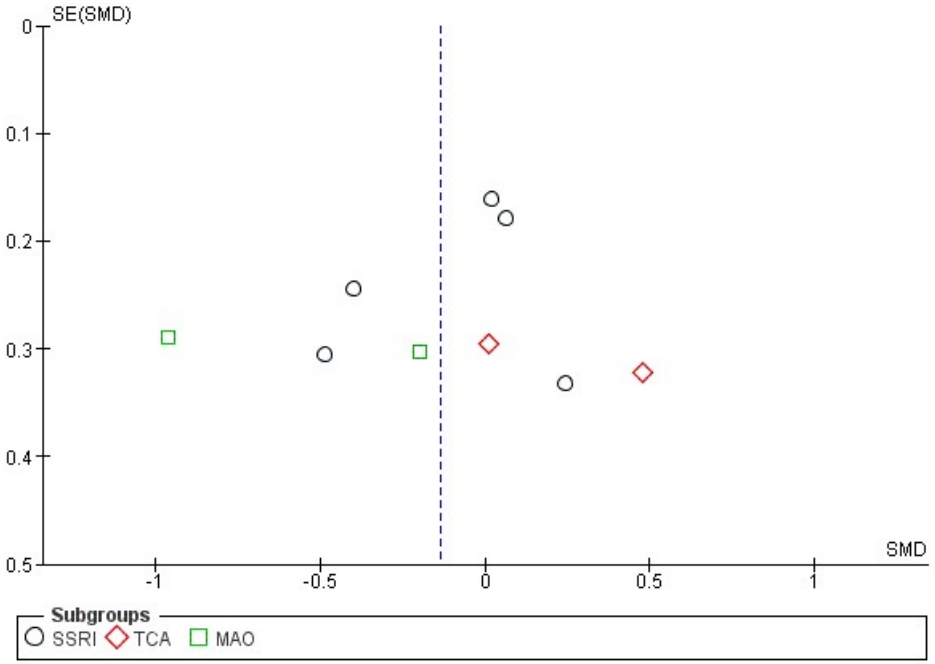
Forest plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.9 Alvorlige bivirkninger (serious adverse events), antal personer.

Figure 10 (Analysis 1.1)



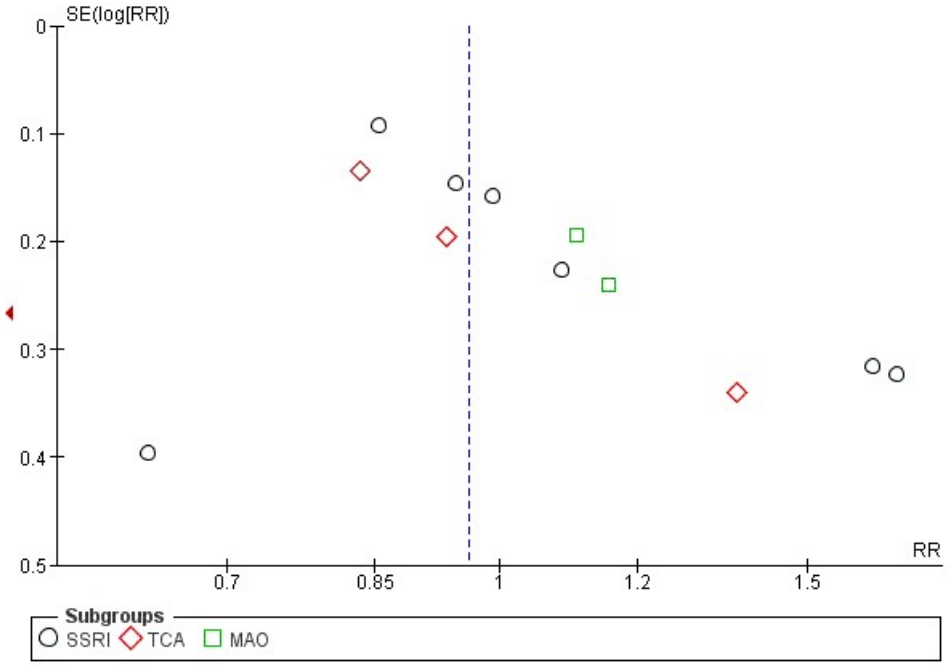
Funnel plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.1 Grad af angst (severity of anxiety).

Figure 11 (Analysis 1.3)



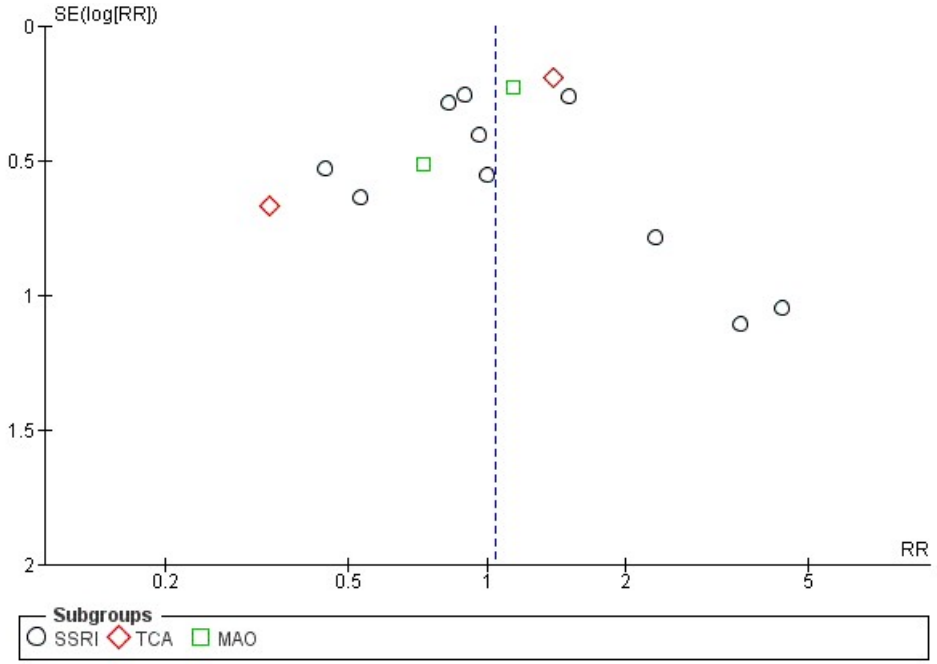
Funnel plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.3 Grad af undgåelse (avoidance).

Figure 12 (Analysis 1.4)



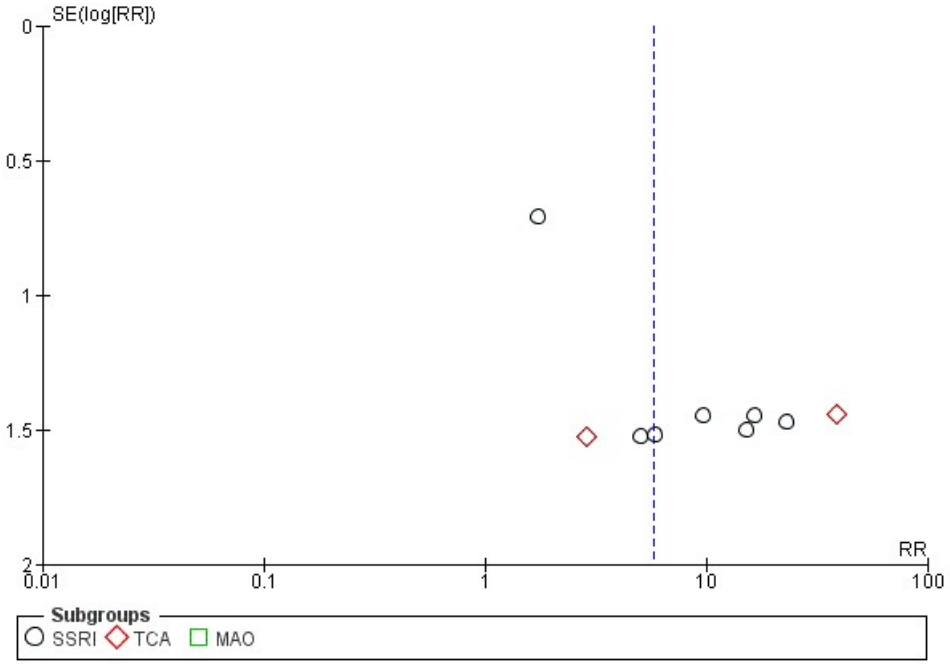
Funnel plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.4 Bedring (Respons).

Figure 13 (Analysis 1.5)



Funnel plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.5 Frafald, alle årsager (dropouts, all cauces).

Figure 14 (Analysis 1.6)



Funnel plot of comparison: 1 Antidepressiv medicin vs.kognitiv adfærdsterapi, outcome: 1.6 Frafald, grundet bivirkninger (dropouts, adverse events).