NKR 58 Kombinationsbehandling med antidepressiv medicin og kognitiv adfærdsterapi for angst

Review information

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Citation example: [Empty name], S. NKR 58 Kombinationsbehandling med antidepressiv medicin og 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)*: 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*: Fluvoxamine. 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 ● *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 FVX50 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* ● **Outcome type**: Continuous Outcome ● **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 **Comments:** **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: "At weekly meetings and at baseline, 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 likely 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

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 permit-ted 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).31,32Mild agoraphobia was operationally defined as a score less than or equal to18 on the ADIS-R avoidance scale. Inaddition, inclusion required at least 1 full or 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. More details are available on request from the authors. Patients with comorbid unipolar depression were not excluded 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), increased every other day by 10 mg until50 mg/d was reached. The dosage wasthen increased more rapidly, with an ef-fort made to reach 100 mg/d by the end of 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 upto 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 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 treatingstudy patients. Clinicians were notrequired 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 pharmacotherapists received ongoing supervision of their cases from the responsiblesite 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 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, 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 upto 300 mg/d by week 5. Blood levels ofimipramine 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 instructions for the conduct of each session. Therapists providing CBT were doctoral-level clinicians who underwent exten-sive training and certification supervised by the Boston site prior to treatingstudy patients. Clinicians were notrequired 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 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 a sample of audiotaped sessions ● *Duration*: 6 months Kontrol 2 ● *Description*: CBT + placebo. Cognitive-behavioral therapy for panic disorder,developed at the Boston site, com-bines interoceptive exposure,

	cogni-tive restructuring, and breathing re-training. This treatment was describedin a manual containing detailed instructions for the conduct of each session. Therapists providing CBT were doctoral-level clinicians who underwent exten-sive training and certification supervised by the Boston site prior to treatingstudy patients. Clinicians were notrequired to have prior training in cognitive-behavioral procedures. Pharmacotherapists were experienced psychia-trists who underwent additional trainingand certification in the study protocol under the direction of the Columbia/Hillside site. All CBT therapists and pharmacotherapists received ongoing super-vision of their cases from the responsiblesite during biweekly telephone calls, andadherence and competence ratings werer outinely collected after listening to asample 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, Gor-man, Shear, and Woods have received research support from the National Institute of Mental Health. Imipramine and matching placebo were provided byTeva 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 Men- tal 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 removed 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

Berger 2004

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● *Mean age, years (SD)*: 33.9 (8.3) ● *Number of females %*: 65.8%

	● *Duration of symptoms/mean years since onset (SD)*: 4.8 (5.8) **Included criteria:** adult outpatients suffering from panic disorder with or without agoraphobia according to DSM-III-R in a 24-week randomized open comparison of drug treatment with paroxetine alone and paroxetine plus cognitive-interpersonal group therapy. The protocol was approvedby the local ethical review board. All patients gave written informed consent. Diagnosis on Axis I was established using the Structured Clinical Interview forDSM-III-R (SCID;Spitzer and National Institute ofMental Health (U.S.), 1990). The International Personality Disorder Examination (IPDE;Loranger et al.,1994) was used to assess personality disorders **Excluded criteria:** Patients were excluded if they had any current so-matic illness, substance abuse or dependence, melancholic depression, and obsessive–compulsive disorder, a life-time history of bipolar disorder, psychosis or seizures, any ongoing psychotherapy, previous cognitive therapy, or lack of response to previous drug-treatment.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Paroxetine. All patients received paroxetine, beginning with 10mg/day in the first week of treatment, and adjustedthereafter up to 60 mg/day (mean dose 31.4 mg/day(S.D. 11.9)). If patients were in remission, paroxetinewas tapered off during the last 4 weeks of treatment.Concomitant p.r.n intake of alprazolam up to 1 mg/day was allowed. ● *Dose*: Paroxetine 10-60 mg/day ● *Duration*: 24 weeks Intervention 2 ● *Description*: Paroxetine + cognitive Behavioral therapy. All patients received paroxetine, beginning with 10mg/day in the first week of treatment, and adjustedthereafter up to 60 mg/day (mean dose 31.4 mg/day(S.D. 11.9)). If patients were in remission, paroxetinewas tapered off during the last 4 weeks of treatment.Concomitant p.r.n intake of alprazolam up to 1 mg/day was allowed. Half the patients were randomly assigned to addi-tional Cognitive–Interpersonal Group Therapy. Thecognitive part of the therapy followed a manualdeveloped for panic disorder (Margraf and Schneider,1990) and the interpersonal therapy was based on amanual developed for depression (Klerman et al.,1984) with adaptations by us for use in panic disorder(Katschnig et al., 1997). Patients could enter thetreatment immediately after baseline. Two individualsessions each preceded and followed group treatmentof 20 weekly sessions. ● *Dose*: Paroxetine 10-60 mg/day + 2 individuel sessions and 20 weekly group sessions of CBT ● *Duration*: 24 weeks
Outcomes	*Bedring, number of participants with improvement on the CGI-I* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: CGI-I ● **Direction**: Higher is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** No information **Country:** Austria **Setting:** Outpatient clinic **Authors name:** Peter Berger **Institution:** Department of Psychiatry, Division of Social Psychiatry, University of Vienna **Email:** peter.berger@akh-wien.ac.at

	Address: Department of Psychiatry, Division of Social Psychiatry, University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austri
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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	Quote: "24-week randomized open comparison of drug treatment with paroxetine alone and paroxetine plus cognitive-inter- personal group therapy." Judgement Comment: No blinding of participants and health care professionals
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: No information of blinding of outcome assessors.
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: 100 patients were included. Only subjects with a minimum of 6 treatment were included in the analysis. 38 in the paroxetine group and 35 in the combination group were included in the analysis.
Selective reporting (reporting bias)	High risk	Judgement Comment: No protocol available. The study fails to reports on all the outcomes stated in the methods section. No reporting of Sheran disability scale.
Other bias	Low risk	Judgement Comment: The study appears to be free of other sources of bias

Blanco 2010a

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 treatmentwith phenelzine or CBT defined as nonresponse 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 and4. 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, andprocedures 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 aspecific patient was also receiving the other treatment, and they could not consult each otheror 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 4–6participants. 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, tochallenge logical errors in ATs, and to formulate rational alternatives. Thereafter, they confronted increasingly difficult feared situations, first through role-playing in the sessionand 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 oflogical 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 attainmentand 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 4–6participants.
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

Crits Christoph 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years (SD)*: 46.4 (19,3) ● *Number of females %*: 52.5% Intervention 2 ● *Mean age, years (SD)*: 46.3 (15.0) ● *Number of females %*: 68.8%

	Included criteria: To be eligible, patients needed to be over the age of 18, meet DSM-IV criteria for GAD (based on a diagnostic interview at baseline) and obtain scores over or equal to 4 on the Clinical Global severity scale(CGI-S) and over or equal to 20 on the Hamilton Anxiety Rating Scale (HAM-A). **Excluded criteria:** To eliminate patients with co-morbid disorders, patients were excluded if they had a score over 18 on the Hamilton Depression Scale (HAM-D), an episode of major depressive disorder in the previous six months, or any other current DSM-IV anxiety diagnoses. Patients also could not have any regular use of buspirone, anti convulsants, neuroleptics or antidepressants within 14 days of the commencement of the study,
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: venlafaxine. All post-baseline assessments were performed by a psychiatrist, who also administered the venlafaxine XR in a flexible dose of 75–225mg/d. ● *Dose*: Venlafaxine in flexible doses of 75–225mg/day ● *Duration*: 24 weeks for medication Intervention 2 ● *Description*: Cognitive behavioral therapy (CBT). Participants who were offered to add CBT and elected to receive CBT received treatment sessions weekly for 12 weeks. No fees were charged for the CBT sessions. The CBT for GAD treatment manual that was implemented in the Borkovec and Costello(1993) and Borkovecet al.(2002) studies was used to guide treatment.This package includes the following techniques, applied relaxation/self-control desensitization (SCD) involving presentation of the multiple coping response CBT model and rationale; training in self-monitoring of environmental, somatic, affective, imaginal, and thought (especially worry) cues that trigger anxiety spirals with special emphasis on increasingly early cue detection; external and especially internal cue hierarchy development; for-malslowed diaphragmatic breathing and progressive relaxation; trainingin cue-controlled and differential relaxation; applied relaxation training; development of coping self-statements to use in response to cues; and employment of self-statements and applied relaxation during formal SCDi magery for rehearsal of coping responses. Hierarchies for SCD are constructed from daily self-monitoring and in-session discussion with the patient. The CBT package also included the following cognitive therapy (Beck & Emery,1985) techniques: presentation of the role of cognitionin anxiety; training in self-monitoring of early worry and automatic thought occurrence, identification of cognitive predictions, interpretations, beliefs, assumptions,and core beliefs underlying the threatening nature of events orcues; logical analysis;examination of evidence; labeling of logical errors; decatastrophization; generation of alternative thoughts and beliefs; early application of these alternatives to daily living; the creation of behavioral experiments to obtain evidence for new beliefs, and use of cognitive perspective shifts learned in cognitive therapy during SCD rehearsals ● *Dose*: Venlafaxine in flexible doses of 75–225mg/day and CBT with weekly sessions for 12 weeks ● *Duration*: 12 weeks + 24 weeks for medication
Outcomes	*Grad af angst, HAM-A, mean, SD* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **Range**: 0-56 ● **Direction**: Lower is better ● **Data value**: Endpoint *Funktion, Penn State Worry Questionnaire* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: *Penn State Worry Questionnaire*

	● **Range**: ● **Direction**: Lower is better ● **Data value**: Endpoint Livskvalitet, General Health Questionnaire GHQ/120 ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Bedring, mindst 50% reuktion på HAM-A* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: HAM-A ● **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:** This research was supported by National Institute of Mental Health(NIMH) grant R34-MH072678.The parent study was sup-portedby NIMH grant R01 065963. Wyeth Laboratorie sprovided study medications for the parent study. The authors report no financial involvement or affiliation with any organization whose financial interests may be affected by material in this article **Country:** USA **Setting:** Outpatient clinic **Authors name:** PaulCrits-Christoph **Institution:** Department of Psychiatry ,University of Pennsylvania **Email:** crits@mail.med.upenn.edu **Address:** Department of Psychiatry ,University of Pennsylvania, 3535 MarketStreet, Philadelphia, PA19104, United States
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "2:1 (CBT:medication) randomization scheme was used because of the existence of the large comparison group of patients on venlafaxine XR alone (n = 159) that was already available from the parent study." 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: Open label. No blinding of participants and personel. Blinding of CBT not possible.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The SCID, HAM-A, HAM-D, CGI-S, and CGI-I ratings were conducted by research psychiatrists trained and highly experienced in the use of these scales. The evaluators were not informed about which patients received CBT and were instructed to not ask about it." Judgement Comment: Secondary outcomes of interests that were self-reported outcomes were: GHQ/120 QL, Penn state worry questionnaire. Patients were not blinded for group allocation
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: 3/29 dropped out in the CBT + venlafaxine group and 5/40 in the venlaxaxine group. No intention to treat analyses.
Selective reporting (reporting bias)	Low risk	Judgement Comment: Protocol available (NCT00620776), reported as stated.
Other bias	Low risk	Quote: "This research was supported by National Institute of Mental Health (NIMH) grant R34-MH072678. The parent study was supported by NIMH grant R01-065963. Wyeth Laboratories provided study medications for the parent study. The authors report no financial involvement or affiliation with any organization whose financial interests may be affected by material in this article." Judgement Comment: The study appears to be free of other sources of bias

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-IVdiagnosis of GSP; (2) age be-tween 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 least 4 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. Unless adverse effects became problematic, the goal was for subjectsto reach 40 mg/d. At days 43 and 57, the dose could be raised to 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 atreatment developed by Heimberg et al. CCBT differs from Heimberg group CBT in that CCBT includes specific social skillstraining (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 con-sisted 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 (5-7 times) 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 each role-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 to help them confront fearful social situations using the techniques learned in therapy. Session 14 included a discussion of treatment 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."

King 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years (SD)*: 33.7 (9.6) ● *Mean age at onset (SD)*: 33.5 (11.0) Intervention 2 ● *Mean age, years (SD)*: 44.5 (12.8) ● *Mean age at onset (SD)*: 27.1 (6.8) Overall ● *Number of females %*: 78% **Included criteria:** The inclusion criteria for the study were that the patients should be over 18 years old of either gender with a diagnosis of panic disorder and agoraphobia. **Excluded criteria:** but without severe co-morbidities such as bipolar disorder, schizophrenia and other psychotic disorders, mental retardation, mental disorder due to a general medical condition or alcohol and substance-related disorders. **Pretreatment:** The medication + CBT group and the medication alone groups differed significantly in age. The minimum age for both groups was 22 and the maximum was more than 55. However, the mean age for the medication + CBT group was 44.5 (standard deviation, SD = 12.8; 95% confidence interval, CI = 39.0-49.8) and for the medication alone group, it was 33.7 (SD =9.6; 95% CI = 29.7-37.7). The ANOVA test on the means showed significance of 0.000, i.e. lower than the P-value of 0.05, with 95% confidence. There were also significant differences in age at the onset of panic disorder. In the medication alone group (which was a younger group), the disorder was identified earlier than among the patients in the medication

	+ CBT group (which was an older group) with CBT. Among the controls, the mean age at onset was 27.1 (SD = 6.8; 95% CI = 24.3-29.9), whereas it was 33.5 (SD = 11.0; 95% CI = 29.0-38.1) in the intervention group. The ANOVA test on the means showed significance of 0.017, which was lower than the P-value of 0.05, with 95% confidence.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: medication (tricyclic antidepressants or selective serotonin reuptake inhibitors) ● *Dose*: No information ● *Duration*: No information Intervention 2 ● *Description*: Medication (tricyclic antidepressants or selective serotonin reuptake inhibitors) + Cognitive behavioral therapy. CBT sessions were based on previous studies,2 with changes and adaptations according to the characteristics of the sample of patients treated. The sessions included the following topics: clarification of the course of panic disorder by explaining the concepts of anxiety, agoraphobia, panic, hyperventilation, breathing retraining exercise and muscle relaxation; development of hierarchies for “patients’ fears” from the least to the most stressful; identification of maladaptive cognition and cog-nitive reorganization; symptom induction exercises; interoceptive exposure; introduction to “in vivo” exposure; strengthening of achievements; observation of difficulties in the procedure; and maintenance of treatment gains. ● *Dose*: 16 CBT sessions along with medication. 16 one-hour individual CBT sessions, ● *Duration*: No information
Outcomes	*Bedring, responders on the Beck Anxiety Inventory* ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: *Beck Anxiety Inventory* ● **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:** Sources of funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and INCT-Translational Medicine (CNPq) **Country:** Brazil **Setting:** Outpatient clinic **Authors name:** Anna Lucia Spear King

	Institution: Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro, Brazil **Email:** E-mail: annaluciaking@gmail.com **Address:** Anna Lucia Spear KingInstituto de Psiquiatria (IPUB) Centro de Ciências da Saúde (CCS)Universidade Federal do Rio de Janeiro (UFRJ)Av. Venceslau Brás, 71 Praia Vermelha — Rio de Janeiro (RJ) — BrasilCEP 22290- 140
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients in both groups were randomly selected. The random- ization was done by means of sealed envelopes and was performed by a researcher not directly involved in patient evaluations."
Allocation concealment (selection bias)	Low risk	Quote: "The patients in both groups were randomly selected. The random- ization was done by means of sealed envelopes and was performed by a researcher not directly involved in patient evaluations. The eval- uators did not have access to the envelopes during the study, and thus did not know which patients were receiving CBT and which were not. During the CBT sessions, the topic of medications was not mentioned to the patients at any time."
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Open label. Blinding of CBT not feasible
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The evaluators did not have access to the envelopes during the study, and thus did not know which patients were receiving CBT and which were not. During the CBT sessions, the topic of medications was not mentioned to the patients at any time. However, they could talk about medications during their visits to their physicians. The physi- cian who prescribed the drugs did not participate in implementing the instruments relating to the study. Patients did not talk to the evaluator about the treatment that they were receiving." Judgement Comment: Beck depression inventory were rated by clinicians.
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No information of dropouts. No information of intention to treat analysis.
Selective reporting (reporting bias)	High risk	Judgement Comment: The study mainly reports the effect in the group receiving medication + CBT.The trial protocol available at clinicaltrials.gov: Primary outcome stated here were the number of panic attacks. Secondary Outcome Measures: Decrease agoraphobic symptoms. Fails to report on the primary outcome in the prespecified way. Reports on several outcomes not stated in the protocol but only data for the medication + CBT group
Other bias	Low risk	Judgement Comment: The study appears top 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 1 ● *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 Panic disorder dioagnosis. To prevent the inclusion of severely depressed patients, subjects were eligible if their scoreon 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 psychosurgery; 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 were pregnant, lactating or not using reliable contraception were excluded.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Sertraline and placebo were provided within the context of clinical management sessions as described by Fawcett et al. (1987). Study drugs were initiated at 25 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) was obtained. The targeted maximal dose for acute treatment was 200 mg/day. During extension treatment, patients were maintained at the dose achieved by week 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 workbook that contained monitoring forms for homework. The tapes and workbook were developed for this study by psychologists with expertise in CBT (D.K. and Z.S.).Each tape described the principles of treatment andprovided detailed instructions and homework.Treatment components included

	extensive psychoeducation about anxiety and the cognitive model ofPD, breathing retraining and relaxation skills, cognitive restructuring that addressed misappraisal ofpanic symptoms, interoceptive and situational exposure, and relapse prevention. Tapes were distributed weekly during acute treatment by a researchcoordinator and a standard format was adopted for instructions to be given to patients. Compliance was assessed at each visit by asking patients how muchtime they spent listening to the tape, whether they attempted the suggested homework and whether they recorded their homework in the workbook. 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 workbook ● *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

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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 thepatient was assigned to SCBT. Patients were instructed not to divulge their SCBT assignment to the investigators.Outcomes of interests were slinician 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.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Paroxetine. The medication used was paroxetine (paroxetine hydrochloride). It was administered as capsules manufactured by the pharmaceutical laboratory at St. Olav's University Hospital to make them identical to the placebo. The placebo capsules contained lactose. 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 psychiatrists. 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. 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 for-mat 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 Cognitive 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.

	● *Dose*: ● *Duration*: 26 weeks
Outcomes	*Grad af angst, Beck anxiety inventory, mean, SD* ● **Outcome type**: ContinuousOutcome ● **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**: DichotomousOutcome ● **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**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: the Fear of negative evaluation questionnaire ● **Direction**: Lower is better ● **Data value**: Endpoint *Frafald, alle årsager* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Alvorlige bivirkninger, SAE, antal personer* ● **Outcome type**: AdverseEvent ● **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)

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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. The" 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 of participants and personnel (performance bias)	High risk	Quote: "In the groups receiving pills, we applied triple masking, and the patient, the psychia- trists, 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, spe- cific 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." Judgement Comment: 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 identi- fier: 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. There are reprted on more outcomes in the published study 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 appointment, 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 suggested 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 ses- sions 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 appoint- ment, 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 contra-indications toeither 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 their therapist nine times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. Each visitlasted approximately 20 min. SSRI prescriptions were in conformance with the pharmacotherapeutical guidelines as formulated by the Dutch Psychiatry Association (26). Pharmacotherapists could choose between five SSRIs currently prescribed inthe Netherlands: fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram. During the first SSRI session, patients received some general information on the role of serotonergic pathways in thebrain involved in anxiety disorders and the working of SSRIs in PD. Patients were administered aminimum dosage which was titrated upwards up to the effective range in the first month, and adjusted according 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 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 Intervention 2 ● *Description*: SSRI + Cognitive behavioral therapy (CBT). CBT + SSRI. This treatment was administeredaccording to the CBT and SSRI manuals. The two 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 sessionseach lasting approximately 50 min. Kontrol 1 ● *Description*: Cognitive behavioral therapy (CBT). The CBT protocol is based on the work ofClark (23) and Craske and Barlow (24). Patients inthe CBT group received up to 18 CBT sessions each lasting approximately 50 min. To prevent return of fear, interval between sessions were extended in the course of treatment (from once aweek to twice a week, and from session 16 onward with 5 week intermissions) (25). During the first session, the treatment rationale was provided which was based on the cognitive model of panic as 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 newevidence. Both automatic appraisals (such as if Ipanic, I will faint) and core-level beliefs orschemata (such as I am weak) were examined inthis manner. Based on this hypothesis testing, alternative hypotheses were generated that were evidence based. In the 10th session, exposurein 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 writtendown 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 thetwo was left to the clinical judgment of thetherapist. Homework assignments were giventhroughout the treatment and were thoroughlydiscussed at the beginning of each session. Eachnew 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 sessionseach 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 *Funktion, SCL-90* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: *SCL-90* ● **Range**: ● **Direction**: ● **Data value**: Endpoint *Grad af undgåelse, Fear Questionnaire, agoraphobia subscale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: FQ (a*goraphobia 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 *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 groupReasons 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

Xie 2019

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 40.0 (11.8) ● *Number of females (%)*: 51.7% Intervention 2 ● *mean age, years (SD)*: 36.1 (9.7) ● *Number of females (%)*: 56.8% **Included criteria:** Inclusion criteria for the study participants were as follows: (a)aged between 18 and 65 years old; (b) diagnosed with GAD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association,1994) (The diagnostic screenings were made by two attending psychiatrists independently according to DSM-IV.); (c) scored higher than 14 on the HAMA (d) had the ability to understand and complete the treatment; and (e) had no language communication barrier. **Excluded criteria:** The exclusion criteria were as follows: (a) any past or present history of an organic mental disorder, schizophrenia, schizoaffective disorder, major depression, bipolar disorder, or any other typeof anxiety disorder based on the DSM-IV; (b) any alcohol or substance abuse disorder in the past 12 months; and (c) any serious suicidal tendencies. During the study period, participants were removed if they (a) had any suicidal behaviour or made a suicide attempt during the study period; (b) withdrew the informed consent; or (c) were absent for more than three therapy sessions.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Duloxetine alone. All participants continued their regular outpatient psychiatrist visits for medication management and general support throughout the research period.Like the treatment group, all control group participants continued their outpatient psychiatrist visits. While the control group did not meet in person as a group, they received general health and GAD psycho-education materials weekly in the form of a leaflet for the 8 weeks that the treatment group received GCBT. The educational leaflet materials were not a reproduction of the GCBT content, but general advices on how to understand and cope with anxiety, with self-help tips, in essay forms developed by the team.All control group participants actively signed up to a dedicated group account and received the leaflet using an internet-based social media application (WeChat) ● *Dose*: No description of doses ● *Duration*: 8 weeks Intervention 2 ● *Description*: GCBT and duloxetine. We developed the process and content of the GCBT based on a literature review on GCBT for GAD (Dugas & Robichaud,2007;Tian,2007; Luciani,2010; Bielinget al.,2017) and informed by previous clinical experience of our research team. All of the treatment contents were reviewed by two external experts in the field to ensure that standard active components of CBT were effectively incorporated in the treatment.The overall treatment contents and processes were written as a study manual to standardise the implementation of the study. The theme for each session is listed in Table 1. Each GCBT group consisted of 6–14 participants, led by 2 therapists, who had either a

	psychiatry or psychotherapy background. At the end of each session, homework corresponding tot he standardised content was assigned. Time to share and discuss the homework was incorporated into the following session.This technique was designed to help the participants to practice,reflect, and master the associated techniques. There was a total of 8 weekly, 90-min sessions. All participants continued their regular outpatient psychiatrist visits for medication management and general support throughout the research period. ● *Dose*: 8 weekly, 90-min sessions. ● *Duration*: 8 weeks
Outcomes	*Grad af angst,* Liebowitz Social Anxiety Scale (*LSAS)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Liebowitz Social Anxiety Scale (LSAS) ● **Range**: ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This research was supported by Beijing Municipal Scienceand Technology Commission Capital Citizen Health Training Project(Z151100003915104) **Country:** China **Setting:** Outpatient clinic **Authors name:** Zhi-Juan Xie **Institution:** Department of Psychiatry, Peking University People's Hospital, Beijing, China **Email:** huangxuebing@bjmu.edu.cn
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation protocol employed a SPSS-generated random number table, and group assignment based on these random numbers was prepared using sequentially numbered, opaque, sealed envelopes for concealing the randomisation sequence."
Allocation concealment (selection bias)	Low risk	Quote: "Recruited participants were given the sequentially numbered envelops in order and learned of their group assignment after the written informed consent was signed." Quote: "The randomisation protocol employed a SPSS-generated random number table, and group assignment based on these random numbers was prepared using sequentially numbered, opaque, sealed envelopes for concealing the randomisation sequence."
Blinding of participants and personnel (performance bias)	High risk	Quote: "The current study was conducted as a randomised, open-label trial with masked endpoint assessment; only the outcome assessors were blinded to the treatment allocation." Judgement Comment: Open label trial in combination with self-reported outcomes
Blinding of outcome assessment (detection bias)	Low risk	Quote: "open-label trial with masked endpoint assessment; only the outcome assessors were blinded to the treatment allocation." Judgement Comment: Assessments were conducted by two blinded outcomes assessors.

Incomplete outcome data (attrition bias)	Low risk	Quote: "All data were analysed based on an intention-to-treat approach." Judgement Comment: Stated that all analyses were based on the intention to treat principle, but they only included participants that completed the 4 week evaluation in this analyses. Before the end week four 7/89 dropped out in the medication group and 2/81 in the combination group. reasons for dropout stated. No large differences in the dropout rate between the groups
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	Quote: "Financial support. This research was supported by Beijing Municipal Science and Technology Commission Capital Citizen Health Training Project (Z151100003915104)." Judgement Comment: The study appears to be free of other sources of bias

Yoshinaga 2016

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *mean age, years (SD)*: 31.6 (9.2) ● *Number of females (%)*: 42.9% Intervention 2 ● *mean age, years (SD)*: 32.5 (8.2) ● *Number of females (%)*: 38.1% **Included criteria:** Prospective patients were included according to the following criteria: a primary diagnosis of SAD according to the DSM-IV criteria (no restriction on subtype); age 18–65 years; symptomatic status of at least a moderate level of severity (Liebowitz Social Anxiety Scale, LSAS score above or equal to 50 and having received adequate treatment with at least one SSRI at maximum-dose treatment for at least 12 weeks, or intolerance to at least one SSRI. Co-morbid diagnoses were permitted if they were clearly secondary **Excluded criteria:** Exclusion criteria included psychosis, pervasive developmental disorder/mental retardation, autism spectrum disorders, current high risk of suicide, substance abuse/dependence within the 6 months prior to enrolment, antisocial personality disorder, any unstable medical condition, pregnancy, or lactation. Patients were also excluded if they reported ‘much’ to ‘very much’ improvement in the Clinical Global Impression (CGI) scale following any type of treatment (e.g. medication, psychotherapy, or both) in the 12 weeks prior to the study.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Usual care. Antidepressants. Primary psychiatrists referred patients to the trial, but continued to provide UC to the patients in both groups. They had no restrictions placed on UC available to them, and medication change was allowed. However, the initiation of a strictly structured CBT program was banned in the UC group in order to properly assess the effectiveness of CBT. All treatment changes, with the reasons for these changes, were recorded throughout the study. ● *Duration*: 16 weeks Intervention 2 ● *Description*: Usual care + CBT. Primary psychiatrists referred patients to the trial, but continued to provide UC to the patients in both groups. They had no restrictions placed on UC available to them, and medication change was allowed. However, the initiation of a strictly structured CBT

	program was banned in the UC group in order to properly assess the effectiveness of CBT. All treatment changes, with the reasons for these changes, were recorded throughout the study. Our CBT program was based on the model of Clark and Wells [19] and conducted over 16 weekly individual sessions. Most sessions lasted for 50 min; however, the treatment manual allowed therapists to extend up to 6 sessions to a maximum of 90 min each to facilitate behavioral experiments. ● *Dose*: 16 weekly individual sessions. Most sessions lasted for 50 min ● *Duration*: 16 weeks
Outcomes	*Grad af angst,* Liebowitz Social Anxiety Scale (*LSAS)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Liebowitz Social Anxiety Scale (LSAS) ● **Range**: ● **Direction**: Lower is better ● **Data value**: Endpoint *Funktion, Sheehan Disability Scale* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: *Sheehan Disability Scale* ● **Direction**: Lower is better ● **Data value**: Endpoint *Livskvalitet,* WHO quality of life ● **Outcome type**: Dichotomous Outcome ● **Reporting**: Fully reported ● **Scale**: WHO quality of life ● **Direction**: ● **Data value**: Endpoin *Bedring, percentages with 31% reduction on LSAS* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: LSAS ● **Direction**: Higher is better ● **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 antal personer* ● **Outcome type**: Dichotomous Outcome

	● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This study was supported by the Grant-in-Aid for the Japan Society for the Promotion of Science (JSPS) Fellows from the JSPS (grant 13J00177 to N.Y.), part of the Grant for Scientific Research on Priority Areas from the University of Miyazaki (to N.Y.), the Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare (grant 22SE1P0051 to E.S.), and part of the Special Budget for Project from the Japanese Ministry of Education, Culture, Sports, Science and Technology (to E.S.) **Country:** Japan **Setting:** Outpatient clinic **Authors name:** Naoki Yoshinaga **Institution:** Organization for Promotion of Tenure Track, University of Miyazaki, Miyazaki and Departments of Cognitive Behavioral Physiology Chiba University Hospital, Chiba , Japan; **Email:** naoki-y@med.miyazaki-u.ac.jp **Address:** Organization for Promotion of Tenure Track, University of Miyazaki General Education and Research Building (G704), 5200 Kihara Kiyotake, Miyazaki 889-1692 (Japan)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At the end of baseline assessment, eligible patients were randomly assigned to the CBT + UC or UC group in a 1: 1 ratio using the minimization method with biased-coin assignment balancing on primary outcome score (LSAS 50–70 or ≥ 70) [15], sex, and presence or absence of current treatment with SSRIs"
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Insufficient information on allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: No information of blinding of participants and health care providers. blinding of CBT not feasible Open-label and outcomes are self-reported
Blinding of outcome assessment (detection bias)	High risk	Quote: "The EuroQol-5 Dimensions (EQ-5D), The CGI-Severity/Improvement (CGI-S/I) were evaluated by independent assessors." Quote: "To ensure blinding, the independent assessors had no other contact with the patients. Success of blinding was assessed at weeks 8 and 16 based on Bang's method [18] by asking 'Which type of treatment do you think the patient received during the trial?' with possible responses being 'CBT + UC', 'UC alone', or 'don't know'." Secondary outcomes were self-reported using the Social Phobia and Anxiety Inventory, the Beck Depression Inventory-II (BDI-II), the Sheehan Disability Scale (SDS), the WHO Quality of Life-26 item version (WHOQOL-26), and the EuroQol-5 Dimensions (EQ-5D) and patients were not blinded to treatment allocation. .
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: only one dropped out (allocted to the usual care group)
Selective reporting (reporting bias)	Low risk	Quote: "the trial was registered as UMIN000007552." Judgement Comment: The trial proticol is available and the study reports on all the outcomes stated in the protocol

Other bias	Low risk	Quote: "This study was supported by the Grant-in-Aid for the Japan Society for the Promotion of Science (JSPS) Fellows from the JSPS (grant 13J00177 to N.Y.), part of the Grant for Scientific Research on Priority Areas from the University of Miyazaki (to N.Y.), the Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare (grant 22SE1P0051 to E.S.), and part of the Special Budget for Project from the Japanese Ministry of Education, Culture, Sports, Science and Technology (to E.S.). The funding sources had no role in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication." Judgement Comment: The study appears to bee free of other sources of bias

Footnotes

Characteristics of excluded studies

Barlow 2016

Reason for exclusion	genoptryk af gammelt studie

Blanco 2010

Reason for exclusion	Duplicate

Bond 2002

Reason for exclusion	Wrong intervention

Clark 1991

Reason for exclusion	Wrong intervention

Crits Christoph 2011a

Reason for exclusion	Duplicate

Gladsjo 2001

Reason for exclusion	Wrong intervention

Habecker 2018

Reason for exclusion	genoptryk af gammelt studie

King 2011a

Reason for exclusion	Duplicate

Koszycki 2011a

Reason for exclusion	Duplicate

Loerch 1999

Reason for exclusion	Wrong comparator

Markell 2014

Reason for exclusion	Wrong intervention

Marks 1993

Reason for exclusion	Wrong intervention

Meuldijk 2016

Reason for exclusion	Wrong patient population

Power 1990

Reason for exclusion	Wrong intervention

Prasko 2006

Reason for exclusion	Wrong intervention

Spinhoven 1996

Reason for exclusion	Wrong intervention

vanApeldoorn 2014

Reason for exclusion	Wrong study design

Wetherell 2013

Reason for exclusion	only an abstract with no data

Wiborg 1996

Reason for exclusion	Wrong intervention

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Azhar 2000

Azhar, M. Z.. Comparison of Fluvoxamine alone, Fluvoxamine and cognitive psychotherapy and psychotherapy alone in the treatment of panic disorder in Kelantan--implications for management by family doctors. The Medical journal of Malaysia 2000;55(4):402-408. [DOI:]

Barlow 2000

Barlow, D. H.; Gorman, J. M.; Shear, M. K.; Woods, S. W.. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. Jama 2000;283(19):2529-2536. [DOI: joc90799 [pii]]

Berger 2004

Berger, P.; Sachs, G.; Amering, M.; Holzinger, A.; Bankier, B.; Katschnig, H.. Personality disorder and social anxiety predict delayed response in drug and behavioral treatment of panic disorder. Journal of affective disorders 2004;80(1):75-78. [DOI: 10.1016/S0165-0327(03)00043-0 [doi]]

Blanco 2010a

Blanco, C.; Heimberg, R. G.; Schneier, F. R.; Fresco, D. M.; Chen, H.; Turk, C. L.; Vermes, D.; Erwin, B. A.; Schmidt, A. B.; Juster, H. R.; Campeas, R.; Liebowitz, M. R.. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. Archives of General Psychiatry 2010;67(3):286-295. [DOI: 10.1001/archgenpsychiatry.2010.11 [doi]]

Crits Christoph 2011

Crits-Christoph, P.; Newman, M. G.; Rickels, K.; Gallop, R.; Gibbons, M. B.; Hamilton, J. L.; Ring-Kurtz, S.; Pastva, A. M.. Combined medication and cognitive therapy for generalized anxiety disorder. Journal of anxiety disorders 2011;25(8):1087-1094. [DOI: 10.1016/j.janxdis.2011.07.007 [doi]]

Davidson 2004

Davidson, J. R.; Foa, E. B.; Huppert, J. D.; Keefe, F. J.; Franklin, M. E.; Compton, J. S.; Zhao, N.; Connor, K. M.; Lynch, T. R.; Gadde, K. M.. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. Archives of General Psychiatry 2004;61(10):1005-1013. [DOI: 61/10/1005 [pii]]

King 2011

King, A. L.; Valenca, A. M.; de Melo-Neto, V. L.; Freire, R. C.; Mezzasalma, M. A.; Silva, A. C.; Nardi, A. E.. Efficacy of a specific model for cognitive-behavioral therapy among panic disorder patients with agoraphobia: a randomized clinical trial. Sao Paulo medical journal = Revista paulista de medicina 2011;129(5):325-334. [DOI: S1516-31802011000500008 [pii]]

Koszycki 2011

Koszycki, D.; Taljaard, M.; Segal, Z.; Bradwejn, J.. A randomized trial of sertraline, self-administered cognitive behavior therapy, and their combination for panic disorder. Psychological medicine 2011;41(2):373-383. [DOI: 10.1017/S0033291710000930 [doi]]

Nordahl 2016

Nordahl, Hans M.; Vogel, Patrick A.; Morken, Gunnar; Stiles, Tore C.; Sandvik, Pal; Wells, Adrian. Paroxetine, Cognitive Therapy or Their Combination in the Treatment of Social Anxiety Disorder with and without Avoidant Personality Disorder: A Randomized Clinical Trial.. Psychotherapy & Psychosomatics 2016;85(6):346-356. [DOI:]

Sharp 1996

Sharp, Donald M.; Power, Kevin G.; Simpson, R. J.; Swanson, Vivien; Moodie, Eleanor; Anstee, Julie A.; Ashford, J. J.. Fluvoxamine, placebo, and cognitive behaviour therapy used alone and in combination in the treatment of panic disorder and agoraphobia. Journal of Anxiety Disorders 1996;10(4):219-242. [DOI: https://doi.org/10.1016/0887-6185(96)00008-4]

vanApeldoorn 2008

Van Apeldoorn, Franske J.; Van Hout,Wiljo J P J.; Timmerman, Marieke E.; Mersch, Peter Paul A.; den Boer, Johan A.. Rate of improvement during and across three treatments for panic disorder with or without agoraphobia: cognitive behavioral therapy, selective serotonin reuptake inhibitor or both combined.. Journal of affective disorders 2013;150(2):313-319. [DOI:]

van Apeldoorn, F. J.; van Hout, W. J.; Mersch, P. P.; Huisman, M.; Slaap, B. R.; Hale, W. W.,3rd; Visser, S.; van Dyck, R.; den Boer, J. A.. Is a combined therapy more effective than either CBT or SSRI alone? Results of a multicenter trial on panic disorder with or without agoraphobia. Acta Psychiatrica Scandinavica 2008;117(4):260-270. [DOI: 10.1111/j.1600-0447.2008.01157.x [doi]]

van Apeldoorn, Franske J.; Timmerman, Marieke E.; Mersch, Peter Paul A.; van Hout,Wiljo J P J.; Visser, Sako; van Dyck, Richard; den Boer, Johan A.. A randomized trial of cognitive-behavioral therapy or selective serotonin reuptake inhibitor or both combined for panic disorder with or without agoraphobia: treatment results through 1-year follow-up.. Journal of Clinical Psychiatry 2010;71(5):574-586. [DOI:]

Xie 2019

Xie, Zhi-Juan; Han, Nan; Law, Samuel; Li, Zhi-Wen; Chen, Shu-Yan; Xiao, Ju-Ping; Zhang, Yi; Gao, Bing-Ling; Jiang, Si-Si; Gao, Hui-Min; Huang, Xue-Bing. The efficacy of group cognitive-behavioural therapy plus duloxetine for generalised anxiety disorder versus duloxetine alone.. Acta Neuropsychiatrica 2019;1-9(Journal Article). [DOI:]

Yoshinaga 2016

Yoshinaga, Naoki; Matsuki, Satoshi; Niitsu, Tomihisa; Sato, Yasunori; Tanaka, Mari; Ibuki, Hanae; Takanashi, Rieko; Ohshiro, Keiko; Ohshima, Fumiyo; Asano, Kenichi; Kobori, Osamu; Yoshimura, Kensuke; Hirano, Yoshiyuki; Sawaguchi, Kyoko; Koshizaka, Masaya; Hanaoka, Hideki; Nakagawa, Akiko; Nakazato, Michiko; Iyo, Masaomi; Shimizu, Eiji. Cognitive Behavioral Therapy for Patients with

Social Anxiety Disorder Who Remain Symptomatic following Antidepressant Treatment: A Randomized, Assessor-Blinded, Controlled Trial.. Psychotherapy & Psychosomatics 2016;85(4):208-217. [DOI:]

Excluded studies

Barlow 2016

Barlow, David H.; Gorman, Jack M.; Shear, M. Katherine; Woods, Scott W.. Chapter: Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial.. The neurotic paradox: Progress in understanding and treating anxiety and related disorders., Vol. 1 2016;(Journal Article):125-140. [DOI:]

Blanco 2010

Blanco, Carlos; Heimberg, Richard G.; Schneier, Franklin R.; Fresco, David M.; Chen, Henian; Turk, Cynthia L.; Vermes, Donna; Erwin, Brigette A.; Schmidt, Andrew B.; Juster, Harlan R.; Campeas, Raphael; Liebowitz, Michael R.. A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder.. Archives of General Psychiatry 2010;67(3):286-295. [DOI:]

Bond 2002

Bond, A. J.; Wingrove, J.; Valerie Curran, H.; Lader, M. H.. Treatment of generalised anxiety disorder with a short course of psychological therapy, combined with buspirone or placebo. Journal of affective disorders 2002;72(3):267-271. [DOI: S0165032701004694 [pii]]

Clark 1991

Clark, D. B.; Agras, W. S.. The assessment and treatment of performance anxiety in musicians. The American Journal of Psychiatry 1991;148(5):598-605. [DOI: 10.1176/ajp.148.5.598 [doi]]

Crits Christoph 2011a

Crits-Christoph, Paul; Newman, Michelle G.; Rickels, Karl; Gallop, Robert; Gibbons, Mary Beth Connolly; Hamilton, Jessica L.; Ring-Kurtz, Sarah; Pastva, Amy M.. Combined medication and cognitive therapy for generalized anxiety disorder.. Journal of anxiety disorders 2011;25(8):1087-1094. [DOI:]

Gladsjo 2001

Gladsjo, J. A.; Rapaport, M. H.; McKinney, R.; Auerbach, M.; Hahn, T.; Rabin, A.; Oliver, T.; Haze, A.; Judd, L. L.. Absence of neuropsychologic deficits in patients receiving long-term treatment with alprazolam-XR for panic disorder. Journal of clinical psychopharmacology 2001;21(2):131-138. [DOI: 10.1097/00004714-200104000-00003 [doi]]

Habecker 2018

Habecker, Erin; Wasser, Tobias. Chapter: Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia.. 50 studies every psychiatrist should know 2018;(Journal Article):9-15. [DOI:]

King 2011a

King, Anna Lucia Spear; Valenca, Alexandre Martins; de Melo-Neto, Valfrido Leao; Freire, Rafael Christophe; Mezzasalma, Marco Andre; Silva,Adriana Cardoso de Oliveira e; Nardi, Antonio Egidio. Efficacy of a specific model for cognitive-behavioral therapy among panic disorder patients with agoraphobia: a randomized clinical trial.. Sao Paulo medical journal = Revista paulista de medicina 2011;129(5):325-334. [DOI:]

Koszycki 2011a

Koszycki, D.; Taljaard, M.; Segal, Z.; Bradwejn, J.. A randomized trial of sertraline, self-administered cognitive behavior therapy, and their combination for panic disorder.. Psychological medicine 2011;41(2):373-383. [DOI:]

Loerch 1999

Loerch, B.; Graf-Morgenstern, M.; Hautzinger, M.; Schlegel, S.; Hain, C.; Sandmann, J.; Benkert, O.. Randomised placebo-controlled trial of moclobemide, cognitive-behavioural therapy and their combination in panic disorder with agoraphobia. The British journal of psychiatry : the journal of mental science 1999;174(Journal Article):205-212. [DOI: S0007125000261898 [pii]]

Markell 2014

Markell, Hannah M.; Newman, Michelle G.; Gallop, Robert; Gibbons, Mary Beth Connolly; Rickels, Karl; Crits-Christoph, Paul. Combined medication and CBT for generalized anxiety disorder with African American participants: reliability and validity of assessments and preliminary outcomes.. Behavior Therapy 2014;45(4):495-506. [DOI:]

Marks 1993

Marks, I. M.; Swinson, R. P.; Basoglu, M.; Kuch, K.; Noshirvani, H.; O'Sullivan, G.; Lelliott, P. T.; Kirby, M.; McNamee, G.; Sengun, S.. Alprazolam and exposure alone and combined in panic disorder with agoraphobia. A controlled study in London and Toronto. The British journal of psychiatry : the journal of mental science 1993;162(Journal Article):776-787. [DOI: S0007125000180912 [pii]]

Meuldijk 2016

Meuldijk, D.; Carlier, I. V. E.; van Vliet, I. M.; van Veen, T.; Wolterbeek, R.; van Hemert, A. M.; Zitman, F. G.. The clinical effectiveness of concise cognitive behavioral therapy with or without pharmacotherapy for depressive and anxiety disorders; a pragmatic randomized controlled equivalence trial in clinical practice.. Contemporary Clinical Trials 2016;47(Journal Article):131-138. [DOI:]

Power 1990

Power, K. G.; Simpson, R. J.; Swanson, V.; Wallace, L. A.; Feistner, A. T. C.; Sharp, D.. A controlled comparison of cognitive- behaviour therapy, Diazepam, and placebo, alone and in combination, for the treatment of generalised anxiety disorder. Journal of Anxiety Disorders 1990;4(4):267-292. [DOI: https://doi.org/10.1016/0887-6185(90)90026-6]

Prasko 2006

Prasko, J.; Dockery, C.; Horacek, J.; Houbova, P.; Kosova, J.; Klaschka, J.; Paskova, B.; Praskova, H.; Seifertova, D.; Zalesky, R.; Hoschl, C.. Moclobemide and cognitive behavioral therapy in the treatment of social phobia. A six-month controlled study and 24 months follow up. Neuro endocrinology letters 2006;27(4):473-481. [DOI: NEL270406A20 [pii]]

Spinhoven 1996

Spinhoven, Philip; Onstein, Evert J.; Klinkhamer, René A.; Knoppert-van, der Klein. Panic Management, Trazodone and a Combination of Both in the Treatment of Panic Disorder. Clinical Psychology & Psychotherapy 1996;3(2):86-92. [DOI: 10.1002/(SICI)1099-0879(199606)3:2<86::AID-CPP91>3.0.CO;2-3]

vanApeldoorn 2014

van Apeldoorn, F. J.; Stant, A. D.; van Hout,W J P J.; Mersch, P. P. A.; den Boer, J. A.. Cost-effectiveness of CBT, SSRI, and CBT+SSRI in the treatment for panic disorder.. Acta Psychiatrica Scandinavica 2014;129(4):286-295. [DOI:]

Wetherell 2013

Wetherell, J. L.. The best of both worlds: Medication and cognitive behavioral therapy for generalized anxiety disorder in older adults.. International Psychogeriatrics.Conference: 16th International Congress of the International Psychogeriatric Association, IPA 2013.Seoul South Korea.Conference Publication: (var.pagings) 2013;25(SUPPL. 1):S25. [DOI:]

Wiborg 1996

Wiborg, I. M.; Dahl, A. A.. Does brief dynamic psychotherapy reduce the relapse rate of panic disorder? Archives of General Psychiatry 1996;53(8):689-694. [DOI: 10.1001/archpsyc.1996.01830080041008 [doi]]

Data and analyses

1 Kombinationsterapi vs CBT

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Grad af angst (anxiety severity)	6	585	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.77, 0.21]
1.1.1 SSRI	4	335	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.48, 0.54]
1.1.2 TCA	1	205	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.56, 0.03]
1.1.3 MAO	1	45	Std. Mean Difference (IV, Random, 95% CI)	-1.78 [-2.48, -1.08]
1.2 Funktion (disability)	3	231	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.09, -0.06]
1.2.1 SSRI	2	186	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.33, 0.23]
1.2.2 MAO	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-1.29, -0.08]
1.3 Grad af undgåelse (avoidance)	4	409	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.98, 0.03]
1.3.1 SSRI	3	364	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.75, 0.18]
1.3.2 MAO	1	45	Std. Mean Difference (IV, Random, 95% CI)	-1.14 [-1.78, -0.51]
1.4 Bedring (respons)	6	685	Risk Ratio (IV, Random, 95% CI)	1.08 [0.91, 1.27]
1.4.1 SSRI	4	414	Risk Ratio (IV, Random, 95% CI)	0.99 [0.80, 1.22]
1.4.2 TCA	1	205	Risk Ratio (IV, Random, 95% CI)	1.13 [0.90, 1.42]
1.4.3 MAO	1	66	Risk Ratio (IV, Random, 95% CI)	1.53 [1.01, 2.32]
1.5 Frafald, alle årsager, antal personer	8	904	Risk Ratio (IV, Random, 95% CI)	1.02 [0.83, 1.26]
1.5.1 SSRI	6	617	Risk Ratio (IV, Random, 95% CI)	1.04 [0.79, 1.36]
1.5.2 TCA	1	205	Risk Ratio (IV, Random, 95% CI)	0.99 [0.62, 1.60]
1.5.3 MAO	1	82	Risk Ratio (IV, Random, 95% CI)	1.01 [0.62, 1.62]
1.6 Frafald, grundet bivirkninger (dropouts due to adverse events)	5	728	Risk Ratio (M-H, Random, 95% CI)	4.78 [1.79, 12.78]
1.6.1 SSRI	4	523	Risk Ratio (M-H, Random, 95% CI)	4.35 [1.54, 12.30]
1.6.2 TCA	1	205	Risk Ratio (M-H, Random, 95% CI)	10.68 [0.52, 219.38]
1.7 Alvorlige bivirkninger (serious adverse events) antal personer	1	50	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.07, 0.07]

1.8 Subgruppeanalyse Grad af angst (anxiety severity)	6	585	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.77, 0.21]
1.8.1 Panikangst	3	312	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.77, 0.40]
1.8.2 Socialfobi	3	273	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-1.48, 0.61]
1.9 Subgruppeanalyse Funktion (disability)	3	231	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.09, -0.06]
1.9.1 Panikangst	2	186	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.33, 0.23]
1.9.2 Socialfobi	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-1.29, -0.08]

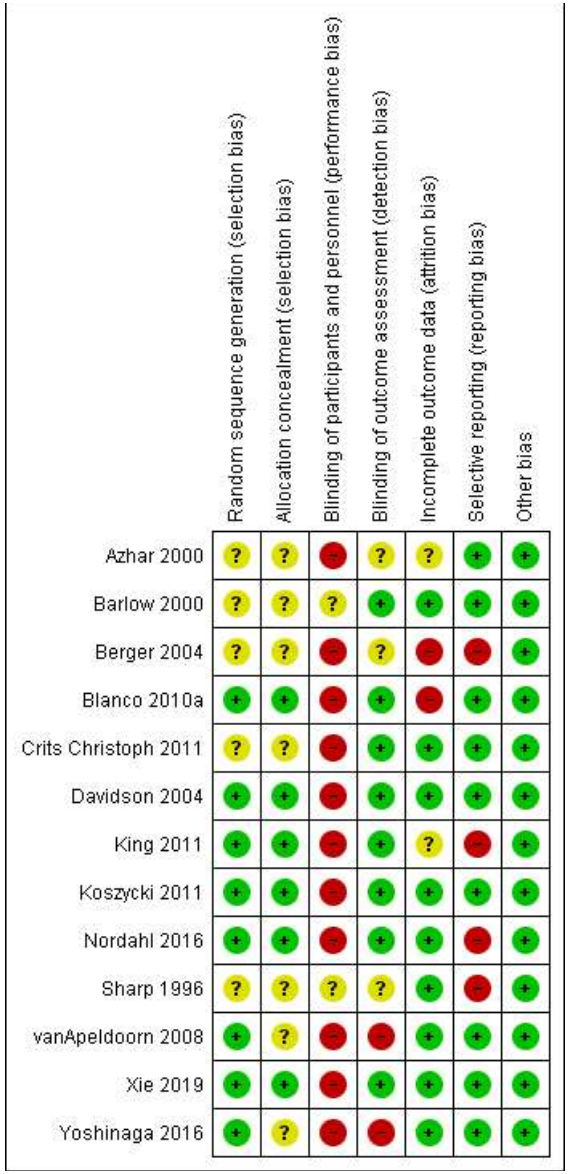
2 Kombinationsterapi vs Antidepressiv medicin

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Grad af angst (anxiety severity)	9	712	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.62, 0.20]
2.1.1 SSRI	5	317	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-1.03, 0.26]
2.1.2 TCA	1	148	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.55, 0.10]
2.1.3 MAO	1	45	Std. Mean Difference (IV, Random, 95% CI)	-1.05 [-1.68, -0.42]
2.1.4 SNRI	2	202	Std. Mean Difference (IV, Random, 95% CI)	0.49 [0.07, 0.91]
2.2 Funktion (disability)	5	438	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.46, -0.08]
2.2.1 SSRI	3	236	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.55, -0.00]
2.2.2 TCA	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
2.2.3 MAO	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
2.2.4 SNRI	2	202	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.62, 0.20]
2.3 Livskvalitet (quality of life)	3	242	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.61, 0.03]
2.3.1 SSRI	1	42	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-1.18, 0.06]
2.3.2 SNRI	2	200	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.63, 0.27]
2.4 Grad af undgåelse (avoidance)	4	355	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.57, 0.11]
2.4.1 SSRI	3	310	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.31, 0.14]
2.4.2 MAO	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.90 [-1.52, -0.28]

2.5 Bedring (responce)	11	914	Risk Ratio (IV, Random, 95% CI)	1.17 [1.03, 1.32]
2.5.1 SSRI	6	427	Risk Ratio (IV, Random, 95% CI)	1.18 [0.95, 1.46]
2.5.2 TCA	1	148	Risk Ratio (IV, Random, 95% CI)	1.34 [1.01, 1.79]
2.5.3 MAO	1	67	Risk Ratio (IV, Random, 95% CI)	1.32 [0.91, 1.92]
2.5.4 SNRI	2	222	Risk Ratio (IV, Random, 95% CI)	1.11 [0.81, 1.52]
2.5.5 SSRI or TCA	1	50	Risk Ratio (IV, Random, 95% CI)	1.07 [0.67, 1.72]
2.6 Alvorlige bivirkninger (serious adverse events)	1	52	Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.07, 0.07]
2.7 Frafald, alle årsager (dropouts, all cauces)	12	1123	Risk Ratio (IV, Random, 95% CI)	0.96 [0.80, 1.16]
2.7.1 SSRI	8	649	Risk Ratio (IV, Random, 95% CI)	1.09 [0.87, 1.38]
2.7.2 TCA	1	148	Risk Ratio (IV, Random, 95% CI)	0.72 [0.45, 1.16]
2.7.3 MAO	1	87	Risk Ratio (IV, Random, 95% CI)	0.89 [0.57, 1.37]
2.7.4 SNRI	2	239	Risk Ratio (IV, Random, 95% CI)	0.47 [0.14, 1.55]
2.8 Frafald, grundet bivirkninger (dropouts due to adverse event)	5	559	Risk Ratio (IV, Random, 95% CI)	0.67 [0.30, 1.48]
2.8.1 SSRI	4	411	Risk Ratio (IV, Random, 95% CI)	0.87 [0.40, 1.90]
2.8.2 TCA	1	148	Risk Ratio (IV, Random, 95% CI)	0.23 [0.05, 1.01]
2.9 Subgruppeanalyse Grad af angst (anxiety severity)	9	712	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.62, 0.20]
2.9.1 Panikangst	3	255	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.35, 0.14]
2.9.2 Socialfobi	4	255	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.69, 0.08]
2.9.3 Generaliseret angst	2	202	Std. Mean Difference (IV, Random, 95% CI)	0.49 [0.07, 0.91]
2.10 Subgruppeanalyse Funktion (disability)	5	438	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.46, -0.08]
2.10.1 Panikangst	3	236	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.55, -0.00]
2.10.2 Socialfobi	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
2.10.4 Generaliseret angst	2	202	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.62, 0.20]

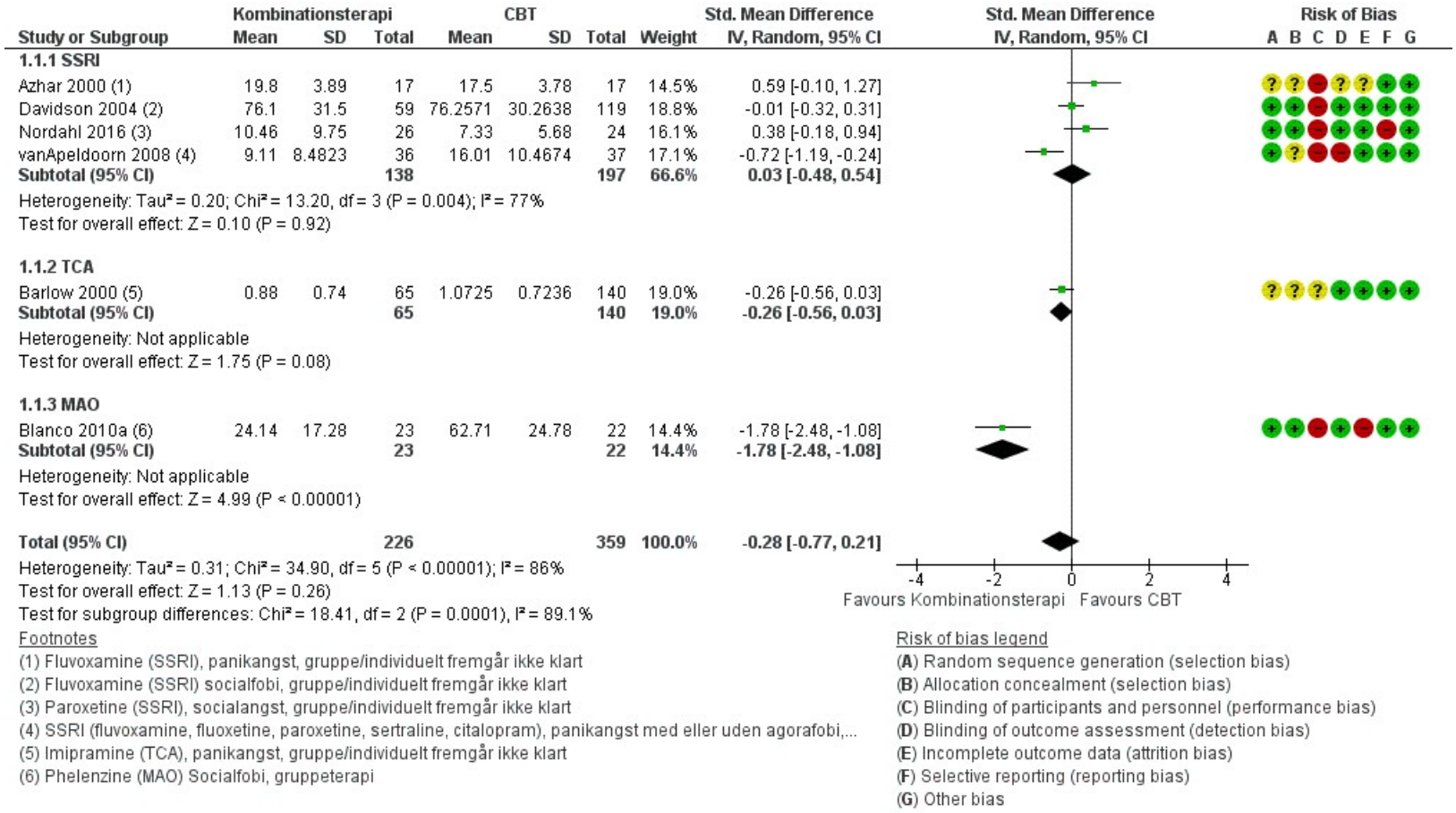
Figures

Figure 1



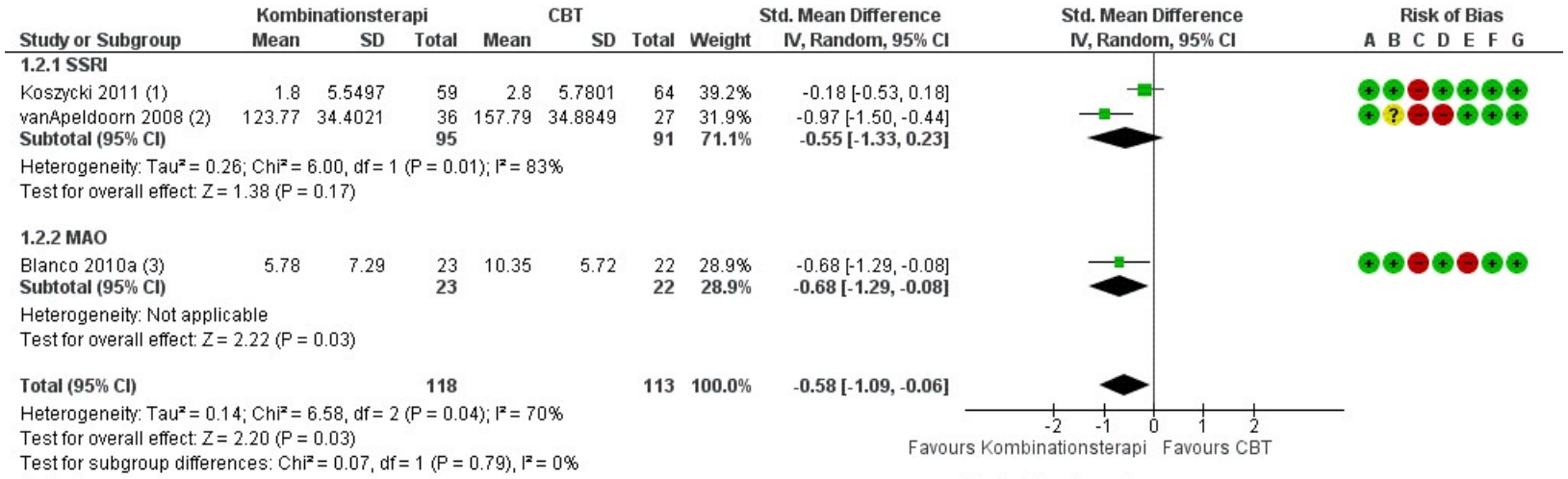
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 1.1)



Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.1 Grad af angst (anxiety severity).

Figure 3 (Analysis 1.2)



Footnotes

(1) Sertraline, panikangst, gruppe/individuelt fremgår ikke klart

(2) SSRI (fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram), panikangst med eller uden agorafobi,...

(3) Phelenzine (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)

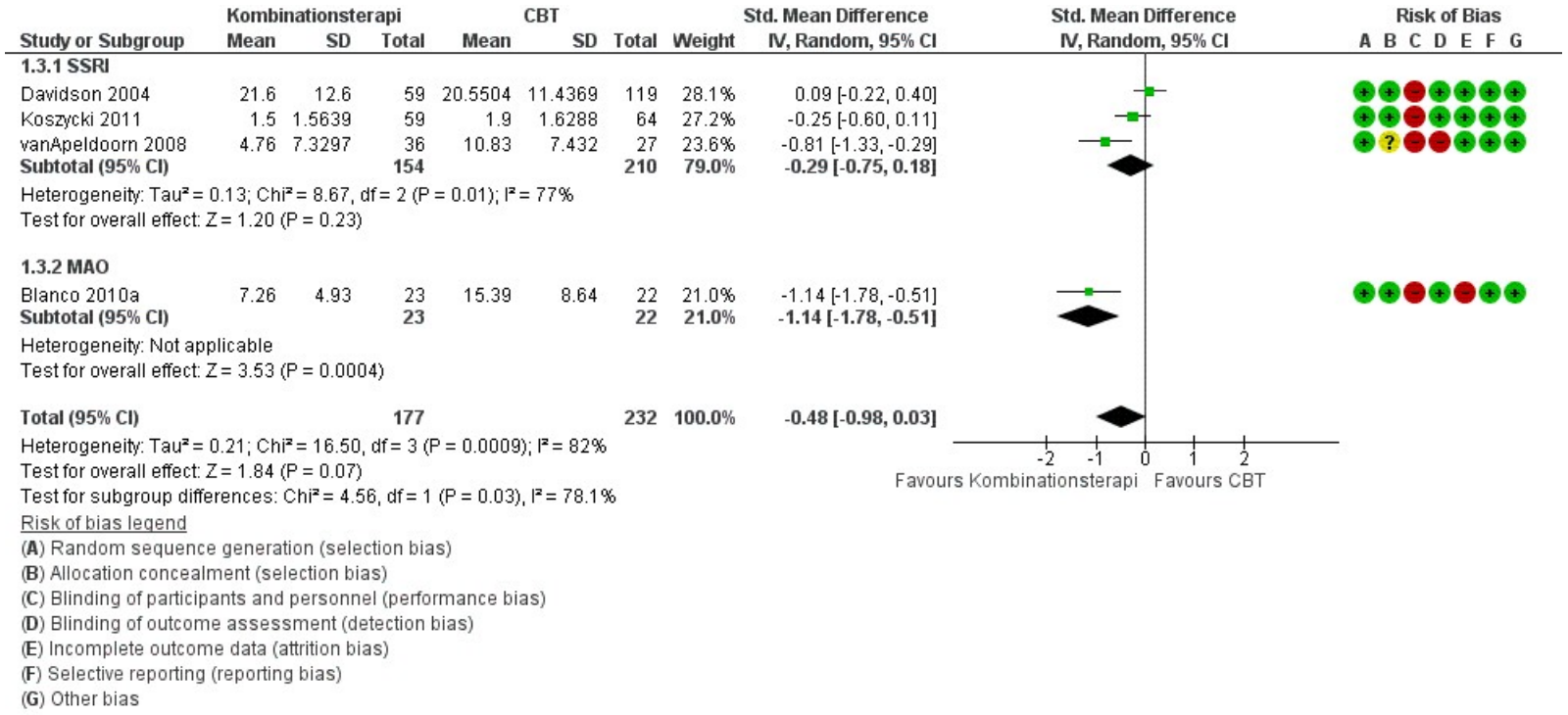
(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

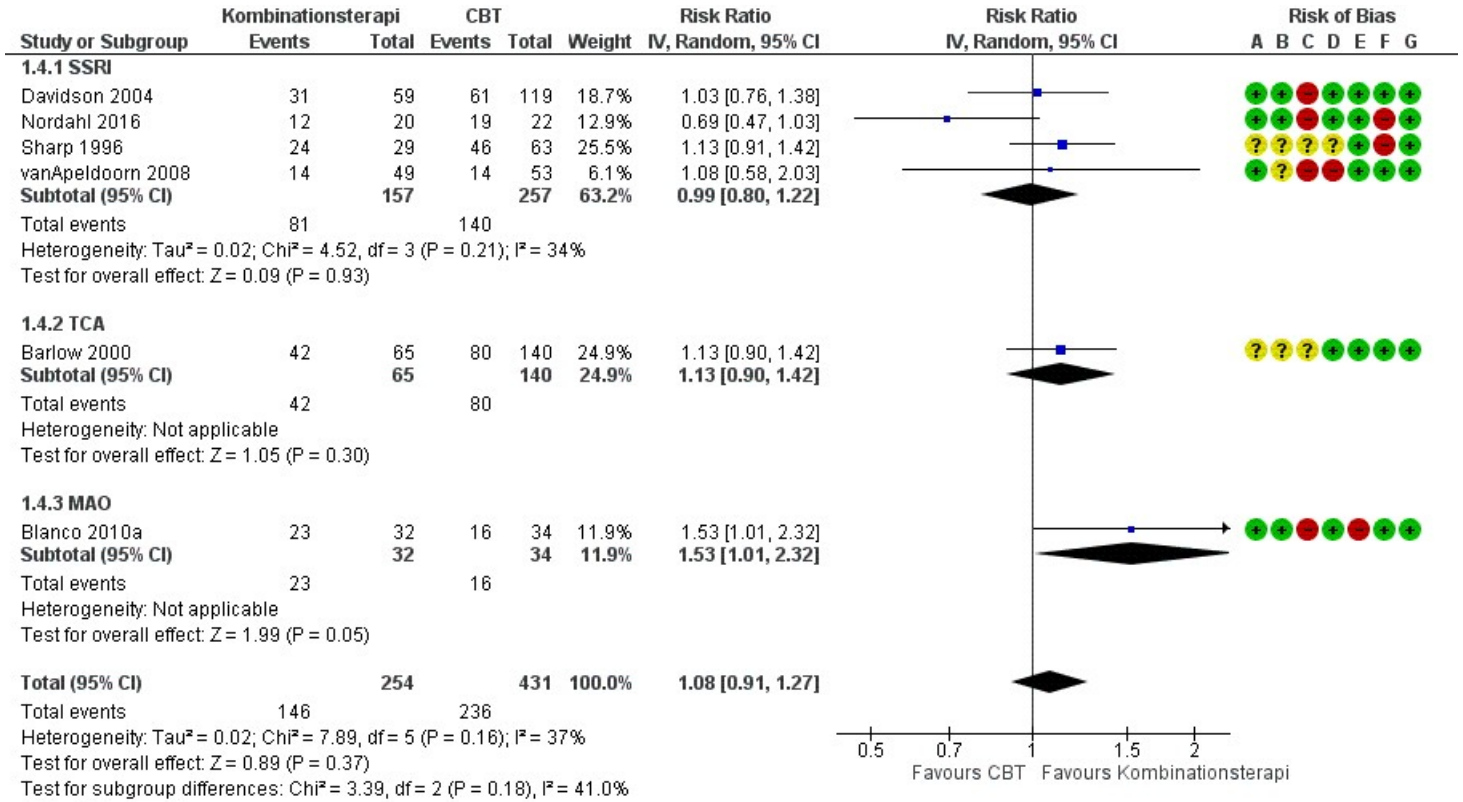
Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.2 Funktion (disability).

Figure 4 (Analysis 1.3)



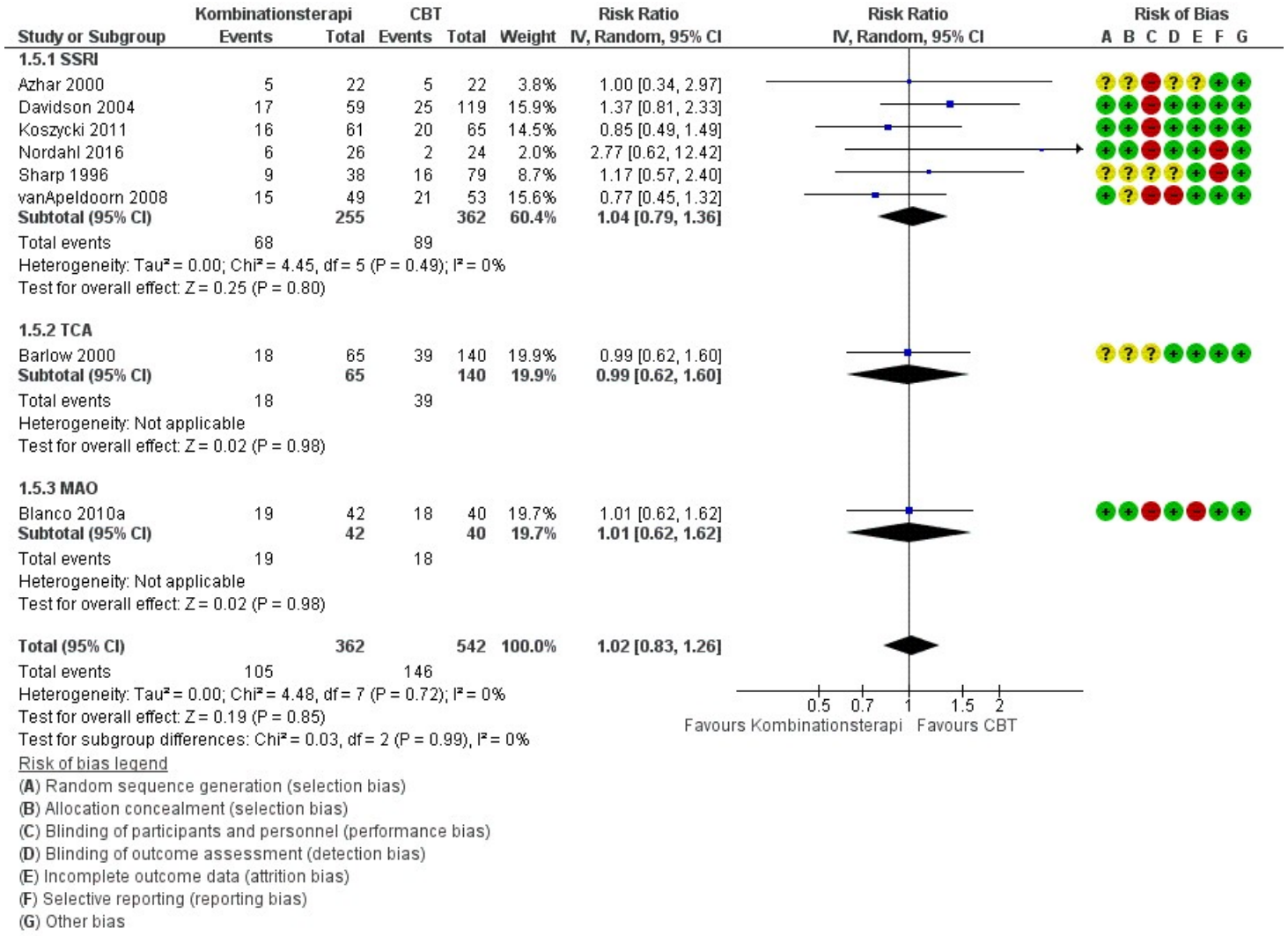
Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.3 Grad af undgåelse (avoidance).

Figure 5 (Analysis 1.4)



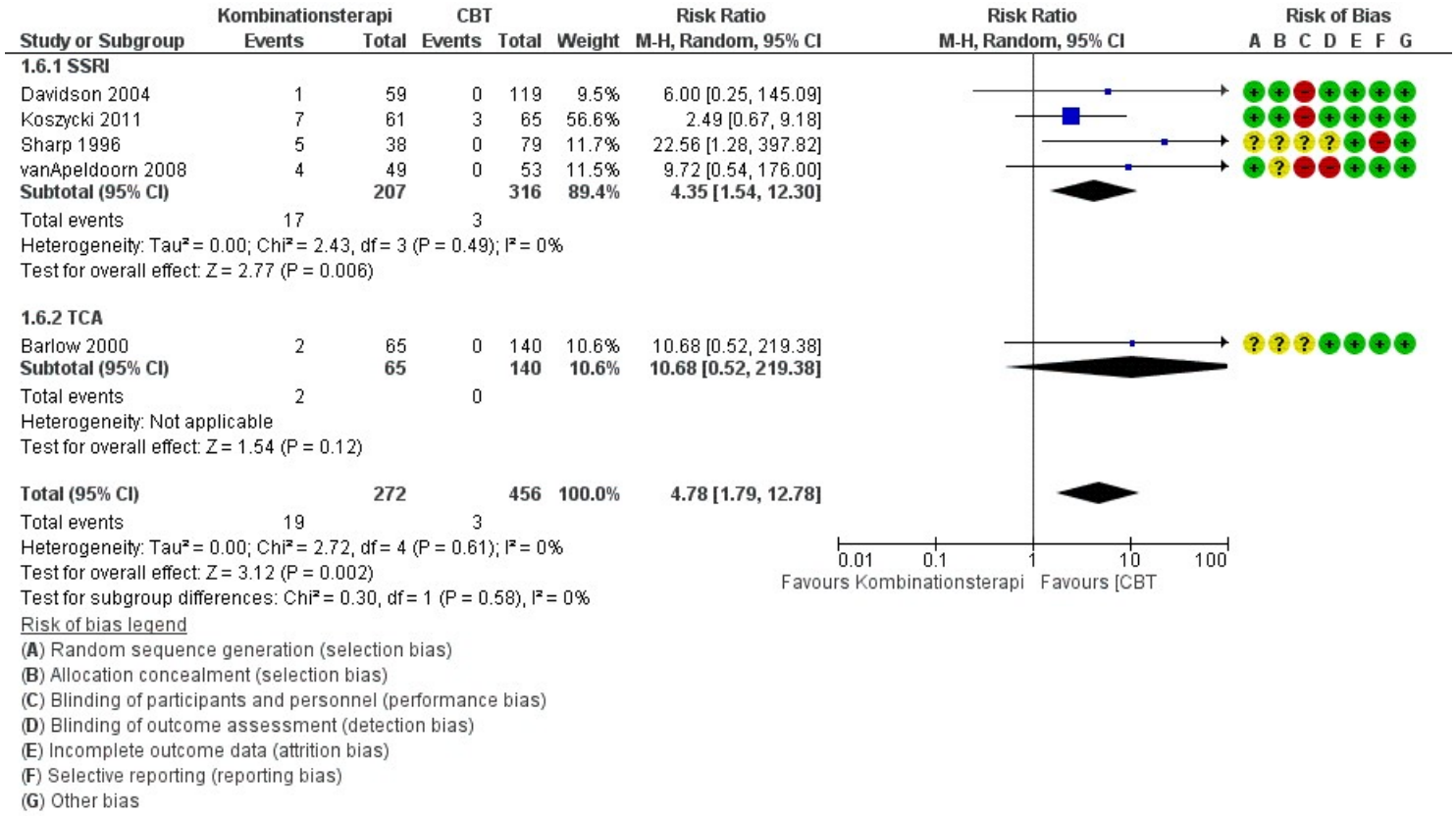
Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.4 Bedring (respons).

Figure 7 (Analysis 1.5)



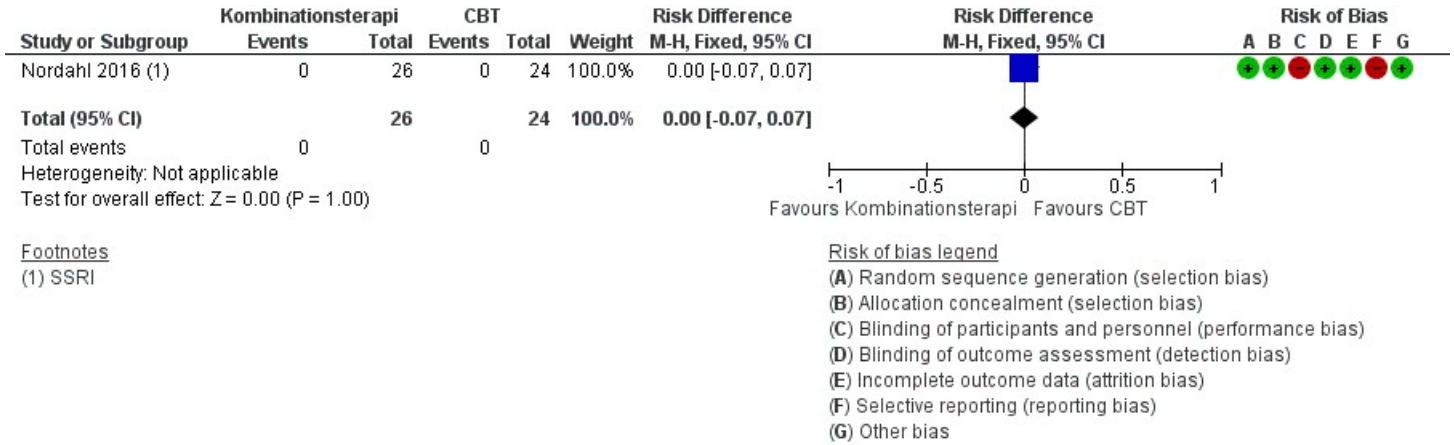
Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.5 Frafald, alle årsager, antal personer.

Figure 8 (Analysis 1.6)



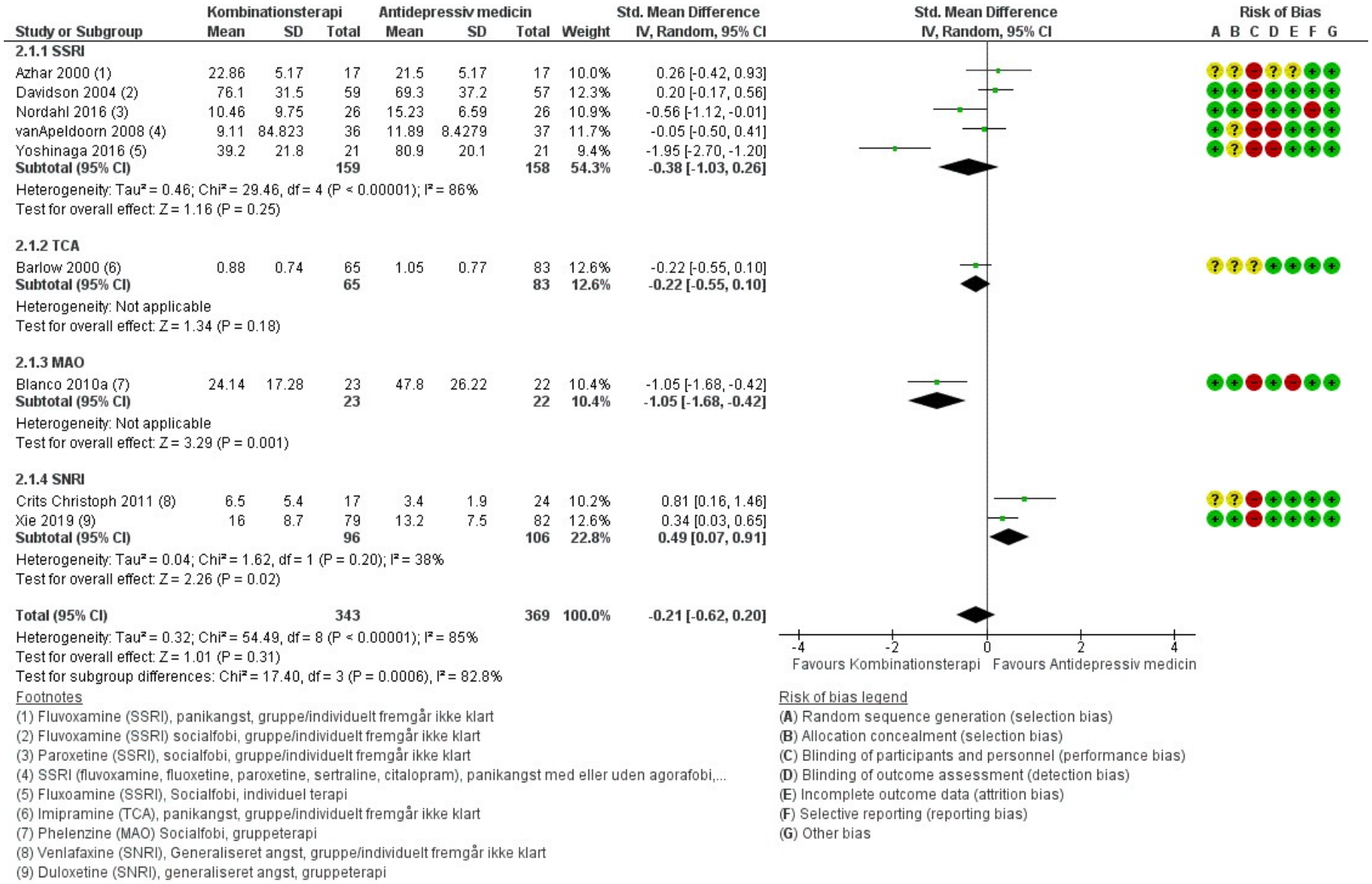
Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.6 Frafald, grundet bivirkninger (dropouts due to adverse events).

Figure 9 (Analysis 1.7)



Forest plot of comparison: 1 Kombinationsterapi vs CBT, outcome: 1.7 Alvorlige bivirkninger (serious adverse events) antal personer.

Figure 10 (Analysis 2.1)



Footnotes

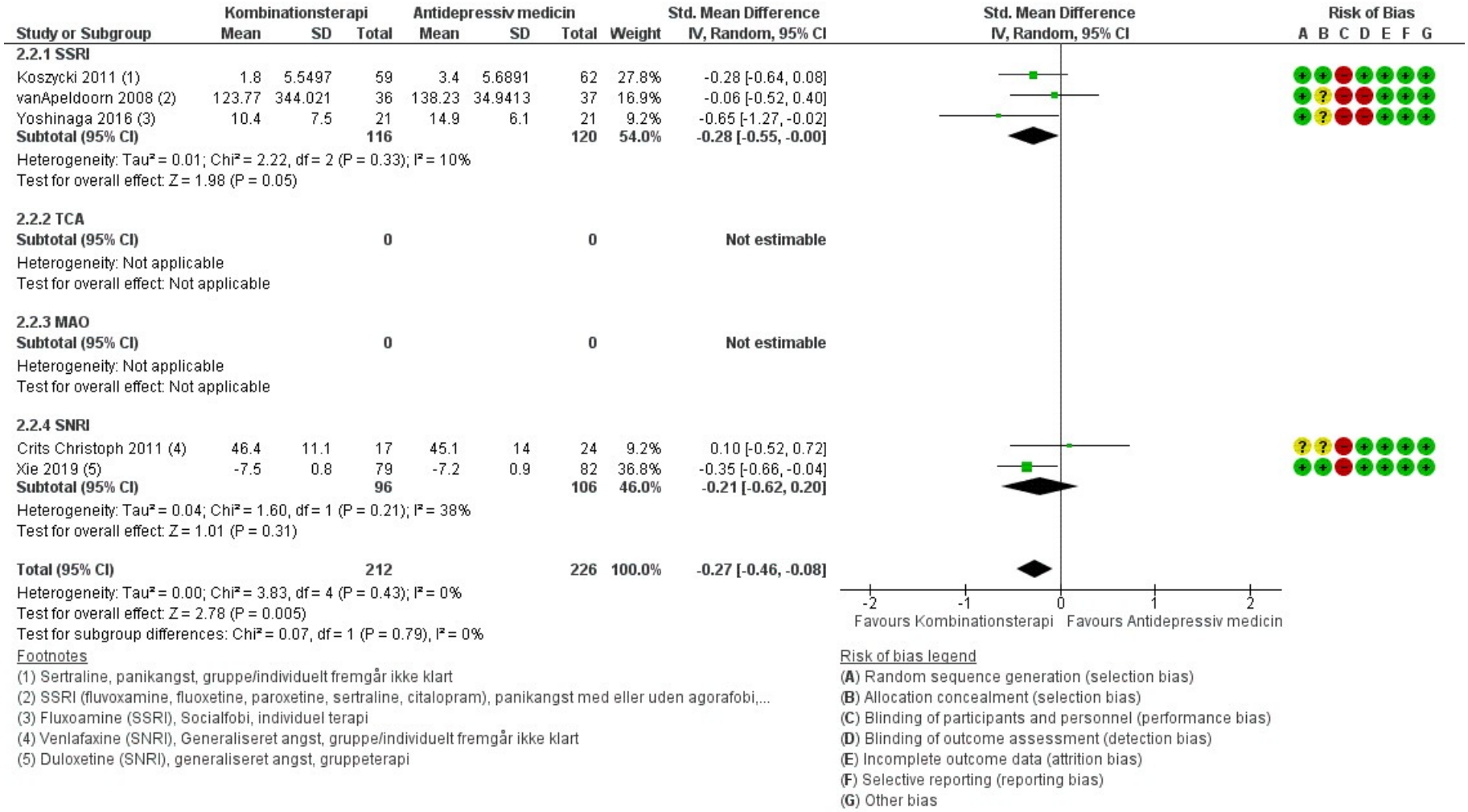
(1) Fluvoxamine (SSRI), panikangst, gruppe/individuelt fremgår ikke klart
(2) Fluvoxamine (SSRI) socialfobi, gruppe/individuelt fremgår ikke klart
(3) Paroxetine (SSRI), socialfobi, gruppe/individuelt fremgår ikke klart
(4) SSRI (fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram), panikangst med eller uden agorafobi,...
(5) Fluxoamine (SSRI), Socialfobi, individuel terapi
(6) Imipramine (TCA), panikangst, gruppe/individuelt fremgår ikke klart
(7) Phelenzine (MAO) Socialfobi, gruppeterapi
(8) Venlafaxine (SNRI), Generaliseret angst, gruppe/individuelt fremgår ikke klart
(9) Duloxetine (SNRI), generaliseret angst, 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

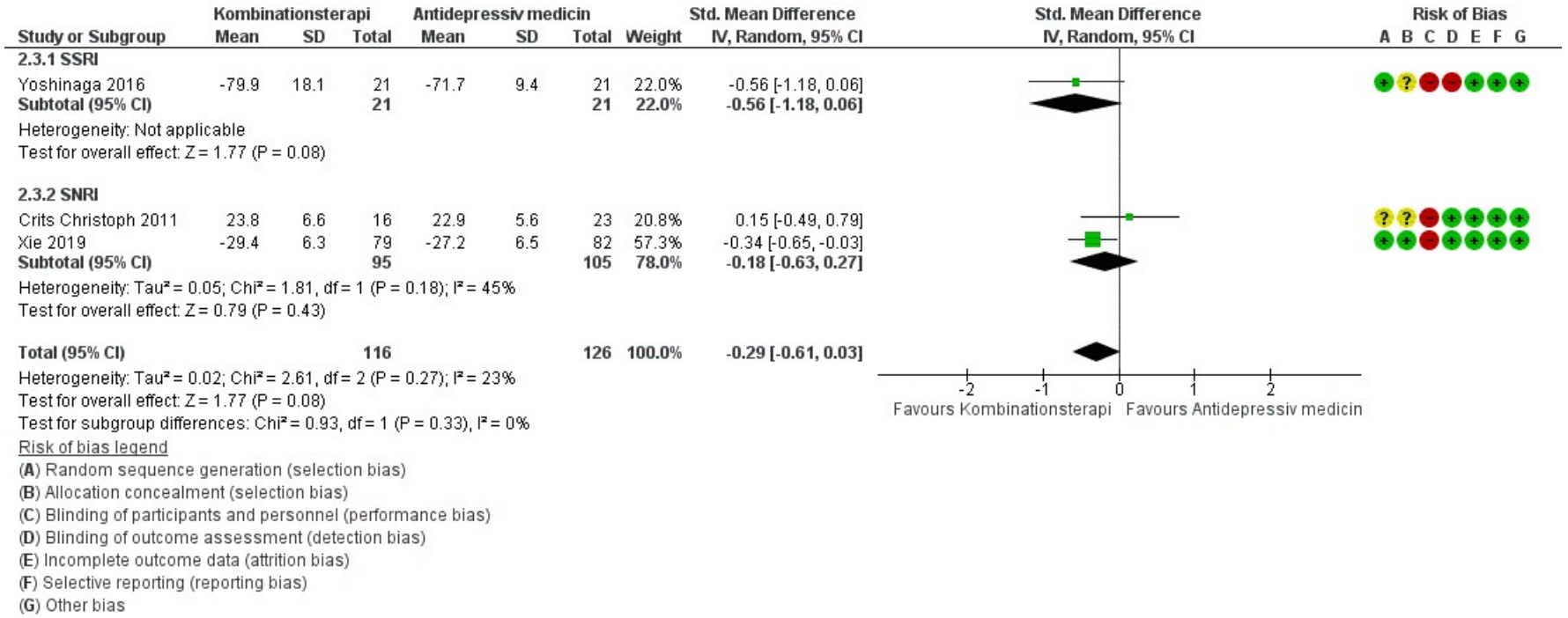
Forest plot of comparison: 2 Antidepressiv medicin vs Kombinationsterapi, outcome: 2.1 Grad af angst (anxiety severity).

Figure 11 (Analysis 2.2)



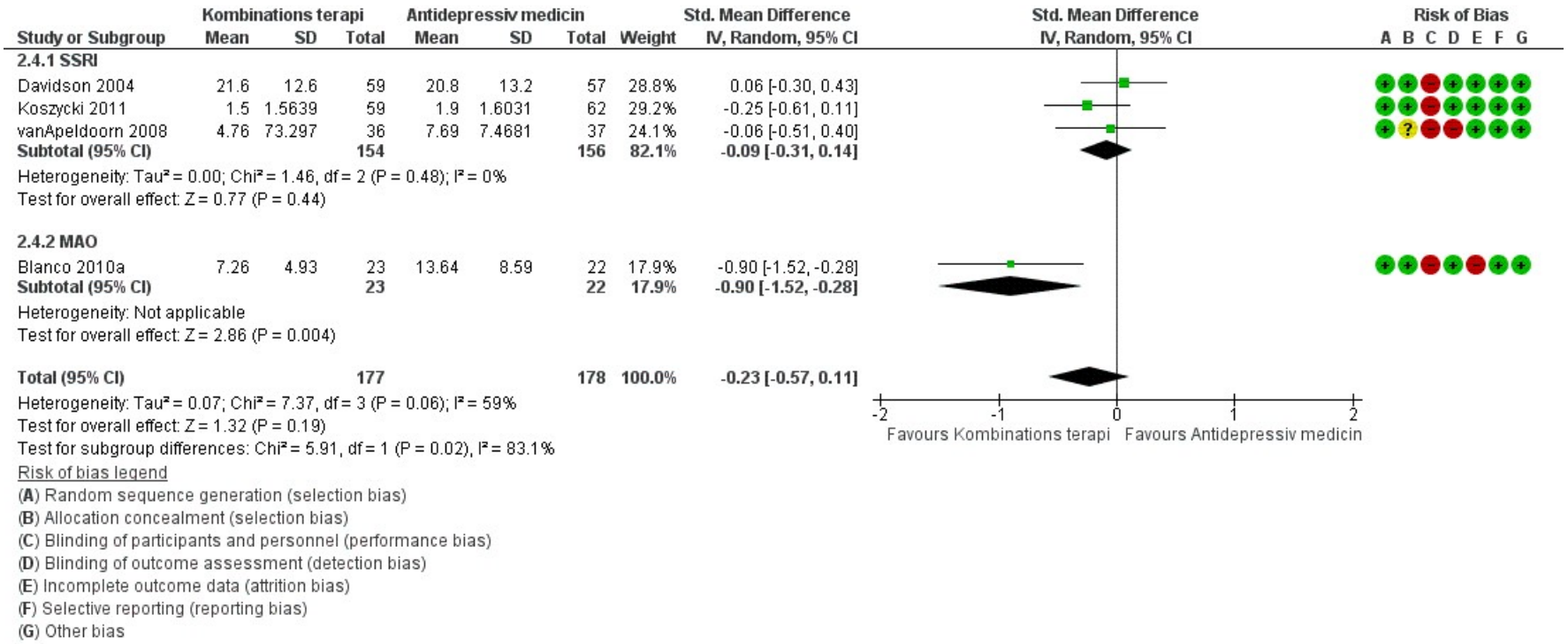
Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.2 Funktion (disability).

Figure 12 (Analysis 2.3)



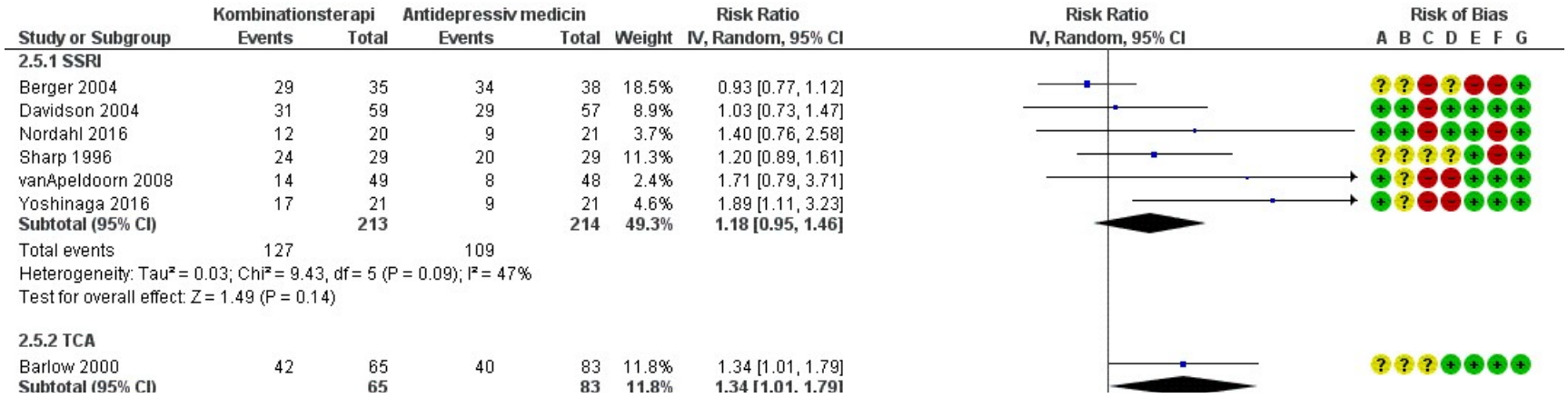
Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.3 Livskvalitet (quality of life).

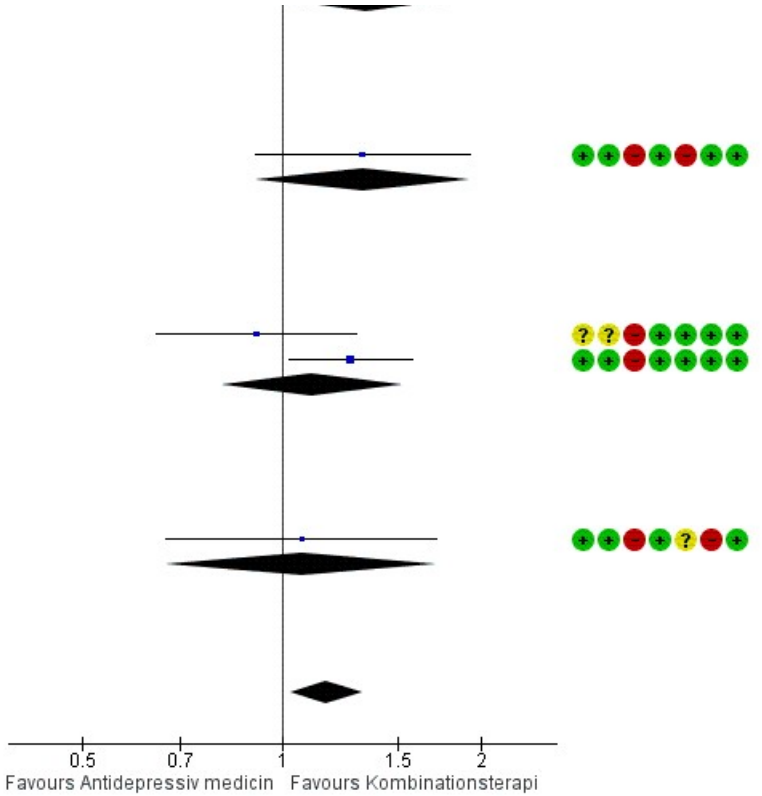
Figure 13 (Analysis 2.4)



Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.4 Grad af undgåelse (avoidance).

Figure 14 (Analysis 2.5)



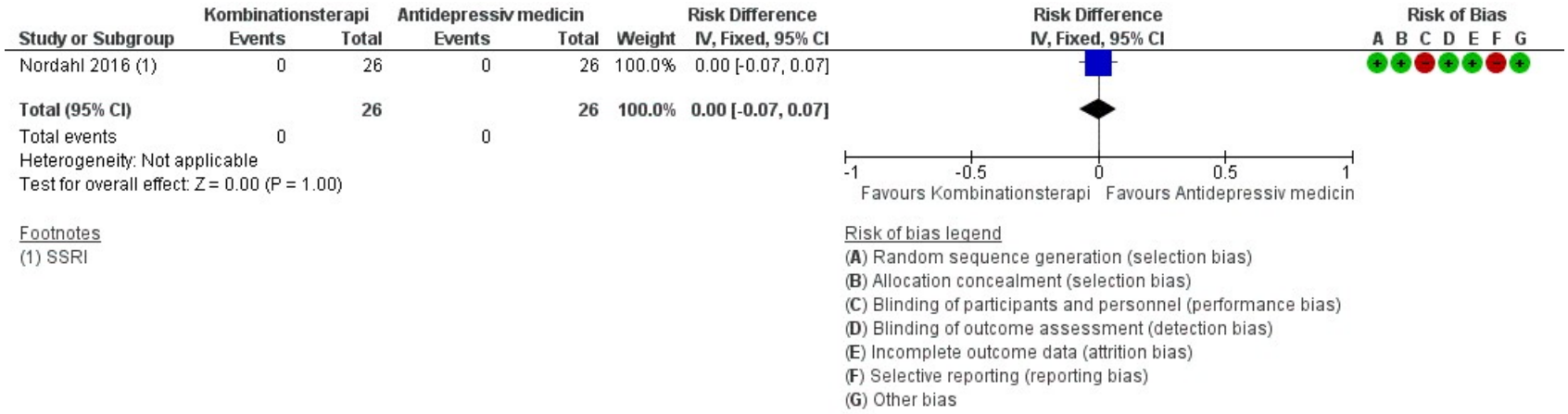


Total events	42		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
2.5.3 MAO						
Blanco 2010a	23	32	19	35	8.2%	1.32 [0.91, 1.92]
Subtotal (95% CI)		**32**		**35**	**8.2%**	**1.32 [0.91, 1.92]**
Total events	23		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
2.5.4 SNRI						
Crits Christoph 2011	17	26	25	35	9.0%	0.92 [0.65, 1.30]
Xie 2019	60	79	49	82	16.1%	1.27 [1.02, 1.58]
Subtotal (95% CI)		**105**		**117**	**25.1%**	**1.11 [0.81, 1.52]**
Total events	77		74			
Heterogeneity: Tau² = 0.03; Chi² = 2.45, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 0.65 (P = 0.51)						
2.5.5 SSRI or TCA						
King 2011	15	25	14	25	5.7%	1.07 [0.67, 1.72]
Subtotal (95% CI)		**25**		**25**	**5.7%**	**1.07 [0.67, 1.72]**
Total events	15		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**440**		**474**	**100.0%**	**1.17 [1.03, 1.32]**
Total events	284		256			
Heterogeneity: Tau² = 0.01; Chi² = 14.53, df = 10 (P = 0.15); I² = 31%						
Test for overall effect: Z = 2.46 (P = 0.01)						
Test for subgroup differences: Chi² = 1.31, df = 4 (P = 0.86), I² = 0%						

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

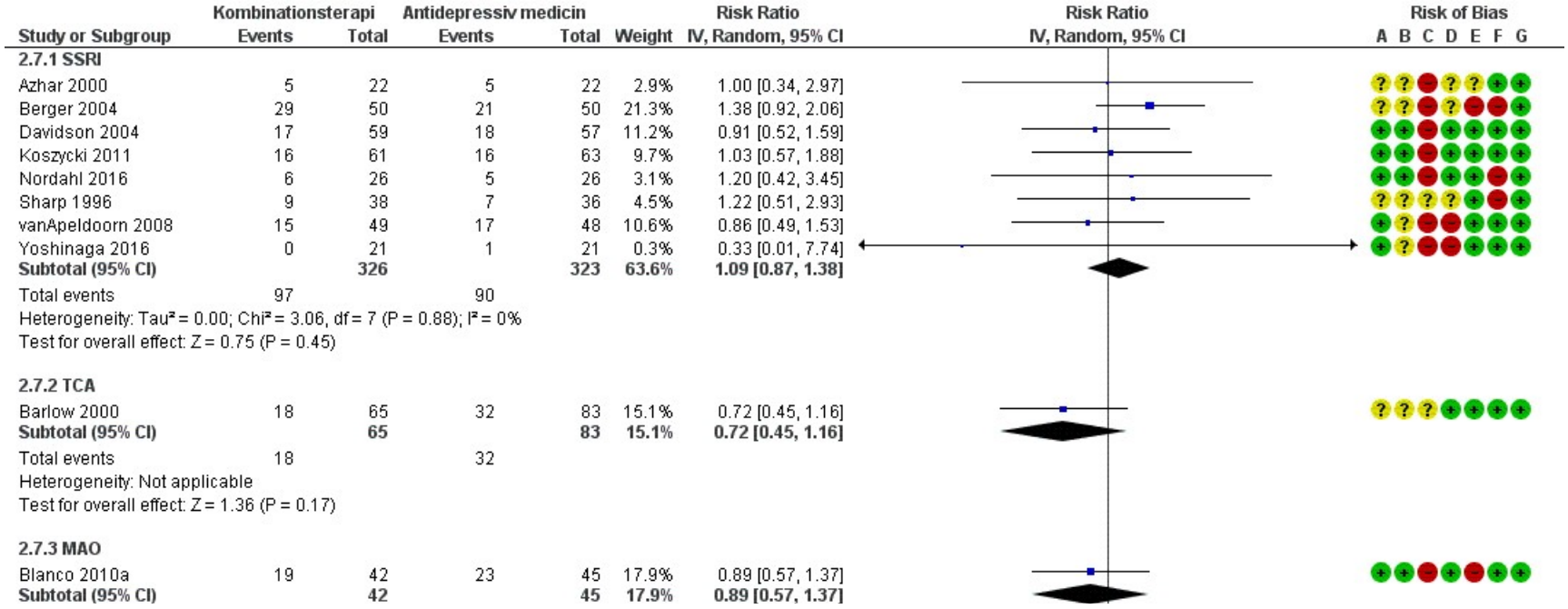
Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.5 Bedring (responce).

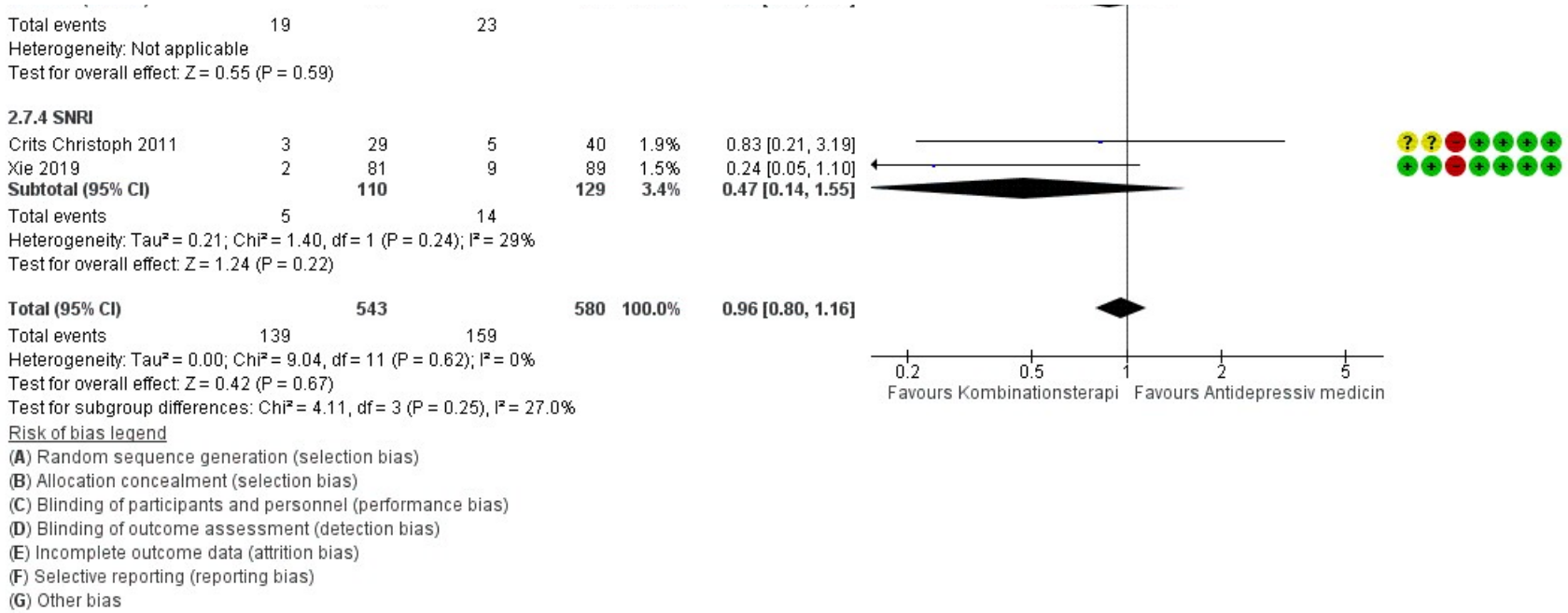
Figure 16 (Analysis 2.6)



Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.6 Alvorlige bivirkninger (serious adverse events).

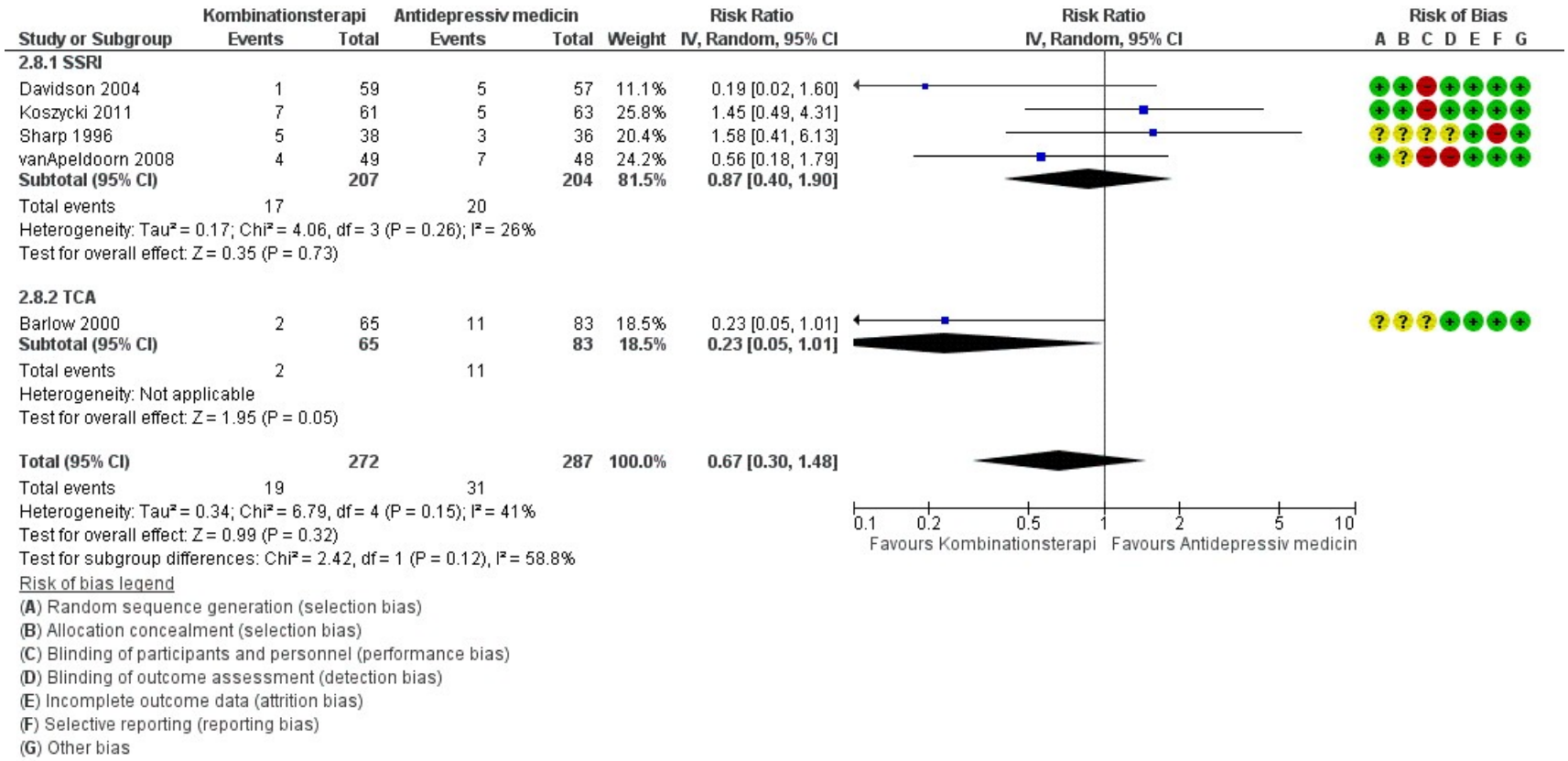
Figure 17 (Analysis 2.7)





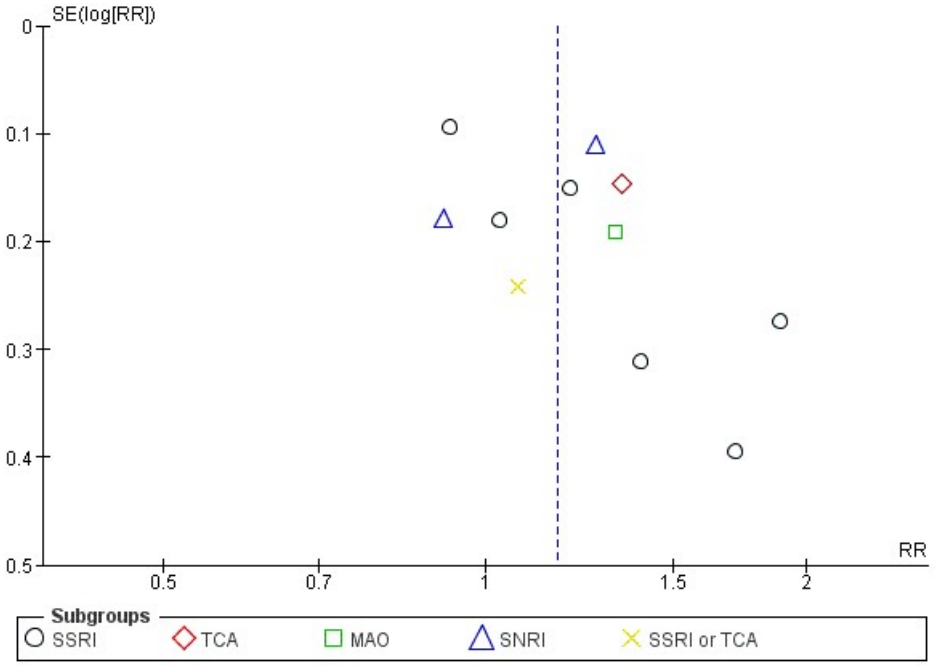
Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.7 Frafald, alle årsager (dropouts, all cauces).

Figure 18 (Analysis 2.8)



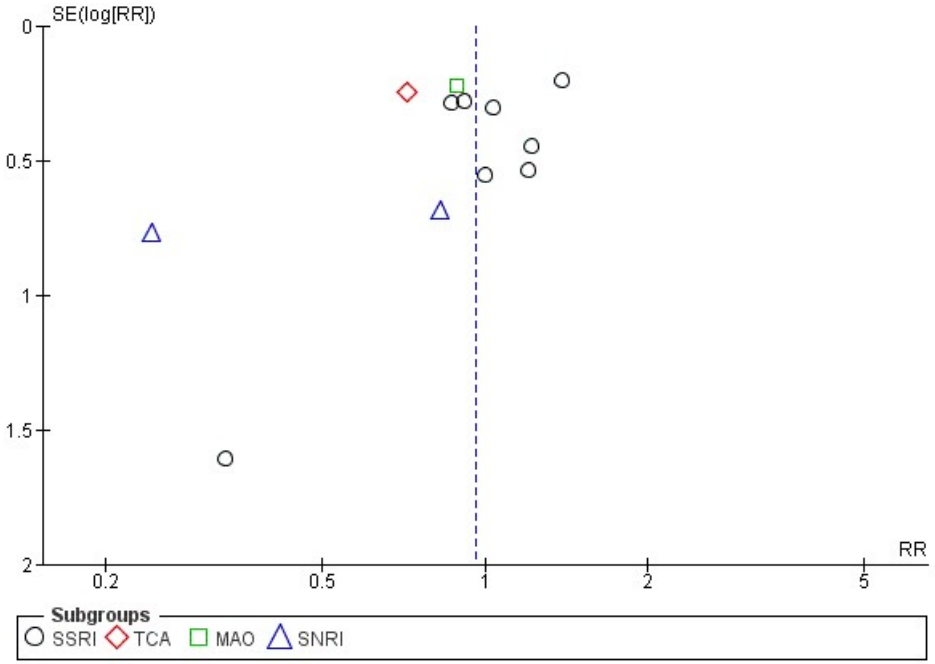
Forest plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.8 Frafald, grundet bivirkninger (dropouts due to adverse event).

Figure 19 (Analysis 2.5)



Funnel plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.5 Bedring (responce).

Figure 20 (Analysis 2.7)



Funnel plot of comparison: 2 Kombinationsterapi vs Antidepressiv medicin, outcome: 2.7 Frafald, alle årsager (dropouts, all cauces).