NKR24 - PICO3 - Schizophrenia: Antidepressants vs. placebo as add-on treatment

Characteristics of studies

Characteristics of included studies

Arango 2000

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** fluoxetine ● *Age*: 35.8 (10) ● *Duration of illness*: 7.2 (1.7) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: 23.5 (13.9) ● *Gender, men*: 75% placebo ● *Age*: 37.4 (6) ● *Duration of illness*: 7.1 (1.9) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: 21.1 (9.7) ● *Gender, men*: 69% **Included criteria:** schizophrenia, minimum severity of positive OR negative symptoms, treated with FGA **Excluded criteria:**
Interventions	**Intervention Characteristics** fluoxetine ● *duration*: 8 weeks ● *dose*: 36.2 (20.9) placebo ● *duration*: 8 weeks ● *dose*:
Outcomes	*Continuous*: ● PANSS negative symptoms ● SANS negative symptoms ● PANSS Positive symptoms ● AEs ● Quality of life ● BPRS positive symptoms ● AEs MIMS Parkinsonism *Dichotomous*: ● All-cause discontinuation ● Suicide (completed or serious attempt)
Identification	**Sponsorship source:** Grant from Eli Lilly and PHS grant **Country:** US **Setting: outpatients** **Comments:** **Authors name:** Celso Arango et al. **Institution:** Maryland Psychiatric Research Center, **Email:** **Address:** P.O. BOX 21247, University of Maryland, Baltimore, Maryland 21228
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** *Elisabeth Ginnerup-Nielsen* Hamilton intervention: 14.8 (10.2)placebo: 10.9 (8.7) **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Insufficiently described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described at all
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Nothing about personnel. Patients probably blinded, but not clear what was done
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Nothing described about assessors.
Incomplete outcome data (attrition bias)	Low risk	Comment: ITT analysis, 3 + 2 withdrew, LOCF
Selective reporting (reporting bias)	Low risk	Comment: No protocol available, but relevant outcomes reported
Other bias	Unclear risk	Comment: Grant from Eli Lilly, independency not stated

Buchanan 1996

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** fluoxetine ● *Age*: 36.8 (6.4) ● *Duration of illness*: 16.2 (4.3) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: 29.5 (15.3) ● *Gender, men*: 83% ● *Hamilton depression rating scale*: 13.3 (10.0) placebo ● *Age*: 32.8 (6.0) ● *Duration of illness*: 15.6 (6.4) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: 23.9 (10.9) ● *Gender, men*: 53% ● *Hamilton depression rating scale*: 12.6 (9.0) **Included criteria:** outpatients, schizophrenia diagnosis, at least 6 months of clozapine treatment, minimum level of residual positive or negative symptoms **Excluded criteria:** Patients with concurrent alcohol orstance abuse. organic brain disorder. mental retardation. or a mcdical condition that contraindicated Jozapine or tluoxetinc treatment were excluded.
Interventions	**Intervention Characteristics** fluoxetine ● *duration*: 8 weeks ● *dose*: 48.9 (14.1) placebo ● *duration*: ● *dose*:
Outcomes	*Continuous*: ● SANS negative symptoms ● AEs ● AEs MIMS Parkinsonism ● PANSS negative symptoms ● PANSS Positive symptoms ● Quality of life ● BPRS positive symptoms *Dichotomous*: ● Suicide (completed or serious attempt) ● All-cause discontinuation
Identification	**Sponsorship source:** Not reported **Country:** US **Setting: outpatients** **Comments:** **Authors name:** Robert Buchanan et al. **Institution:** Maryland Psychiatric Research Center **Email:** **Address:** Maryland Psychiatric ResearchCenter, P.O. Box 21247, Baltimore. MD 21228.
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:**

	Intervention characteristics: **Pretreatment:** **Continuous outcomes:** *Elisabeth Ginnerup-Nielsen* Hamiltonintervention: 13.2 (9.4)Placebo: 11.5 (7.3) **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not sufficiently reported
Allocation concealment (selection bias)	Unclear risk	Comment: Not desrcibed
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "fluoxetine or placebo tablets in an 8-week, double-blind," Comment: Probably done
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Nothing desribed
Incomplete outcome data (attrition bias)	Low risk	Comment: only one dropout
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol
Other bias	Low risk	Comment: No other apparent biases

Goff 1995

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** fluoxetine ● *Age*: 42.2 (9.1) ● *Duration of illness*: ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: ● *Gender, men*: 90% ● *Hamilton depression scale*: 13.9 (4.7) ● *BPRS total score*: 33.5 (6.0) ● *BPRS negative symptoms*: 7.1 (2.5) placebo ● *Age*: 42.8 (9.4) ● *Duration of illness*: ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: ● *Gender, men*: 95% ● *Hamilton depression scale*: 12.8 (3.6) ● *BPRS total score*: 34.6 (4.8) ● *BPRS negative symptoms*: 8.5 (2.0) **Included criteria:** schizophrenia or schizoaffective disorder (depressed type), depot FGA, BRRS at least 30 **Excluded criteria:** major depression, treated with lithium or an antidepressant within the previous month, history of significant medical or neurological illness, current subtance abuse
Interventions	**Intervention Characteristics** fluoxetine ● *duration*: 6 weeks ● *dose*: 20 mg placebo ● *duration*: 6 weeks ● *dose*:
Outcomes	*Continuous*: ● SANS negative symptoms ● AEs ● AEs MIMS Parkinsonism ● PANSS negative symptoms ● PANSS Positive symptoms ● Quality of life ● BPRS positive symptoms ● BPRS negative symptoms ● SAS Akathisia ● SAS minus akathisia *Dichotomous*: ● Suicide (completed or serious attempt) ● All-cause discontinuation

Identification	**Sponsorship source:** supported in part by NIMHgrant MH-19052, Medical Research Council of Canada grant PG-34, and a grant from the Eli Lilly Company. **Country:** US **Setting: outpatients** **Comments:** **Authors name:** Donald Goff et al. **Institution:** Freedom Trial Clinic **Email:** **Address:** 25 Staniford St., Boston MA 02114, USA
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not sufficiently described
Allocation concealment (selection bias)	Unclear risk	Comment: not sufficiently described
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: quo: patients were givenplacebo capsules under single-blind conditions (personnel not blinded?)
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Not described but personnel and assessors probablythe same. Even thugh the study is defined double blind...
Incomplete outcome data (attrition bias)	Low risk	Quote: "Forty-three patients were entered into the study; two patients dropped out prior to completing the placebo lead-in and the remaining 41 completed the 6-week trial"
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but all relevant outcome measures reported
Other bias	Unclear risk	Comment: grant from Eli Lilly, unclear how this could have affected any stage of the trial

Hinkelmann 2013

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** citalopram ● *Age*: mean 38.5 (SD 7.5) ● *Gender*: male 62.5 % ● *Duration of illness*: mean 9.2 (SD 12.8) ● *Psychopathology total score*: ● *Negative symptoms*: 24.7 (10.2) ● *Depressive symptoms: Hamilton*: 17.8 (7.8) placebo ● *Age*: 38.3 (8.4) ● *Gender*: male 56.25% ● *Duration of illness*: 9.7 (9.3) ● *Psychopathology total score*: ● *Negative symptoms*: 26.7 (7.9) ● *Depressive symptoms: Hamilton*: 12.2 (5.6) **Included criteria:** schizophrenia accordingto Diagnostic and Statistical Manual of Mental Disorders, FourthEdition and predominantly negative symptoms (scoring Q4 pointsin at least 1 item of the Positive and Negative Syndrome Scale[PANSS] negative subscale). Patients had to be on stable antipsychotic medicationfor at least 2 weeks before inclusion **Excluded criteria:** Exelusion criteria includedconcomitant alcohol or substance abuse, other psychiatricor somatic disorders;, and abnormal laboratory findings.
Interventions	**Intervention Characteristics** citalopram ● *dose*: 20-40 mg ● *duration*: 4 weeks placebo ● *dose*: ● *duration*: 4 weeks

Outcomes	*Continuous*: ● PANSS negative ● PANSS positive ● QoL ● AEs *Dichotomous*: ● All-cause discontinuation ● Suicide (completed or serious attempt)
Identification	**Sponsorship source:** Stanley Medical Research Institute(grant ID 01T-076). **Country:** Germany **Setting:** **Comments:** **Authors name:** Kim Hinkelman n, MD.,. t Alexander Yassouridis, PhD,:t Michael Kellner, MD. ● Holger Jahn, MD.* Klaus Wiedemann, MD.,. and Thomas J Raedle1; MD§ **Institution:** Department of Psychiatry and Psychotherapy, University of Hamburg **Email:** kim.hinkelmann@charite.de **Address:**
Notes	**Identification:** **Participants:** **Study design:** *Lone Baandrup* there was also a reboxetine arm, not reported because not relevant for our review **Baseline characteristics:** *Lone Baandrup* PANSS negative symptoms **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Randomization via statistical program = random
Allocation concealment (selection bias)	Low risk	Comment: sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: blinding not described except that each medication was delivered as capsules
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Quote: psychopat. was assessed .... by to experienced raters.." Nothing described about blinding in this proces
Incomplete outcome data (attrition bias)	Low risk	Comment: The 3 treatment groups did not differ in age, duration of illness, sex, or dropout rates.For statistical evaluation of outcome criteria, we used theITT sample of 51 patients who had completed at least the day 7assessment with the last-observation-carried-forward approach.
Selective reporting (reporting bias)	Low risk	Comment: No protocol available, not at clinicaltrials.gov but all relevant outcomes reported with negative symptoms as primary
Other bias	Low risk	

Iancu 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** citalopram ● *Age*: ● *Gender*: ● *Duration of illness*: ● *Depressive symptoms: Hamilton*: ● *PANSS total*: ● *PANSS negative symptoms*: placebo ● *Age*: 38.8(6.88) ● *Gender*: men 70% ● *Duration of illness*: 13.8(6.6) ● *Depressive symptoms: Hamilton*: 7.4 (5) ● *PANSS total*: 86.1 (19.6) ● *PANSS negative symptoms*: 25.9 (6.7)

	escitalopram ● *Age*: 35.5(8.7) ● *Gender*: male 75% ● *Duration of illness*: 14.2(9.5) ● *Depressive symptoms: Hamilton*: 5.2 (4.2) ● *PANSS total*: 79.9 (17.8) ● *PANSS negative symptoms*: 24.1 (5.5) **Included criteria:** age of 18–60 years, diagnosisof chronic schizophrenia, a total Positive and Negative Syndrome Scale (PANSS) score of≥ 50 and stable treatment with antipsychotics. **Excluded criteria:** axis Icomorbid disorders (Major Depressive Disorder (MDD) and mania), pregnancy,lactation, impaired renal or hepatic function and history of sensitivity to SSRIs. MDDwas an exclusion criterion in order to ascertain that the improvement was not due tothe abating of a depressive state.
Interventions	**Intervention Characteristics** citalopram ● *dose*: ● *duration*: placebo ● *dose*: NA ● *duration*: 10 weeks escitalopram ● *dose*: 20 mg ● *duration*: 10 weeks
Outcomes	*Continuous*: ● PANSS negative ● QoL ● PANSS positive ● AEs *Dichotomous*: ● All-cause discontinuation ● Suicide (completed or serious attempt)
Identification	**Sponsorship source:** supported by H. Lundbeck (producer of IMP) **Country:** Israel **Setting:** **Comments:** **Authors name:** Iulian Iancu et al. **Institution:** Yavne Mental Health Center, Yavne and the Beer Yaakov Mental Health Center, Beer Yaakov, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel **Email:** iulian1@bezeqint.net **Address:** Yavne Mental Health Center, 4 Dekel Street, Yavne, Israel
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** *Elisabeth Ginnerup-Nielsen* duration of ilness "mean" unclear if weeks, months, years. **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: "randomized" But Nothing written about how random number were found
Allocation concealment (selection bias)	Low risk	Comment: Done, opaque sealed envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Participants probably blinded, but nothing said about personnel
Blinding of outcome assessment (detection bias)	High risk	Comment: probably not blinded
Incomplete outcome data (attrition bias)	Low risk	Comment: All patients analysed, in total 4 withdrew
Selective reporting (reporting bias)	Low risk	Comment: Outcome from trial protocol (NCT00148447) assessed
Other bias	Unclear risk	Comment: supported by an Investigator grand from H. Lundbeck (producer of study medication)

Jockers Scherubl 2005

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** fluoxetine ● *Age*: ● *Duration of illness*: ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: ● *Gender, men*: ● *Hamilton depression rating scale*: placebo ● *Age*: 40.8 (11.8) ● *Duration of illness*: 9.9 (7.4) ● *PANSS total score*: ● *PANSS negative symptoms*: 29.64 (4.30) ● *SANS negative symptoms*: ● *Gender, men*: 57% ● *Hamilton depression rating scale*: 6.9 (2.6) paroxetine ● *Age*: 40.0 (6.8) ● *Duration of illness*: 9.9 (8.3) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: 32.27 (4.40) ● *Gender, men*: 36% ● *Hamilton depression rating scale*: 5.7 (2.9) **Included criteria:** chronic schizophrenia, at least 20 points on PANSS negative subscale, at least 4 on CGI, **Excluded criteria:** depressed patients (>12 on Hamilton depression rating scale), EPS (as defined by more than 1 point on the Simpson-Angus scale (SAS), the Barnes Akathisia scale (BAS), the Abnormal Involuntary Movement Scale (AIMS)), more than 3 points on PANSS items: 'delusions, conceptual disorganizatioin, hallucinations or suspiciousness/persecution' or a total of 10 items for two of those items
Interventions	**Intervention Characteristics** fluoxetine ● *duration*: ● *dose*: placebo ● *duration*: ● *dose*: paroxetine ● *duration*: 12 weeks ● *dose*: 20-30 mg
Outcomes	*Continuous*: ● SANS negative symptoms ● AEs ● AEs MIMS Parkinsonism ● PANSS negative symptoms ● PANSS Positive symptoms ● Quality of life ● BPRS positive symptoms ● SAS scale *Dichotomous*: ● Suicide (completed or serious attempt) ● All-cause discontinuation
Identification	**Sponsorship source:** The study was supported as an investigator initiated trial byGlaxoSmithKline. **Country:** Germany **Setting:** **Comments:** **Authors name:** Maria C. Jockers-Scherübl **Institution:** Charity University Medicine Berlin **Email:** maria.jockers@charite.de **Address:** Campus Benjamin Franklin
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:**

	Intervention characteristics: **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** *Elisabeth Ginnerup-Nielsen* 1 out of 15 in the placebo group (of the original sample)3 out of 14 in the intervention group (original sample) ITT analysis only done on 25 patients **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described properly
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind design (the study medication looked exactly the same for the two treatment groups)." Comment: Personnel probbaly also blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: assessors probably personnel but not described
Incomplete outcome data (attrition bias)	Low risk	Quote: "the intention-to-treat (ITT) population (i.e. patients that were randomized, treated and had at least one subsequent assessment). Missing values were imputed using the last obervation carried forward principle." Comment: Still 4 participants not included in the analysisbut: Four patientswithdrew before the first assessment; one due toimpotence and two due to dizziness in the paroxetinetreatedgroup and one patient due to dizziness onplacebo,
Selective reporting (reporting bias)	Low risk	Comment: no protocol available, but relevant outcome measures reported
Other bias	Unclear risk	Quote: "The study was supported as an investigator initiated trial by GlaxoSmithKline." Comment: role of sponsor (GlaxoSmithKline) not stated

Lee 1998

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** fluoxetine ● *Age*: ● *Duration of illness*: ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: ● *Gender, men*: ● *Hamilton depression rating scale*: placebo ● *Age*: 39.7 (9.9) ● *Duration of illness*: 10.8 (6.1) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: ● *Gender, men*: 56% ● *Hamilton depression rating scale*: sertraline ● *Age*: 40. (8.2) ● *Duration of illness*: 10.1 (6.5) ● *PANSS total score*: ● *PANSS negative symptoms*: ● *SANS negative symptoms*: ● *Gender, men*: 56% ● *Hamilton depression rating scale*: **Included criteria:** chronic schizophrenia, clinically significant positive or negative symptoms **Excluded criteria:** depression as defined by Hamilton depression rating scale < 10, EPS as defined by SAS < 5 (to exclude secondary negative symptoms), known organic syndromes, mental retardation, mood disorder, any active major medical problems
Interventions	**Intervention Characteristics** fluoxetine ● *duration*: ● *dose*: placebo

	● *duration*: 8 weeks ● *dose*: sertraline ● *duration*: 8 weeks ● *dose*: 50 mg
Outcomes	*Continuous*: ● SANS negative symptoms ● AEs ● AEs MIMS Parkinsonism ● PANSS negative symptoms ● PANSS Positive symptoms ● Quality of life ● BPRS positive symptoms ● SAS *Dichotomous*: ● Suicide (completed or serious attempt) ● All-cause discontinuation
Identification	**Sponsorship source:** not stated **Country:** Korea **Setting:** **Comments:** **Authors name:** Lee, Min Soo et al. **Institution:** Department of Psychiatry, College of Medicine, Korea University, Seoul, Korea **Email:** leeminso@unitel.co.kr **Address:** Sungbu-Ku, Seoul 136-705, Korea
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** *Elisabeth Ginnerup-Nielsen* pans general 38.3 (11.7) placebo38.2 (9.3) intervention **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	Low risk	Comment: probably done
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "No subjects withdrew as a result of experiencing increased psychotic, extrapyramidal, or any other side effects." Comment: But subject withdrew due to????No itt done
Selective reporting (reporting bias)	Low risk	Comment: no protocol but relevant outcomes reported
Other bias	Low risk	Comment: no other apparent bias

Mico' 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** citalopram ● *Age*: ● *Gender*: ● *Duration of illness*: ● *Depressive symptoms: Hamilton*: ● *Calgary depression rating scale for schizophrenia*: ● *PANSS total score*: placebo ● *Age*: ● *Gender*: male 55%

	● *Duration of illness*: 6.1 (3.2) ● *Depressive symptoms: Hamilton*: ● *Calgary depression rating scale for schizophrenia*: ● *PANSS total score*: duloxetine ● *Age*: ● *Gender*: male 65% ● *Duration of illness*: 6.8 (3.1) ● *Depressive symptoms: Hamilton*: ● *Calgary depression rating scale for schizophrenia*: ● *PANSS total score*: **Included criteria:** 23–48 years, who met theDiagnostic and Statistical Manual and Mental Disorder-IV criteria for schizophrenia and demonstrated persistentpositive and negative symptoms despite an adequate trialof clozapine, were included in this study. **Excluded criteria:** The criteria for exclusion were primary or secondarydiagnosis of bipolar disorder, either manic or mixedepisode, as defined by Diagnostic and Statistical Manualand Mental Disorder-IV Text Revision; active suicideintent, or a suicide attempt in the preceding 6 months;significant concurrent medical illnesses, organic braindisease, dementia, or a traumatic brain injury; history ofsubstance and alcohol dependence (excluding nicotine),mental retardation, and pregnant or lactating women wereexcluded
Interventions	**Intervention Characteristics** citalopram ● *dose*: ● *duration*: placebo ● *dose*: ● *duration*: duloxetine ● *dose*: 60 mg ● *duration*: 16 weeks
Outcomes	*Continuous*: ● PANSS negative ● QoL ● PANSS positive ● AEs *Dichotomous*: ● All-cause discontinuation ● Suicide (completed or serious attempt)
Identification	**Sponsorship source:** **Country:** Italy **Setting:** **Comments:** **Authors name:** Umberto Mico et al. **Institution:** Department of Neurosciences, Section of Psychiatry, Psychiatric and Anaesthesiological Sciences **Email:** mmuscatello@unime.it **Address:** Department of Clinical and Experimental Medicine and Pharmacology, Policlinico Universitario Via Consolare Valeria, Messina, Italy
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Done
Allocation concealment (selection bias)	Low risk	Quote: "The randomization list was held securely throughout the study, and released only after study completion." Comment: Done
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Pt's probably blinded but nothing about personnel

Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "All assessments tools were administered by experienced clinicians and trained raters who were well versed with the use of the rating scales; however, inter-rater reliability for these assessments was not established by formal training. Each patient had the same person administering psychopathological and cognitive tests, and conducting clinical interviews." Comment: Not explicitly described but personnel and assessors were probably identical
Incomplete outcome data (attrition bias)	Low risk	Quote: "An intention-to-treat analysis with last observation carried forward was performed."
Selective reporting (reporting bias)	Low risk	Comment: No trial protocol but relevant outcome a reported
Other bias	Low risk	Comment: No other apparent bias

Mulholland 2003

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized to double-blind treatment with sertraline or placebo using a computer generated list of" Comment: done
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias)	Low risk	Comment: study described as double blind
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Ratings were completed by one of the investigators (C.M.)" Comment: unclear if blinded, and first author
Incomplete outcome data (attrition bias)	High risk	Quote: "Two patients, one from each group, complained of adverse effects and dropped out of the study before the week 1 assessment. Eight other patients did not complete the full 8 weeks of the trial, three in the placebo group and five in the sertraline group" Comment: 10/26 = 38% attriti_ = LOCF, probably risk of bias
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available but relevant outcomes reported
Other bias	Low risk	Comment: no other apparent bias

Niitsu 2012

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** citalopram ● *Age*: ● *Gender*: ● *Duration of illness*: ● *Depressive symptoms: Hamilton*: ● *Depressive symptoms: MADR*: ● *PANSS total score*: placebo ● *Age*: mean 36.3 (SD 9.4) ● *Gender*: men 62.5% ● *Duration of illness*: mean 10.8 (SD 7.5) ● *Depressive symptoms: Hamilton*: ● *Depressive symptoms: MADR*: ● *PANSS total score*: 78.0 (11.0) fluvoxamine ● *Age*: 38.6 (9.5) ● *Gender*: men 61% ● *Duration of illness*: 12.3 (9.3) ● *Depressive symptoms: Hamilton*: ● *Depressive symptoms: MADR*: ● *PANSS total score*: 71.1 (10.3) **Included criteria:** The inclusion criteria were subjects who (1) wereaged 20 to 59 years, eliminating the possibility of includingpatients with dementia; (2) were diagnosed according to theDiagnostic and Statistical Manual of Mental

	Disorders, FourthEdition (DSM-IV) criteria for schizophrenia, confirmed by theStructured Clinical Interview for DSM-IV; and (3) had beenreceiving monotherapy with a stable dose of an atypical antipsychoticdrug for at least 8 weeks before study entry. **Excluded criteria:** Exclusioncriteria were subjects who (1) had cognitive disorders besidesschizophrenia (eg, dementia), (2) were pregnant or breastfeedingwomen, (3) had a history of manic state, (4) had otherDSM-IV Axis I or II comorbidities, and (5) had unstable DSMIVAxis III comorbidities, for example, diabetes mellitus
Interventions	**Intervention Characteristics** citalopram ● *dose*: ● *duration*: placebo ● *dose*: ● *duration*: fluvoxamine ● *dose*: uptitrated to 150 mg/day ● *duration*: 8 weeks
Outcomes	*Continuous*: ● PANSS negative ● QoL (QLS scale) ● PANSS positive ● AEs (DIEPSS) ● SANS negative symptoms *Dichotomous*: ● All-cause discontinuation ● Suicide (completed or serious attempt)
Identification	**Sponsorship source:** Not reported. Dr Hashimoto reports having received speaker's bureau honoraria from Abott Pharmaceuticals **Country:** Japan **Setting:** **Comments:** **Authors name:** Tomihisa Niitsu et. al **Institution:** Department of Psychiatry and Research Center for Child Mental Development **Email:** hashimoto@faculty.chiba-u.jp **Address:** University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba260-8670, Japan
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random assesment in a 1:1 ratio
Allocation concealment (selection bias)	Low risk	Comment: Until the trial was concluded randomization list only availbale to dispensing doctor and a pharmacist
Blinding of participants and personnel (performance bias)	Low risk	Comment: Sufficient blinding of participants, care providers, and outcome assessors
Blinding of outcome assessment (detection bias)	Low risk	Comment: Quote (about randomization) blinding to those assessing outcomes was succesful
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	Comment: Protol UMIN clin trial relevant outomes see s assessed
Other bias	Unclear risk	Comment: 1st author has received honoraria from private medical company. The others nothing

Salokangas 1996

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to either adjuvant placebo or adjuvant citalopram in blocks of 10 patients." Comment: blocks probably done with a program..
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias)	Low risk	Comment: Study described as double blind but nothing else
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "examined at baseline and 3, 6 and 12 weeks thereafter by psychiatrists who were specially trained for the study" Comment: unclear if blinded (and asssor is first author)
Incomplete outcome data (attrition bias)	Unclear risk	Comment: ITT population consists of 40 placebo and 45 citalopram, 45 randomized to each group, unclear how the drop outs were treated, LOCF?
Selective reporting (reporting bias)	Unclear risk	Comment: No trial protocol, but relevant outcome seems assessed
Other bias	Unclear risk	Comment: unclear fincancing from Lundbeck

Silver 1992

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not descrbed
Blinding of participants and personnel (performance bias)	Low risk	Quote: "a double- blind fashion." Comment: Hmm not clearly describedlabelled 'double-blind', not otherwise described but probably done
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Not described. maybe if assessor and personnel are the same
Incomplete outcome data (attrition bias)	Low risk	Comment: all participants completed the trial
Selective reporting (reporting bias)	Low risk	Comment: protocol not available but relevant outcomes reported
Other bias	Unclear risk	Comment: Role of funding source not clear

Silver 2000

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias)	Low risk	Comment: not stated apart from 'fluvoxamine or an identical placebo'; probably done.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Quote assessment done by experienced raters Nothing else described
Incomplete outcome data (attrition bias)	High risk	Comment: No itt and large dropout 12/53all but 1 participant analyzed, 7 dropouts, all from fluvoxamine group, LOCF, because all drop outs from one group, high risk of biased estimate

Selective reporting (reporting bias)	Unclear risk	Comment: No protocol
Other bias	Unclear risk	Comment: role of funding source (Solway Pharmaceuticals) unclear

Spina 1994

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described
Allocation concealment (selection bias)	Unclear risk	Comment: Pt's were randomly and blindly
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Blindly, but not double blind. personnel probably not blinded
Blinding of outcome assessment (detection bias)	Low risk	Comment: 'two independent rates', probably done
Incomplete outcome data (attrition bias)	Low risk	Comment: 3 in intervention group and one in placebo. No dropout. 30 were included in analysis
Selective reporting (reporting bias)	Low risk	Comment: no protocol, but relevant outcomes reported
Other bias	Low risk	Comment: no other apparent bias

Usall 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** citalopram ● *Age*: 42.47 (10.62) ● *Gender*: male 78.3% ● *Duration of illness*: ● *Depressive symptoms: Hamilton*: ● *PANSS negative symptoms*: 25.91 (5.15) placebo ● *Age*: 44.15 (12.36) ● *Gender*: 66.7% ● *Duration of illness*: ● *Depressive symptoms: Hamilton*: ● *PANSS negative symptoms*: 26.21 (6.37) **Included criteria:** schizophrenia, 18-65 y, stable dose of olanzapine or risperidone, presence of significant negative symptoms **Excluded criteria:** substance use disorders, mental retardation, antidepressant or mood stabilizer use previous 4 months, antipsychotic polypharmacy, Hamilton Depression Rating Scale > 20, pregnant and lactating women, severe somatic comorbidity
Interventions	**Intervention Characteristics** citalopram ● *dose*: 30 mg ● *duration*: 6 months placebo ● *dose*: ● *duration*:
Outcomes	*Continuous*: ● PANSS negative ● QoL ● PANSS positive ● AEs *Dichotomous*: ● All-cause discontinuation ● Suicide (completed or serious attempt)

Identification	**Sponsorship source:** grant from Fondo de investigacion sanitario **Country:** Spain **Setting:** **Comments:** **Authors name:** Judith Usall et al. **Institution:** **Email:** jusall@pssjd.org **Address:** Park Sanitary sant Joan de Deju
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: pt's randomly asigned in 3 groups with a 1:1:1 ratio
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Comment: pills equal Quote: all participants and study personnel remained blinded during the duration of the study
Blinding of outcome assessment (detection bias)	Unclear risk	no info
Incomplete outcome data (attrition bias)	Unclear risk	Comment: ITT analysis last obs carried forward. Large dropout (30%) but not skewed
Selective reporting (reporting bias)	Low risk	Comment: protocol: clin. trials NCT01.. relevant outcome seems assessed
Other bias	Low risk	Comment: No other apparent bias

Footnotes

Characteristics of excluded studies

Bustillo 2003

Reason for exclusion	Wrong outcomes

Chaichan 2004

Reason for exclusion	Wrong indication

Poyurovsky 2002

Reason for exclusion	Wrong indication

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Arango 2000

Arango, C.; Kirkpatrick, B.; Buchanan, R. W.. Fluoxetine as an adjunct to conventional antipsychotic treatment of schizophrenia patients with residual symptoms. Journal of Nervous & Mental Disease 2000;188(1):50-3. [DOI:]

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Data and analyses

1 Antidepressants (SSRI) vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Negative symptoms (PANSS, SANS, BPRS) , end of treatment (duration 4 weeks to 6 month), higher=worse	14	565	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.51, -0.10]
1.1.1 Citalopram	3	173	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.56, 0.05]
1.1.2 Escitalopram	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.58, 0.66]
1.1.3 paroxetine	1	25	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-1.11, 0.48]
1.1.4 sertraline	2	62	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.53, 0.46]
1.1.5 fluvoxamine	3	129	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.78, -0.08]
1.1.6 fluoxentine	4	136	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.20, 0.23]
1.2 Positive symptoms (PANSS, SAPS, BPRS), end of treatment (duration 4 weeks to 6 month), higher=worse	12	492	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.25, 0.11]
1.2.1 Citalopram	3	173	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.37, 0.51]
1.2.2 paroxetine	1	25	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.39, 0.23]
1.2.3 Escitalopram	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.64, 0.60]
1.2.4 sertraline	1	36	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.21, 0.12]
1.2.5 fluoxetine	4	136	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.44, 0.23]
1.2.6 fluvoxamine	2	82	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.33, 0.54]
1.3 All-cause discontinuation, End of treatment (duration: 4 weeks to 6 months))	11	473	Risk Ratio (IV, Random, 95% CI)	1.38 [0.88, 2.16]
1.4 Neurological side effects, end of treatment (higher=worse)	8	336	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.32, 0.28]
1.4.4 escitalopram (AIMS)	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.80, 0.45]
1.4.5 citalopram (UKU)	1	85	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.74, 0.12]
1.4.6 fluoxentine (SAS minus akathisia)	2	73	Std. Mean Difference (IV, Random, 95% CI)	0.65 [0.17, 1.12]
1.4.7 sertraline (SAS)	1	36	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-1.11, 0.21]
1.4.8 paroxetine (SAS)	1	25	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.86, 0.72]
1.4.11 fluvoxamine (Simpson-Angus EPS)	2	77	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.60, 0.30]
1.5 Agitation, end of treatment (number of events)	1	26	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.98]
1.5.1 sertraline	1	26	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.98]
1.6 QoL (QLS scale), end of intervention	1	47	Mean Difference (IV, Random, 95% CI)	-6.30 [-17.22, 4.62]
1.6.1 Fluvoxamine	1	47	Mean Difference (IV, Random, 95% CI)	-6.30 [-17.22, 4.62]
1.7 PANSS negative, longest FU	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.8 Suicide/serious attempt	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

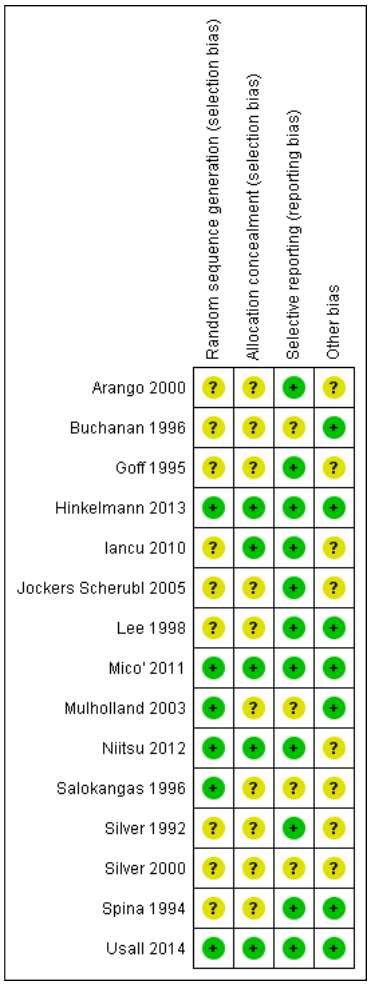
2 Antidepressants (SNRI) vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Negative symptoms (PANSS) , end of treatment (duration 4 weeks to 6 month), higher=worse	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.38 [-2.07, -0.68]
2.1.7 duloxetine	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.38 [-2.07, -0.68]
2.2 Positive symptoms (PANSS), end of treatment (duration 4 weeks to 6 month), higher=worse	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.62, 0.62]
2.2.7 duloxetine	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.62, 0.62]
2.3 All-cause discontinuation, End of treatment (duration: 4 weeks to 6 months))	1	40	Risk Ratio (IV, Random, 95% CI)	0.75 [0.19, 2.93]
2.4 PANSS negative, longest FU	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.5 Neurological side effects, end of treatment (higher=worse)	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable

2.6 Agitation, end of treatment (number of events)	0	0	Odds Ratio (M-H, Random, 95% CI)	Not estimable
2.7 QoL (QLS scale), end of intervention	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
2.8 Suicide/serious attempt	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

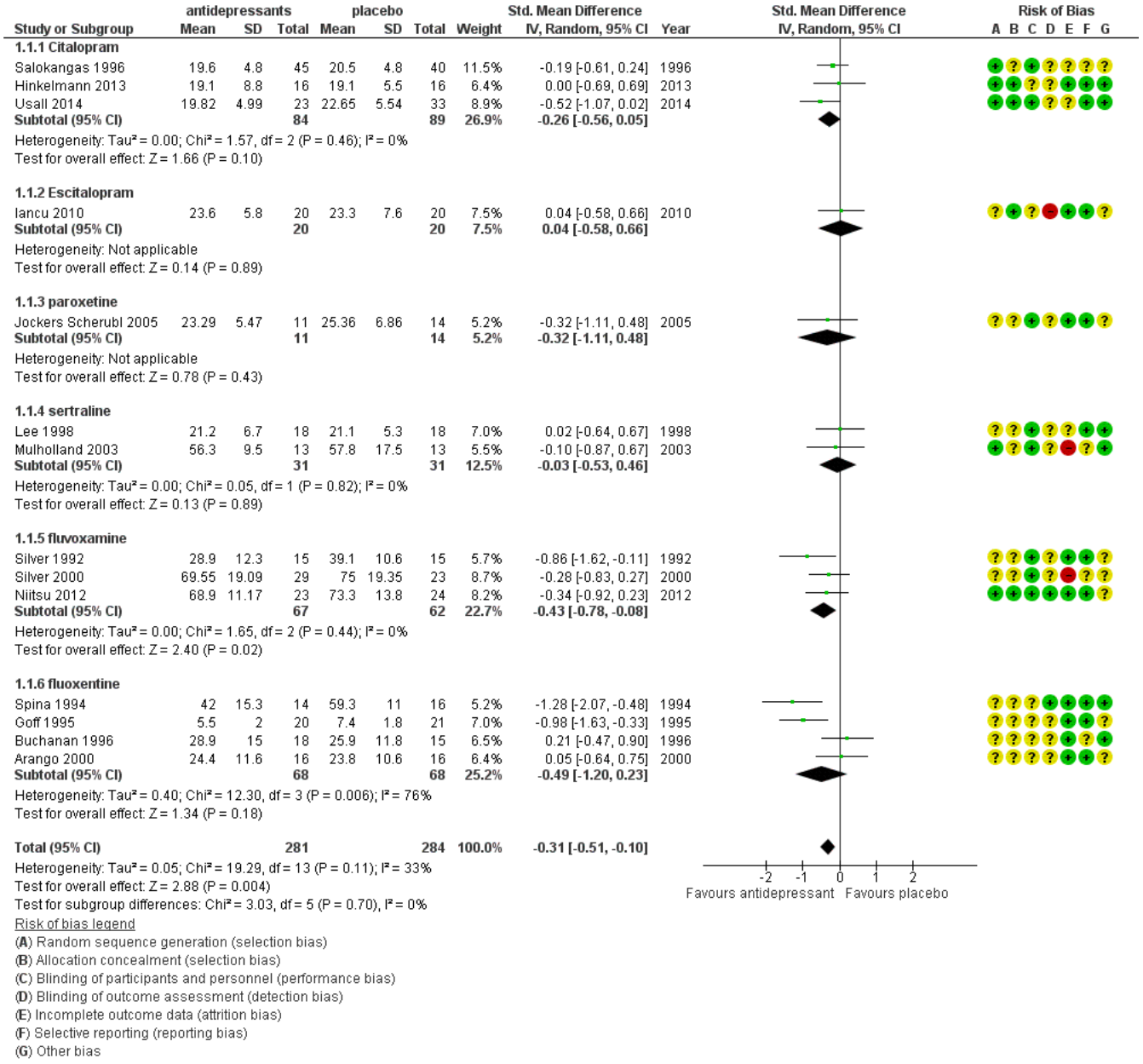
Figures

Figure 1



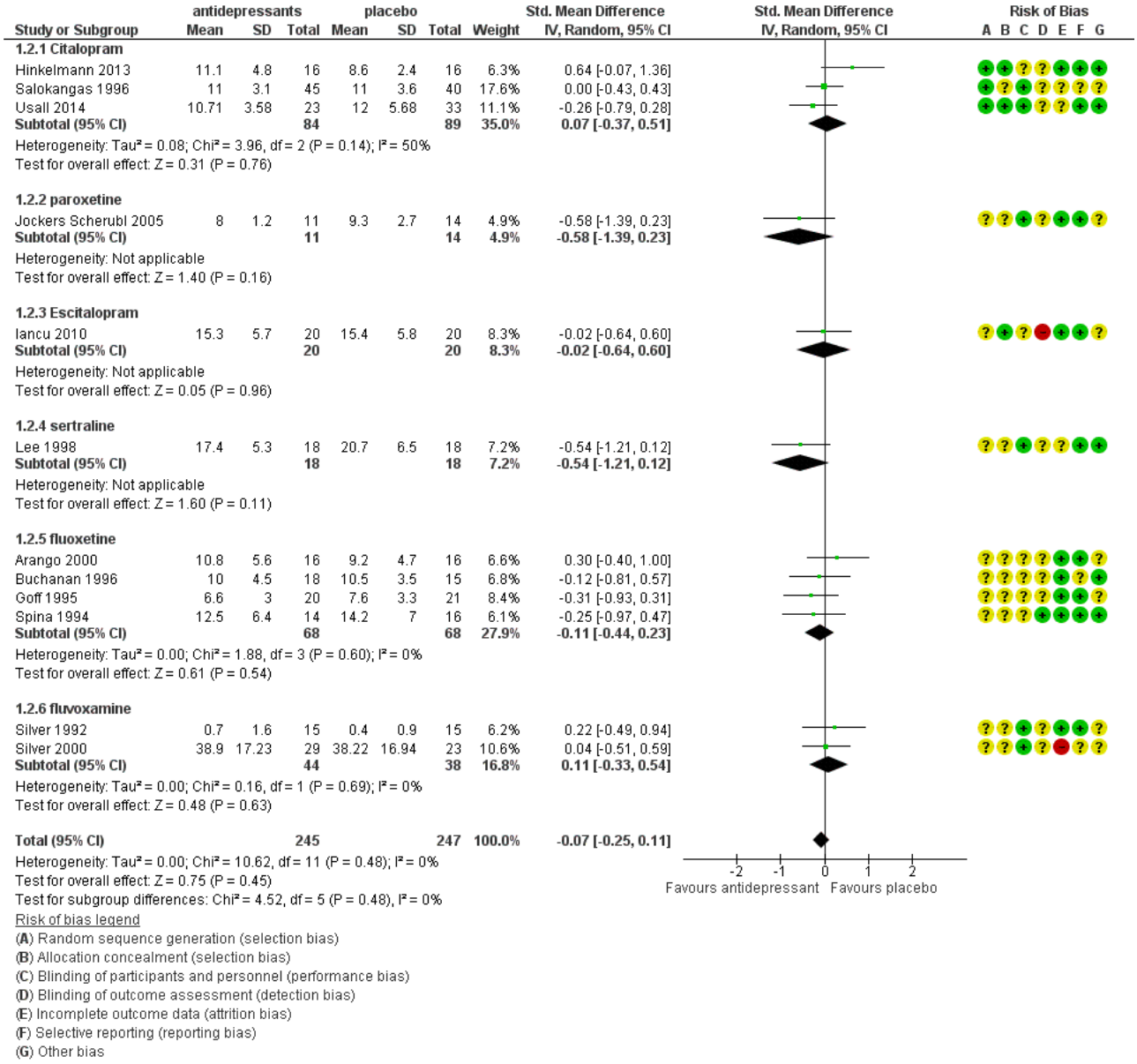
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 1.1)



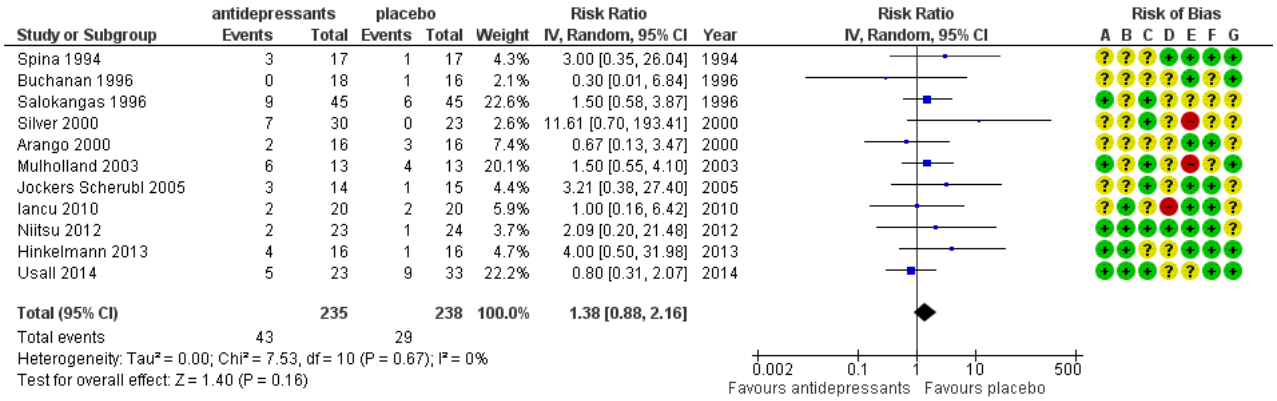
Forest plot of comparison: 1 Antidepressants vs placebo, outcome: 1.1 Negative symptoms (PANSS, SANS, BPRS) , end of treatment (duration 4 weeks to 6 month), higher=worse.

Figure 3 (Analysis 1.2)



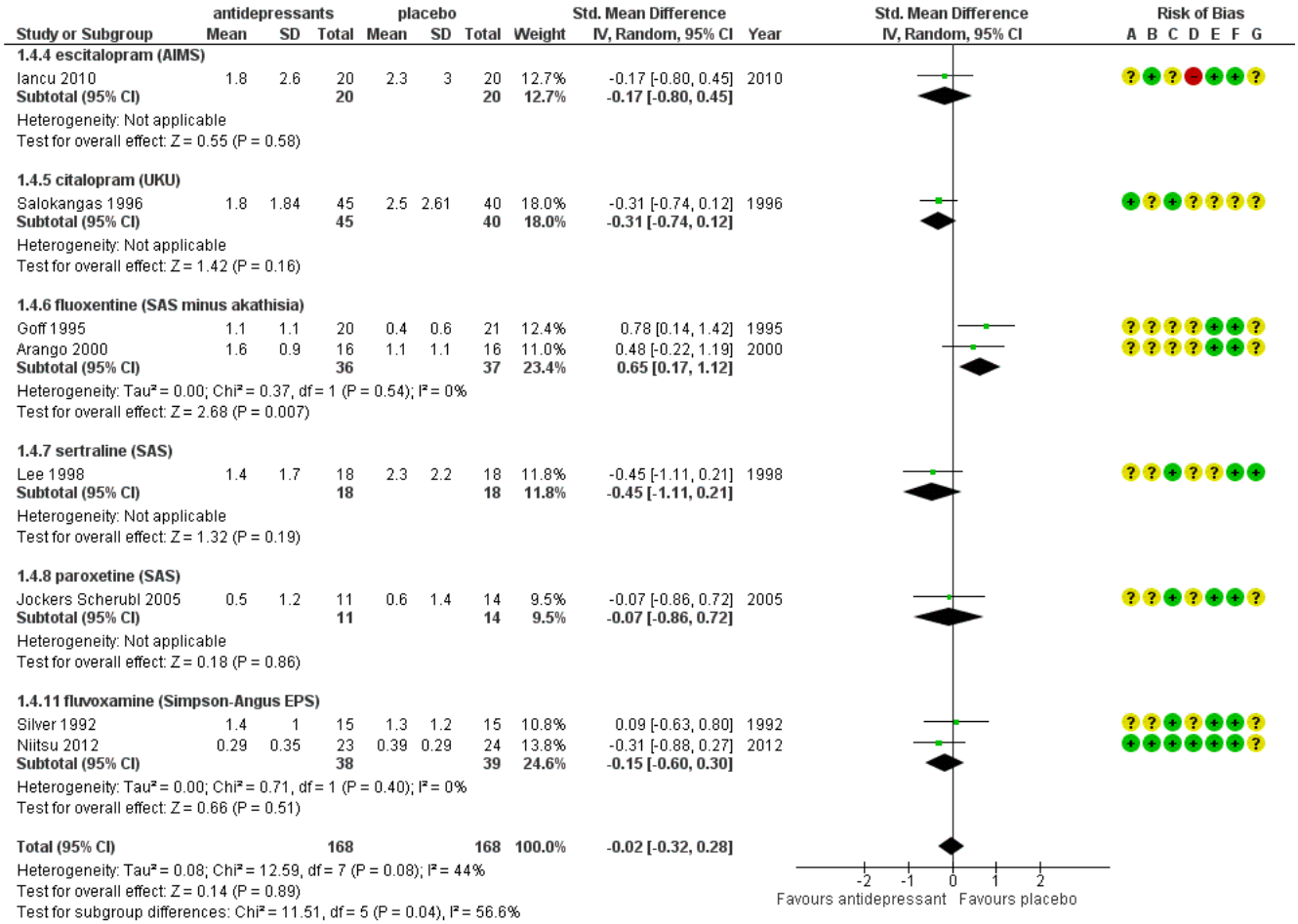
Forest plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.2 Positive symptoms (PANSS, SAPS, BPRS), end of treatment (duration 4 weeks to 6 month), higher=worse.

Figure 4 (Analysis 1.3)



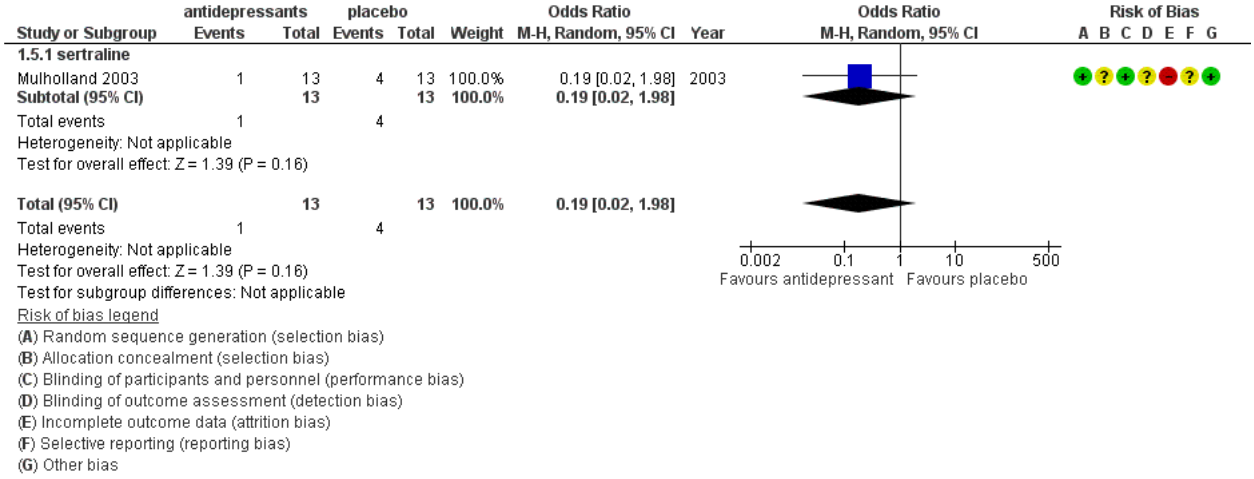
Forest plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.3 All-cause discontinuation, End of treatment (duration: 4 weeks to 6 months)).

Figure 5 (Analysis 1.4)



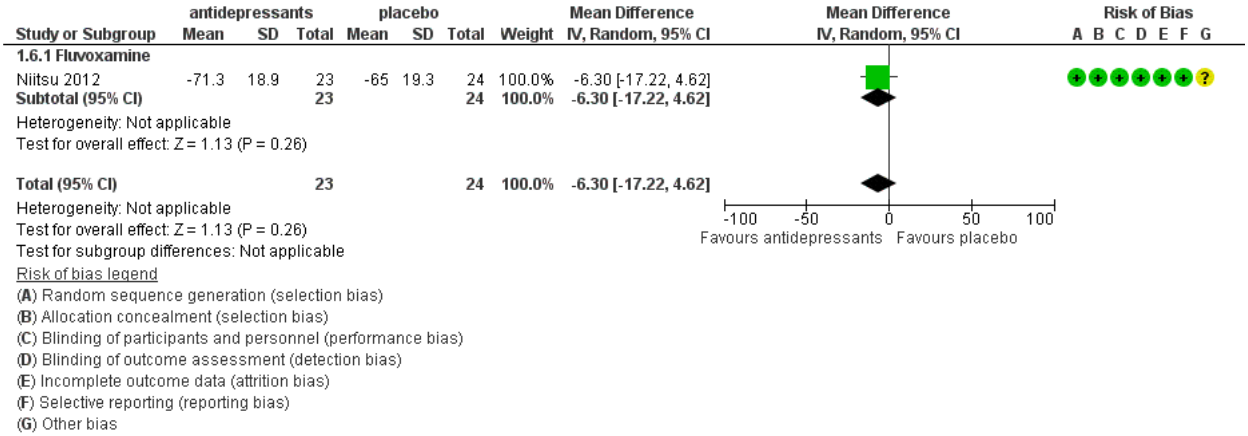
Forest plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.4 Neurological side effects, end of treatment (higher=worse).

Figure 6 (Analysis 1.5)



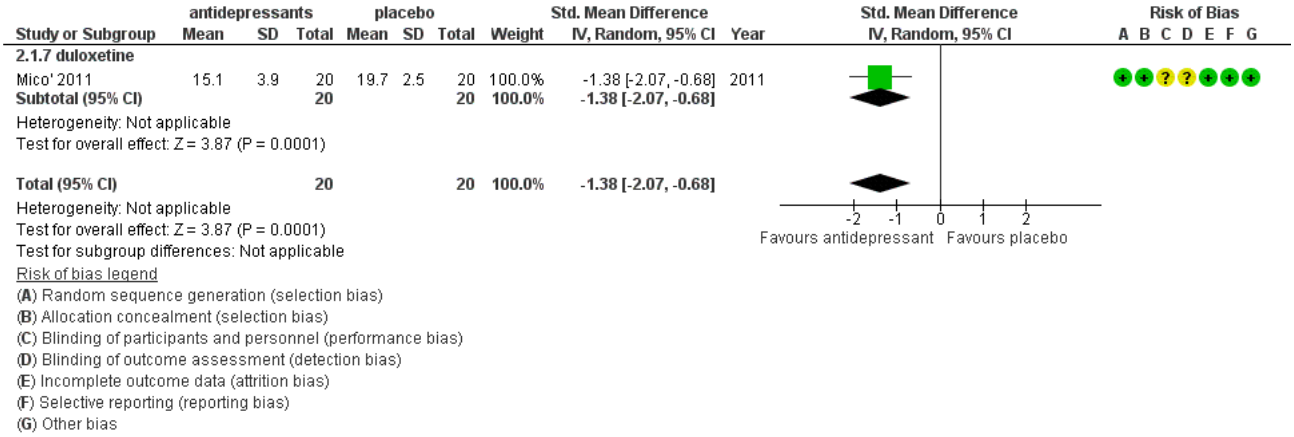
Forest plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.5 Agitation, end of treatment (number of events).

Figure 7 (Analysis 1.6)



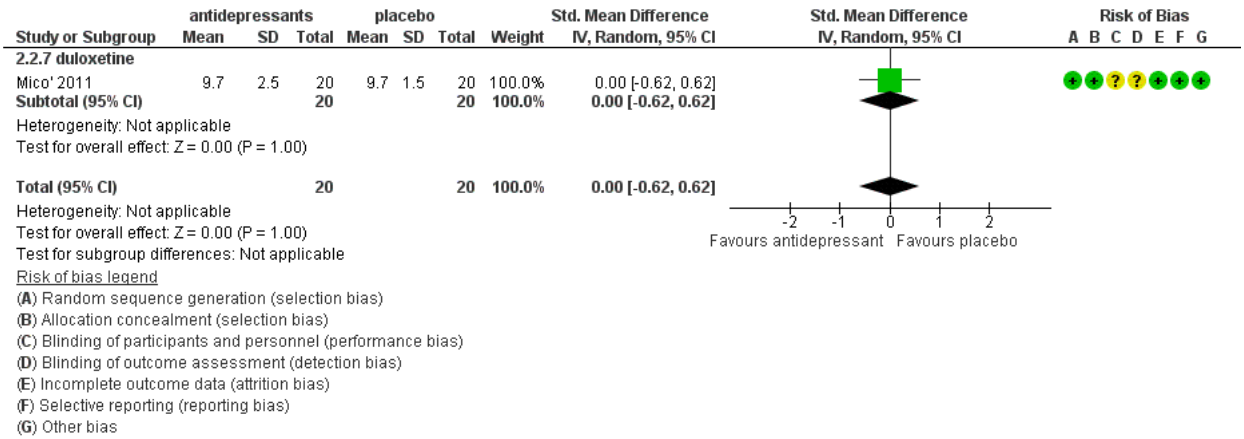
Forest plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.6 QoL (QLS scale), end of intervention.

Figure 8 (Analysis 2.1)



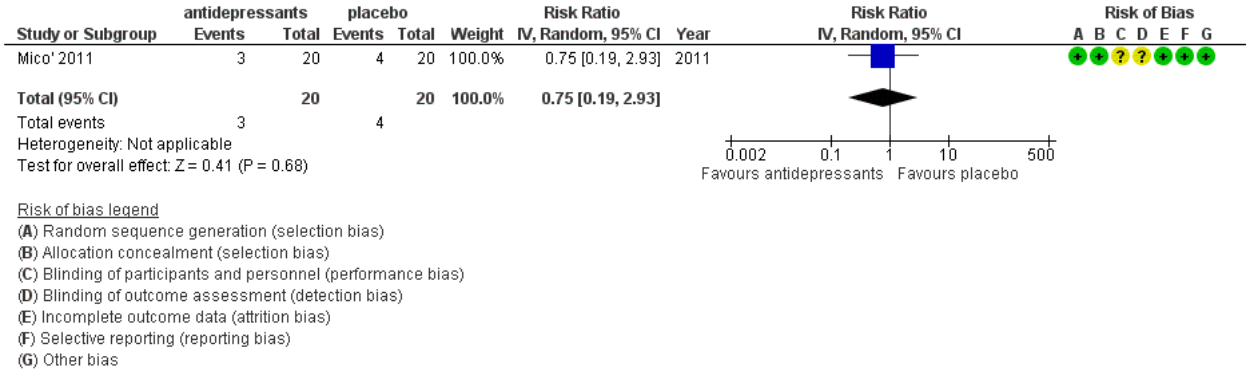
Forest plot of comparison: 2 Antidepressants (SNRI) vs placebo, outcome: 2.1 Negative symptoms (PANSS) , end of treatment (duration 4 weeks to 6 month), higher=worse.

Figure 9 (Analysis 2.2)



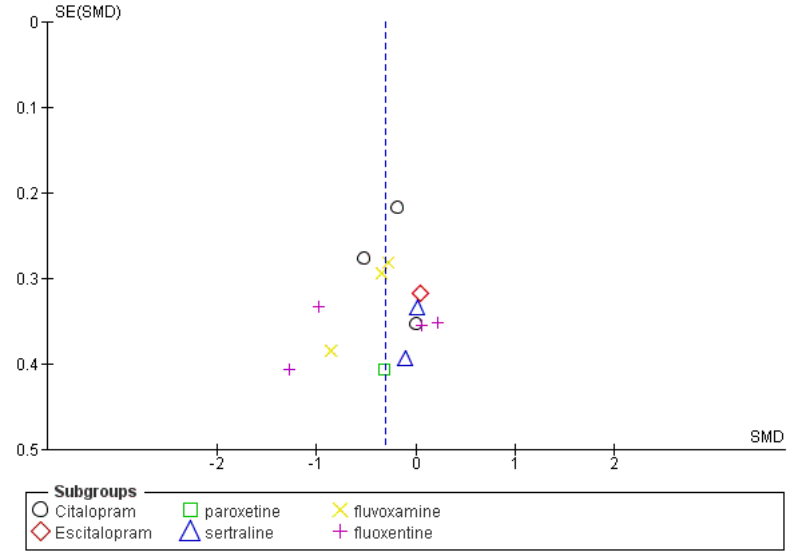
Forest plot of comparison: 2 Antidepressants (SNRI) vs placebo, outcome: 2.2 Positive symptoms (PANSS), end of treatment (duration 4 weeks to 6 month), higher=worse.

Figure 10 (Analysis 2.3)



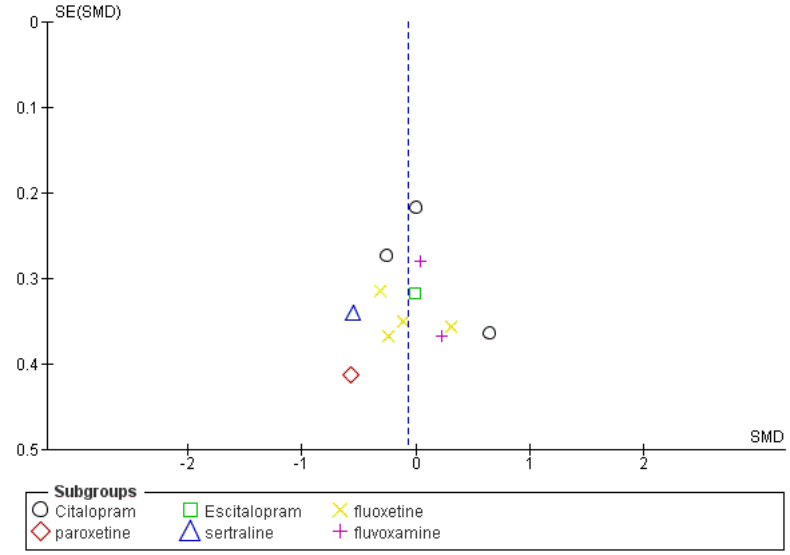
Forest plot of comparison: 2 Antidepressants (SNRI) vs placebo, outcome: 2.3 All-cause discontinuation, End of treatment (duration: 4 weeks to 6 months)).

Figure 11 (Analysis 1.1)



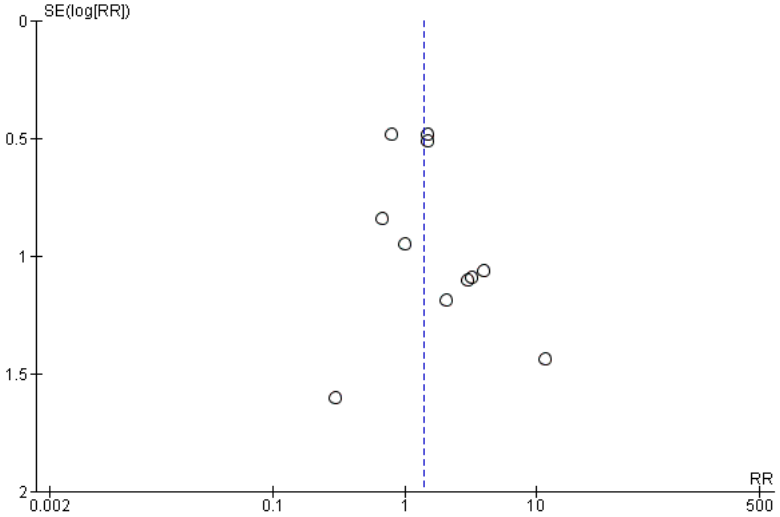
Funnel plot of comparison: 1 Antidepressants vs placebo, outcome: 1.1 Negative symptoms (PANSS, SANS, BPRS) , end of treatment (duration 4 weeks to 6 month), higher=worse.

Figure 12 (Analysis 1.2)



Funnel plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.2 Positive symptoms (PANSS, SAPS, BPRS), end of treatment (duration 4 weeks to 6 month), higher=worse.

Figure 13 (Analysis 1.3)



Funnel plot of comparison: 1 Antidepressants (SSRI) vs placebo, outcome: 1.3 All-cause discontinuation, End of treatment (duration: 4 weeks to 6 months)).