NKR 43 Angst PICO 4 Psykoterapi + SSRI/SNRI vs Psykoterapi alene

Characteristics of studies

Characteristics of included studies

Walkup 2008

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention(psychotherapy) ● *Number with primary social phobia (n, %)*: Not reported specifically ● *Number with primary generalized anxiety disorder (n, %)*: Not reported specifically ● *Number with primary separation anxiety disorder (n, %)*: Not reported specifically ● *Number with other types of primary anxiety disorders (n, %)*: 0,0% ● *Age in years (mean, SD)*: 10.5 (2.9) ● *Age range and proportion of children and adolescents*: 7-17 (77.7% children[7-12]) Control ● *Number with primary social phobia (n, %)*: Not reported specifically ● *Number with primary generalized anxiety disorder (n, %)*: Not reported specifically ● *Number with primary separation anxiety disorder (n, %)*: Not reported specifically ● *Number with other types of primary anxiety disorders (n, %)*: 0,0% ● *Age in years (mean, SD)*: 10.8 (2.8) ● *Age range and proportion of children and adolescents*: 7-17 (74.4% children[7-12]) Intervention(SSRI + therapy) ● *Number with primary social phobia (n, %)*: Not reported specifically ● *Number with primary generalized anxiety disorder (n, %)*: Not reported specifically ● *Number with primary separation anxiety disorder (n, %)*: Not reported specifically ● *Number with other types of primary anxiety disorders (n, %)*: 0,0% ● *Age in years (mean, SD)*: 10.7 (2.8) ● *Age range and proportion of children and adolescents*: 7-17 (72.1% children[7-12]) **Included criteria:** Children between the ages of 7 and 17 years witha primary diagnosis of separation or generalizedanxiety disorder or social phobia (according tothe criteria of the Diagnostic and Statistical Manual ofMental Disorders, fourth edition, text revision[DSM-IV-TR]16), substantial impairment, and anIQ of 80 or more were eligible to participate.Children with coexisting psychiatric diagnosesof lesser severity than the three target disorderswere also allowed to participate; such diagnosesincluded attention deficit–hyperactivity disorder(ADHD) while receiving stable doses of stimulantand obsessive–compulsive, post-traumatic stress,oppositional–defiant, and conduct disorders **Excluded criteria:** Childrenwere excluded if they had an unstable medicalcondition, were refusing to attend school becauseof anxiety, or had tried but had not had aresponse to two adequate trials of SSRIs or anadequate trial of cognitive behavioral therapy.Girls who were pregnant or were sexually activeand were not using an effective method of birthcontrol were also excluded. Children who were receivingpsychoactive medications other than stabledoses of stimulants and who had psychiatric diagnosesthat made participation in the study clinicallyinappropriate (i.e., current major depressiveor substance-use disorder; unmedicated ADHD,combined type; or a lifetime history of bipolar,psychotic, or pervasive developmental disorders)or who presented an acute risk to themselves orothers were

	also excluded. **Pretreatment:** No group differences detected
Interventions	**Intervention Characteristics** Intervention(psychotherapy) ● *Description of type of intervention/control*: Cognitive behavioral therapy involved fourteen 60-minute sessions, which included review and rat-ings of the severity of subjects' anxiety, response to treatment, and adverse events. Therapy was based on the Coping Cat program,which was adapted for the subjects' age and the duration of the study.Each subject who was assigned to re-ceive cognitive behavioral therapy received training in anxiety-management skills, followed by behav-ioral exposure to anxiety-provoking situations. Parents attended weekly check-ins and two parent-only sessions. Experienced psychotherapists, cer-tified in the Coping Cat protocol, received regular site-level and cross-site supervision ● *Length of intervention/control (weeks and sessions)*: 12 weeks, 14 sessions ● *Length of follow-up (in months)*: 6 month but only for responders. There is also a follow up study (CAMELS) that describes remission for a portion of the responders 6 years after randomization Control ● *Description of type of intervention/control*: Pharmacotherapy involved eight sessions of 30 to 60 minutes each that included review and ratings of the severity of subjects' anxiety, their response to treatment, and adverse events. Ser-traline (Zoloft) and matching placebo were ad-ministered on a fixed–flexible schedule begin-ning with 25 mg per day and adjusted up to 200 mg per day by week 8. Through week 8, subjects who were considered to be mildly ill or worse and who had minimal side effects were eligible for dose increases. Psychiatrists and nurse clini-cians with experience in medicating children with anxiety disorders were certified in the study phar-macotherapy protocol and received regular site-level and cross-site supervision. Pill counts and medication diaries were used to facilitate and document adherence ● *Length of intervention/control (weeks and sessions)*: 12 weeks, 8 sessions of medication review and administration ● *Length of follow-up (in months)*: Intervention(SSRI + therapy) ● *Description of type of intervention/control*: Combination therapy consisted of the admin-istration of sertraline and cognitive behavioral therapy. Whenever possible, therapy and medica-tion sessions occurred on the same day for the convenience of subject ● *Length of intervention/control (weeks and sessions)*: 12 weeks, 14 sessions of Copiing Cat and 8 sessions of medication administration ● *Length of follow-up (in months)*:
Outcomes	*Remission of primary anxiety diagnosis (EoT)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Not reported ● **Scale**: ADIS-C/P ● **Direction**: Higher is better ● **Data value**: Endpoint ● **Notes**: Reported in Piacentini et al., 2014 *Youth reported anxiety symptoms (EoT)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported ● **Notes**: No self-report in study *Parent reported anxiety symptoms (EoT)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported ● **Notes**: No parent report in study

Remission of primary anxiety diagnosis (longest FU, at least 3 months)
- **Outcome type**: DichotomousOutcome
- **Scale**: ADIS
- **Direction**: Higher is better
- **Data value**: Endpoint
- **Notes**: 6 year follow-up (based on Ginsburg et al., 2014)

Youth reported anxiety symptoms (longest FU, at least 3 months)
- **Outcome type**: ContinuousOutcome
- **Reporting**: Not reported
- **Notes**: No self-report in study

Parent reported anxiety symptoms (longest FU, at least 3 months)
- **Outcome type**: ContinuousOutcome
- **Reporting**: Not reported
- **Notes**: No parent report in study

Youth reported functioning (EoT)
- **Outcome type**: ContinuousOutcome
- **Reporting**: Not reported
- **Notes**: No self-report in study

Observer reported functioning (EoT)
- **Outcome type**: ContinuousOutcome
- **Reporting**: Fully reported
- **Scale**: Children's Global Assessment Scale (CGAS)
- **Range**: 1-100
- **Unit of measure**: Points
- **Direction**: Higher is better
- **Data value**: Endpoint

Combined youth and observer reported functioning (EoT)
- **Outcome type**: DichotomousOutcome
- **Reporting**: Not reported

Number that discontinued treatment or control (EoT)
- **Outcome type**: DichotomousOutcome
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Suicidal thoughts (EoT)
- **Outcome type**: AdverseEvent
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Suicidal behavior (EoT)
- **Outcome type**: AdverseEvent

	● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Serious adverse events (EoT)* ● **Outcome type**: AdverseEvent ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint ● **Notes**: Moderate to severe adverse events: SSRI: Physical = 50.4%, Psychiatric = 17.3%, Harm-related = 2..3%, Medical or surgical = 0.8%. Sum = 70.8%CBT: Physical = 36.7%, Psychiatric = 9.4%, Harm-related = 5.8%, Medical or surgical = 0.7%. Sum = 52.6%
Identification	**Sponsorship source:** Supported by grants (U01 MH064089, to Dr. Walkup; U01 MH64092, to Dr. Albano; U01 MH64003, to Dr. Birmaher; U01 MH63747, to Dr. Kendall; U01 MH64107, to Dr. March; U01 MH64088, to Dr. Piacentini; and U01 MH064003, to Dr. Compton) from the National Institute of Mental Health (NIMH). Sertraline and matching placebo were supplied free of charge by Pfizer.Dr. Walkup reports receiving consulting fees from Eli Lilly and Jazz Pharmaceuticals and fees for legal consultation to de-fense counsel and submission of written reports in litigation involving GlaxoSmithKline, receiving lecture fees from CMP Media, Medical Education Reviews, McMahon Group, and Di-Medix, and receiving support in the form of free medication and matching placebo from Eli Lilly and free medication from Ab-bott for clinical trials funded by the NIMH; Dr. Albano, receiv-ing royalties from Oxford University Press for the Anxiety Disor-ders Interview Schedule for DSM-IV, Child and Parent Versions, but not for interviews used in this study, and royalties from the Guilford Press; Dr. Piacentini, receiving royalties from Oxford University Press for treatment manuals on childhood obsessive–compulsive disorder and tic disorders and from the Guilford Press and APA Books for other books on child mental health and receiving lecture fees from Janssen-Cilag; Dr. Birmaher, receiv-ing consulting fees from Jazz Pharmaceuticals, Solvay Pharma-ceuticals, and Abcomm, lecture fees from Solvay, and royalties from Random House for a book on children with bipolar disor-der; Dr. Rynn, receiving grant support from Neuropharm, Boeh-ringer Ingelheim Pharmaceuticals, and Wyeth Pharmaceuticals, consulting fees from Wyeth, and royalties from APPI for a book chapter on pediatric anxiety disorders; Dr. McCracken, receiving consulting fees from Sanofi-Aventis and Wyeth, lecture fees from Shire and UCB, and grant support from Aspect, Johnson & Johnson, Bristol-Myers Squibb, and Eli Lilly; Dr. Waslick, receiv-ing grant support from Baystate Health, Somerset Pharmaceuti-cals, and GlaxoSmithKline; Dr. Iyengar, receiving consulting fees from Westinghouse for statistical consultation; Dr. March, receiving study medications from Eli Lilly for an NIMH-funded clinical trial and receiving royalties from Pearson for being the author of the Multidimensional Anxiety Scale for Children, re-ceiving consulting fees from Eli Lilly, Pfizer, Wyeth, and Glaxo-SmithKline, having an equity interest in MedAvante, and serving on an advisory board for AstraZeneca and Johnson & Johnson; and Dr. Kendall, receiving royalties from Workbook Publishing for anxiety-treatment materials. No other potential conflict of interest relevant to this article was reported. **Country:** USA **Setting:** Recruited from Duke University Medical Cen-ter, New York State Psychiatric Institute–Colum-bia University Medical Center–New York Univer-sity, Johns Hopkins Medical Institutions, Temple University, University of California, Los Angeles, and Western Psychiatric Institute and Clinic–University of Pittsburgh Medical Center. **Comments:** ClinicalTrials.gov number, NCT00052078 **Authors name:** Walkup 2008 **Institution:** Johns Hopkins Medical Institutions, Baltimore, New York **Email:** not stated **Address:**
Notes	*Nkr 43 Angst* on 07/04/2016 22:35 **Select** The CAMS study end of treatment

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Quote: "The randomization sequence in a 2:2:2:1 ratio was determined by a computer-generated algorithm"
Allocation concealment	Low risk	Quote: "and maintained by the central pharmacy, with stratification according to age, sex, and study cen- ter."
Blinding of participants and personnel	High risk	Judgement Comment: Not blinded for CBT
Blinding of outcome assessors	Low risk	Quote: "The study protocol called for in- dependent evaluators who completed assessments to be unaware of all treatment assignments."
Incomplete outcome data	Low risk	Judgement Comment: Attrition between 4.32 % to 17.29 %
Selective outcome reporting	Low risk	Judgement Comment: Match to protocol
Other sources of bias	Low risk	Judgement Comment: No other sources detected

Footnotes

Characteristics of excluded studies

Beidel 2007

Reason for exclusion	Wrong comparison

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

References to studies

Included studies

Walkup 2008

Ginsburg G.S.; Becker E.M.; Keeton C.P.; Sakolsky D.; Piacentini J.; Albano A.M.; Compton S.N.; Iyengar S.; Sullivan K.; Caporino N.; Peris T.; Birmaher B.; Rynn M.; March J.; Kendall,P. C.. Naturalistic follow-up of youths treated for pediatric anxiety disorders.. JAMA Psychiatry 2014;71(3):310-318. [DOI:]

Piacentini,John; Bennett,Shannon; Compton,Scott N.; Kendall,Phillip C.; Birmaher,Boris; Albano,Anne Marie; March,John; Sherrill,Joel; Sakolsky,Dara; Ginsburg,Golda; Rynn,Moira; Bergman,R. Lindsey; Gosch,Elizabeth; Waslick,Bruce; Iyengar,Satish; McCracken,James; Walkup,John. 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS).. Journal of the American Academy of Child & Adolescent Psychiatry

2014;53(3):297-310. [DOI:]

Rynn,Moira A.; Walkup,John T.; Compton,Scott N.; Sakolsky,Dara J.; Sherrill,Joel T.; Shen,Sa; Kendall,Philip C.; McCracken,James; Albano,Anne Marie; Piacentini,John; Riddle,Mark A.; Keeton,Courtney; Waslick,Bruce; Chrisman,Allan; Iyengar,Satish; March,John S.; Birmaher,Boris. Child/adolescent anxiety multimodal study: Evaluating safety.. Journal of the American Academy of Child & Adolescent Psychiatry 2015;54(3):180-190. [DOI:]

Walkup,J. T.; Albano,A. M.; Piacentini,J.; Birmaher,B.; Compton,S. N.; Sherrill,J. T.; Ginsburg,G. S.; Rynn,M. A.; McCracken,J.; Waslick,B.; Iyengar,S.; March,J. S.; Kendall,P. C.. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. The New England journal of medicine 2008;359(26):2753-2766. [DOI: 10.1056/NEJMoa0804633 [doi]]

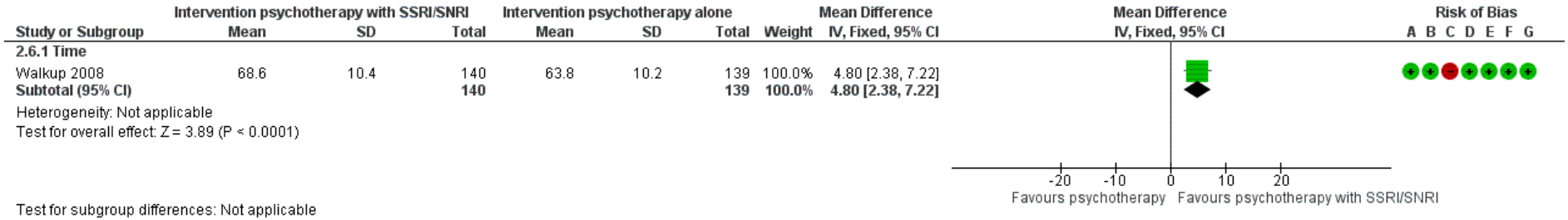
Data and analyses

2 psychotherapy with SSRI/SNRI vs psychotherapy alone

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Youth reported anxiety symptoms (EoT)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Parent reported anxiety symptoms (EoT)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 Youth reported anxiety symptoms (longest FU, at least 3 months)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.4 Parent reported anxiety symptoms (longest FU, at least 3 months)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.5 Youth reported functioning (EoT)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.6 Observer reported functioning (EoT)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.6.1 Time	1	279	Mean Difference (IV, Fixed, 95% CI)	4.80 [2.38, 7.22]
2.7 Remission of primary anxiety diagnosis (EoT)	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.7.1 Time	1	279	Risk Ratio (IV, Fixed, 95% CI)	1.49 [1.20, 1.84]
2.8 Remission of primary anxiety diagnosis (longest FU, 6 years)	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.8.1 Time	1	161	Risk Ratio (IV, Fixed, 95% CI)	0.87 [0.63, 1.20]
2.9 Remission of primary anxiety diagnosis (6 month FU)	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.9.1 Time	1	273	Risk Ratio (IV, Fixed, 95% CI)	1.46 [1.20, 1.78]
2.10 Number that discontinued treatment or control (EoT)	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.10.1 Time	1	279	Risk Ratio (IV, Fixed, 95% CI)	2.15 [0.84, 5.50]
2.11 Combined youth and observer reported functioning (EoT)	0		Risk Ratio (IV, Fixed, 95% CI)	No totals
2.12 Suicidal ideation (EoT)	1	279	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.29, 3.35]
2.13 Suicide attempt (EoT)	1	279	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.14 Serious adverse events (EoT)	1	279	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.12, 72.50]

Figures

Figure 1 (Analysis 2.6)

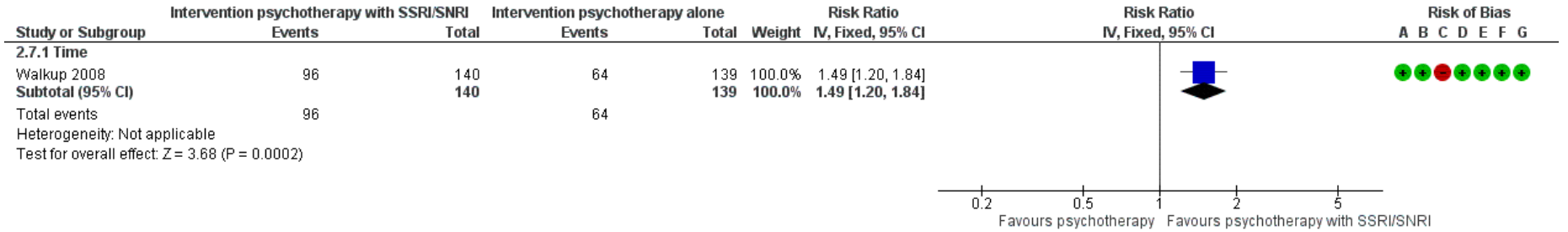


Test for subgroup differences: Not applicable

Risk of bias legend
(**A**) Sequence Generation
(**B**) Allocation concealment
(**C**) Blinding of participants and personnel
(**D**) Blinding of outcome assessors
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.6 Observer reported functioning (EoT).

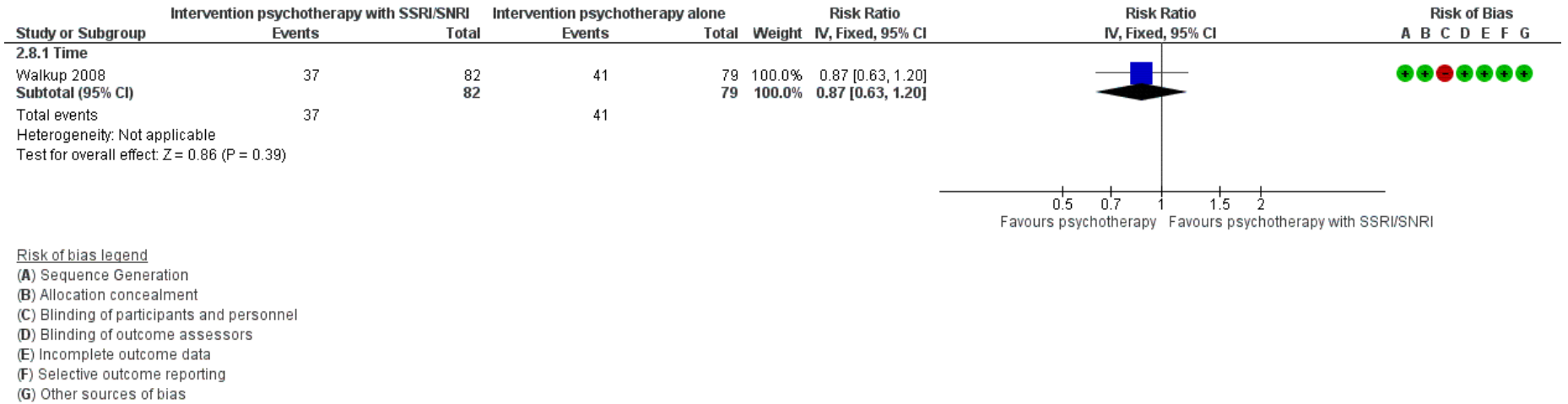
Figure 2 (Analysis 2.7)



Risk of bias legend
(**A**) Sequence Generation
(**B**) Allocation concealment
(**C**) Blinding of participants and personnel
(**D**) Blinding of outcome assessors
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.7 Remission of primary anxiety diagnosis (EoT).

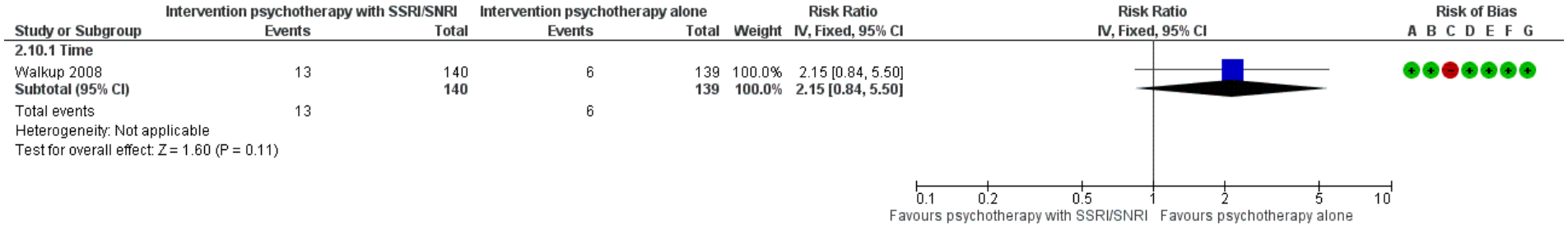
Figure 3 (Analysis 2.8)



Risk of bias legend
(**A**) Sequence Generation
(**B**) Allocation concealment
(**C**) Blinding of participants and personnel
(**D**) Blinding of outcome assessors
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.8 Remission of primary anxiety diagnosis (longest FU, 6 years).

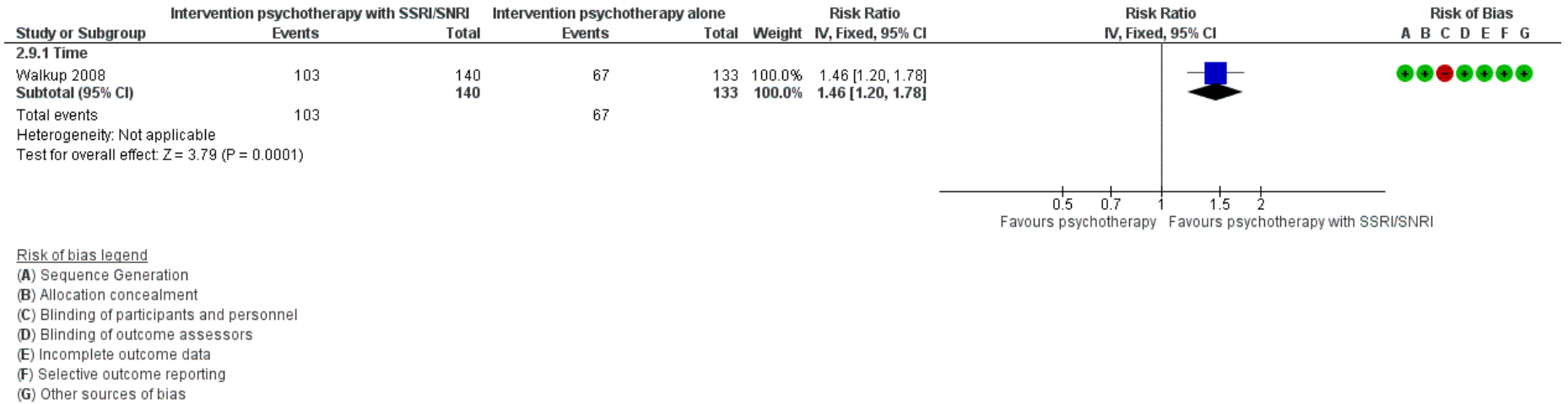
Figure 4 (Analysis 2.10)



Risk of bias legend
(**A**) Sequence Generation
(**B**) Allocation concealment
(**C**) Blinding of participants and personnel
(**D**) Blinding of outcome assessors
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.10 Number that discontinued treatment or control (EoT).

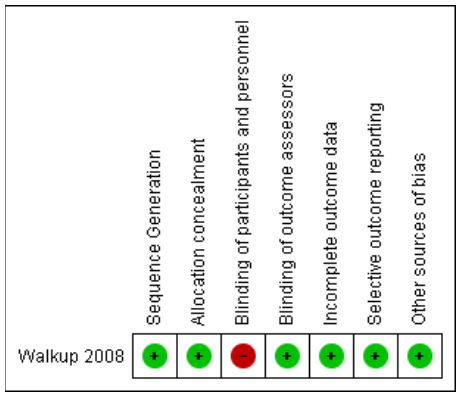
Figure 5 (Analysis 2.9)



Risk of bias legend
(**A**) Sequence Generation
(**B**) Allocation concealment
(**C**) Blinding of participants and personnel
(**D**) Blinding of outcome assessors
(**E**) Incomplete outcome data
(**F**) Selective outcome reporting
(**G**) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.9 Remission of primary anxiety diagnosis (6 month FU).

Figure 6

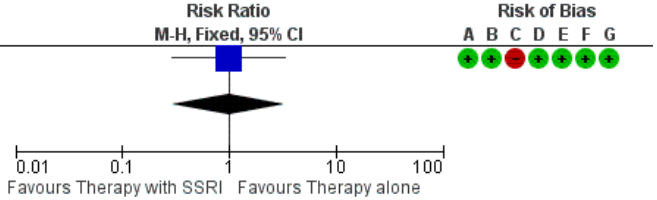


Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 7 (Analysis 2.12)

Study or Subgroup	Intervention psychotherapy with SSRI/SNRI Events	Total	Intervention psychotherapy alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Walkup 2008	5	140	5	139	100.0%	0.99 [0.29, 3.35]
Total (95% CI)		**140**		**139**	**100.0%**	**0.99 [0.29, 3.35]**
Total events	5		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



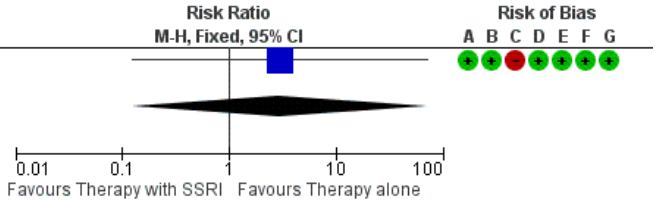
Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.12 Suicidal ideation (EoT).

Figure 8 (Analysis 2.14)

Study or Subgroup	Intervention psychotherapy with SSRI/SNRI Events	Total	Intervention psychotherapy alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Walkup 2008	1	140	0	139	100.0%	2.98 [0.12, 72.50]
Total (95% CI)		**140**		**139**	**100.0%**	**2.98 [0.12, 72.50]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 2 psychotherapy with SSRI/SNRI vs psychotherapy alone, outcome: 2.14 Serious adverse events (EoT).