Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents (Review)

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ABSTRACT

Background
Depressive disorders are common in young people and are associated with significant negative impacts. Selective serotonin reuptake inhibitors (SSRIs) are often used, however, evidence of their effectiveness in children and adolescents is not clear. Furthermore, there have been warnings against their use in this population due to concerns about increased risk of suicidal ideation and behaviour.

Objectives
To determine the efficacy and adverse outcomes, including definitive suicidal behaviour and suicidal ideation, of SSRIs compared to placebo in the treatment of depressive disorders in children and adolescents.

Search strategy
We searched the CCDAN Trials Register, MEDLINE, PSYCHINFO and CENTRAL. Reference lists were checked, letters were sent to key researchers and internet databases searched.

Selection criteria
We included published and unpublished randomised controlled trials.

Data collection and analysis
Two or three review authors selected the trials, assessed the quality and extracted trial and outcome data. We used a fixed-effect meta-analysis. The relative risk was used to summarise dichotomous outcomes and the mean difference to summarise continuous measures.

Main results
Twelve trials were eligible for inclusion, with ten providing usable data. At 8-12 weeks, there was evidence that children and adolescents 'responded' to treatment with SSRIs (RR 1.28, 95% CI 1.17 to 1.41). There was also evidence of an increased risk of suicidal ideation and behaviour for those prescribed SSRIs (RR 1.80, 95% CI 1.19 to 2.72). Fluoxetine was the only SSRI where there was consistent evidence from three trials that it was effective in reducing depression symptoms in both children and adolescents (CDRS-R treatment effect -5.63, 95% CI -7.38 to -3.88), and 'response' to treatment (RR 1.86, 95% CI 1.49 to 2.32). Where rates of adverse events were reported, this was higher for those prescribed SSRIs.

Authors' conclusions
Caution is required to interpret the results. First, there were methodological issues, including high attrition, issues regarding measurement instruments and clinical usefulness of outcomes, often variously defined across trials. Second, patients seen in clinical practice are likely to be more unwell, and at greater risk of suicide, compared to those in the trials, and it is unclear how this group would respond to SSRIs. This needs to be considered, along with the evidence of an increased risk of suicide related outcomes in those treated with SSRIs. It is unclear what the effect of SSRIs is on suicide completion. While untreated depression is associated with the risk of completed suicide and impacts on functioning, it is unclear whether SSRIs would modify this risk in a clinically meaningful way.

PLAIN LANGUAGE SUMMARY

Selective serotonin reuptake inhibitors (new generation antidepressants) for depressive disorders in children and adolescents

Depressive disorders are common in young people and have significant negative impacts. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for the treatment of depressive disorder in children and adolescents. The review of 12 trials highlighted limitations with the data, making it difficult to answer questions about the effectiveness and safety of SSRIs in clinical practice. Overall, there was evidence of greater reduction in depressive symptoms to a predetermined level deemed a "response" on SSRI compared to placebo. However, response was variously defined across trials making interpretation of this outcome difficult. Fluoxetine was the only SSRI where there was consistent evidence from three trials showing that it was effective in reducing symptoms of depressive disorder in both children and adolescents. Those receiving fluoxetine had a greater improvement, scoring on average 5.63 lower on the Children's Depression Rating Scale-Revised (CDRS-R) scale (range 17-113) than those on placebo. It is unclear whether this small difference is a meaningful outcome for children and adolescents with depressive disorders. Nor is it apparent how children and adolescents with co-morbid conditions and at risk of suicide would respond to SSRIs, given this group were largely excluded from the trials.

There is evidence that those prescribed SSRIs are at an increased risk of suicidal ideation and attempts (RR 1.80, 95% CI 1.19 to 2.72) consistent with a number of similar reviews in the area. Additionally, there was an increased risk of other adverse events. It is unclear how this relates to the risk of suicide completion. The trials were not designed to measure any of the suicide related outcomes adequately. At the same time, untreated depression is associated with the risk of completed suicide and impacts on academic and social functioning, however, it is not clear whether treatment with an SSRI will modify this risk in a clinically meaningful way for children and young people.

Clinicians need to provide accurate information to children and adolescents and their families about the uncertainties regarding the benefits and risks of SSRI medication for depressive disorders.

BACKGROUND

Depressive disorders are common in young people, with rates increasing significantly from middle to late adolescence (Kaufman 2001; Pine 1998). A recent meta-analysis of prevalence estimates of depressive disorder (defined as any depressive disorder, major depressive episode or major depressive disorder) in children and adolescents born between 1965 and 1996 showed prevalence estimates of 2.8% (SE 0.5%) for children, and 5.7% (SE 0.3%) for adolescents (girls 5.9% SE 0.3%; boys 4.6% SE 0.3%) (Costello 2006). Prevalence estimates were higher in studies with a six-month time frame compared to a three-month time frame, with no difference between six-month and 12-month prevalence estimates. Life-time estimates range between 15 and 20% (Birmaher 1996). Incidence rates (rate of new diagnoses during a particular time period) range from 3.3% to 7.8% over a year for MDD (Garrison 1997, Lewinsohn 1998).

The core features of depressive disorders are similar in children and adolescents and in adults (Carlson 1988; Marttunen 1998). The DSM includes criteria changes for children and adolescents such as the presence of irritability as an alternative to a depressed mood for this age group (Angold 1988; Essau 1999). Generally, anhedonia and psychomotor retardation are less common in the younger age group where clinical phenotypes can be indistinct with presentations including an admixture of anxiety, depressive and somatic symptoms (Axelson 2001;Rivas-Vasquez 2004. Low self-esteem, concentration and thinking problems and behaviour difficulties are more frequent (Carlson 1988). In adolescents the presentation of a depressive disorder may include substance abuse, antisocial behaviour, social withdrawal and academic failure (Masi 1998) with suicide attempts and ideation also common in adolescents (Marttunen 1998).

Around 50% of children and adolescents remain clinically depressed at 12 months, and 20 to 40% at 24 months (Birmaher 1996; Harrington 2001; Kovacs 1984). Around 30% of cases have recurrences within 5 years, and many of these develop episodes into adult life (Fombonne 2001a; Fombonne 2001b; Lewinsohn 1998, Weissman 1999). In the longer term, those children and young people who develop a recurrent or chronic disorder extending into adulthood are likely to suffer considerable disability and impairment, high rates of co-morbid disorders with poor academic functioning, difficulties in peer and family relationships, and increases in substance use and attempted and completed suicide (Brent 2002; Ebmeier 2006; Fleming 1993; Harrington 1990; Lewinsohn 1998; NHMRC 1997; Rao 1995). The publication of The Global Burden of Disease (Murray 1996) included adolescents aged 15 to 18 years and showed depression as the fourth most important disease in the estimation of disease burden. Moreover, subthreshold syndromes are common with 10 to 30% of young people experiencing depressive symptoms (Bond 2005; Flament 2001; Lewinsohn 1998), which are also associated with significant impairment, co-morbidity, and an increased risk of future depressive disorders (Judd 1996; Gotlib 1995; Lewinsohn 2003; Lewinsohn 2004; Sadek 2000; Solomon 2001).

Overall there are relatively few long term studies on depressive disorders in children and adolescents and despite what is known about its prevalence and impacts, relatively little is known about treatment or its impact on prognosis (NICE 2005). While a range of psychotherapies are effective (NICE 2005), adolescents response to psychotherapies may be weaker than adults (Cuijpers 2005; Gloaguen 1998; Weisz 2006) and overall more research is required (NICE 2005). Tricyclic antidepressants (TCAs) have not been shown to be effective in young people (Hazell 2002; Weller 2000). Selective serotonin reuptake inhibitors (SSRIs), a newer antidepressant, have been increasingly used (Vitiello 2006) with initial studies showing they were well tolerated (Brent 2002; Cooper 1988; Michael 2002; Weller 2000). However, concerns about the increased risk of suicide and suicide attempt on SSRIs have been raised, first in 2003 (Healy 2003). The Committee on Safety of Medicines, Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK (CSM 2004), and the European Medicines Agency (EMEA 2005), and The Food and Drug Advisory Administration (FDA 2004), have cautioned practitioners in the use of SSRIs in children and adolescents, including an FDA 'black box' warning label issued September 14, 2004 (FDA 2004). Meta-analyses examining the risks of suicide-related behaviour and suicidal ideation combined (Hammand 2006) or separately (Dubicka 2006) have shown a consistent and modest increased risk on SSRIs compared to placebo.

The American Academy of Child and Adolescent Psychiatrists, in response to the initial black box warnings, expressed a concern about a stand that will deprive young people of effective treatment for a condition that carries with it considerable morbidity and mortality (Brent 2004; Findling 2004). Similarly, reviews examining the risks and benefits of SSRIs consistently highlight the potentially serious consequences of untreated depression in children and adolescents. These arguments suppose that SSRIs provide an effective treatment option. However, only modest treatment benefits have been shown in these reviews, and the effectiveness of SSRIs has been contested in adults (Moncrieff 2005) and young people (Jureidini 2004). This review attempts to investigate issues of effectiveness and risk for children and adolescents treated with SSRIs for depressive disorder.

OBJECTIVES

1. To determine whether SSRIs are more effective than placebo in the treatment of depression in children and adolescents
2. To determine if the effectiveness of SSRIs differs between children and adolescents

A third objective was added following publication of the protocol. Given the concern and publicity over the potential increase in suicide risk for children and adolescents on SSRIs, and related, adverse outcomes generally, we felt that it was important that this should be a stated objective of the review. Thus the third objective of the review was:

3. To determine whether there is an increased risk of adverse outcomes and suicide-related outcomes (including suicide-related behaviour and suicidal ideation as defined in the FDA review) in children and adolescents treated with an SSRI.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Published (including internet publication) and unpublished randomised controlled trials were included in the investigation of efficacy of SSRIs in children and adolescents. Information on adverse effects from other types of studies were not included in the review. Although no language restrictions were applied, only English language publications were located.

Types of participants

Children and adolescents aged 6-18 years old, both in and outpatients, who were diagnosed by a clinician and met DSM or ICD criteria for a primary diagnosis of depressive disorder (only studies on major depressive disorder were located) were included.

Despite evidence of high prevalence of less severe depressive disorders, and subsyndromal depressive disorders, there were no trials of children or adolescents with dysthymia, depressive disorder not otherwise specified. Neither were there trials where symptom severity on a particular depression rating scale alone was used as a criterion for treatment or of subsyndromal depression. These trials will be included in updates if located, but as they will include participants that could be considered a different population from those diagnosed by a clinician, they will be included as a subgroup for analysis.

Trials where both adults and children/adolescents were treated would have been included in the review if data on the children/adolescents could be extracted, but no such trials were located.

Trials that included participants with co-morbid conditions as well as depressive disorder and who met other inclusion criteria would have been included and a separate analysis would have been done on the efficacy of SSRIs for those with only depressive disorder and those with a depressive disorder and co-morbid condition, but no trials presented data separately by co-morbidity status.

Trials of children and adolescents with an intellectual quotient (IQ) of less than 70, organic brain injury or serious medical condition were excluded.

Types of intervention

Trials that included treatment arms comparing the effectiveness of a SSRI with a placebo were included. SSRI drugs could include

fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram and sertraline.

Trials where SSRIs were used in combination with another pharmacological intervention or psychological intervention exclusively were excluded. The Treatment for Adolescents with Depression study (TADS) includes four comparison groups, a SSRI group, a cognitive behavioural group (CBT), a combined SSRI and CBT group and a placebo group. Data from only the SSRI and placebo groups was extracted.

Types of outcome measures

Primary Outcomes

1. Depressive disorder according to DSM or ICD criteria
2. Suicide completion

Secondary outcomes

a. Depression symptoms (on standardised, validated, reliable depression rating scales)
b. Suicide related outcomes (including suicide-related behaviour and suicidal ideation as defined in the FDA review)
c. Functioning, Children's Global Assessment Scale (CGAS) (academic, cognitive, social (including friends and family))
d. Completion of trial protocol (as a proxy measure for treatment acceptability)
e. Adverse outcomes

Where different depressive disorder symptom severity rating scales were used, for the purpose of pooling results, we chose the single best available outcome measure for each trial according to the hierarchy devised by Hazell and colleagues (Hazell 2002) based on Petti's work (Petti 1985). We determined the order of selection according to the measures' ratings on five criteria: appropriateness to children and adolescents; reliability; construct validity; agreement with clinical interview; track record in psychopharmacological research (Hazell 2002; Petti 1985)

The hierarchy of selection for analysis, and the number of criteria met by each rating scale (in parentheses), were as follows:
1. Structured or semi-structured clinical diagnostic interviews such as the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS), using child report in the first instance, or parent report if child report is unavailable (5)
2. Children's Depression Rating Scale (CDRS) (4)
3. Bellevue Index of Depression (BID) (3)
4. Children's Depression Inventory (CDI) (3)
5. Hamilton Depression Rating Scale (HAM-D) (3)
6. Depressive Adjective Checklist (DACL) (2)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Depression, Anxiety and Neurosis Group methods used in reviews.

For more information see: Depression, Anxiety and Neurosis Collaborative Review Group search strategy

Electronic databases

The register of trials kept by the CCDAN group was searched by the Trials Search Co-ordinator using the following terms:
Age Group = (Children or Adolescent) and Intervention = ("Selective Serotonin Reuptake Inhibitors" or Alaproclate or Citalopram or Escitalopram or Femoxetine or Fluoxetine or Fluvoxamine or Paroxetine or Sertraline) and Diagnosis =(Depress* or Dysthymi*)

A search of the following electronic databases was undertaken:

- MEDLINE (1966-October 2005)
- PSYCINFO (1886-October 2005)
- CENTRAL in *The Cochrane Library*, Issue 2, 2004

The following search terms were used in MEDLINE (see additional tables for search strategy for other databases, Table 01) till October 2005:
1. exp Serotonin Uptake Inhibitors/
2. (serotonin adj (uptake or reuptake or re-uptake)).mp
3. ssri$.mp
4. alaproclat$ or citalopram or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$
5. or/1-4
6. clinical trial.pt
7. (random$ or rct$).mp
8. ((singl$ or doubl$) adj5 (blind$ or mask$)).mp
9. PLACEBOS/
10. placebo$.mp
11. Cross-Over Studies/
12. (crossover$ or cross over$ or cross-over$).mp
13.or/6-12
14.5 and 13
15. limit 14 to all child<0-18>

Internet databases were searched including the National Research Register (http://www.update-software.com/National/nrr-frame.html), Clinical Trials (http://www.clincaltrials.gov/ct/gui/c/r) and Current Controlled Trials (http://www.controlled-trials.com). Additionally, the trial databases of pharmaceutical companies were searched.

Reference lists

The reference lists of articles and other reviews retrieved in the search were searched.

Handsearches

Handsearching of specialist journals: the main journals most likely to contain trials in this area were identified using MEDLINE and content experts in the area. They were handsearched if they had not already been handsearched and were locally available.

Conference abstracts
Conference abstracts for the American Academy of Child and Adolescent Psychiatry were searched.

Personal Communication
To ensure as many as possible RCTs and CCTs were identified, the authors of the included trials and other experts in the field were consulted to find out if they knew of any published or unpublished RCTs/ CCTs in the area, that were not yet identified.

METHODS OF THE REVIEW

Selection of Studies
The selection of trials for inclusion in the review was performed independently by two review authors (SH and MP) after employing the search strategy described previously. Where a title or abstract appeared to describe a trial eligible for inclusion, we obtained the full article and inspected it to assess relevance to this review based on the inclusion criteria. We have reported the reasons for exclusion of trials in the 'Characteristics of Excluded Studies' tables.

Assessment of Risk of Bias
We assessed the risk of bias in the included trials using quality ratings devised by Moncrieff and colleagues (Moncrieff 2001). All assessments of the quality of trials were performed independently by reviewers (SH, PS and AW). Discrepancies were resolved by a fourth review author (JM). In addition, we assessed risk of bias using a proposed set of criteria presented at the Cochrane Colloquium, Melbourne 2005. The assessment is presented in an additional table (Table 02).

We did not use a formal score; rather items considered important sources of bias were reported in the Table of Included Studies and in Table 02.

Data Management
Information on each trial, including quality characteristics and details regarding participants, interventions, comparisons, and outcomes were independently extracted by review authors (SH, PS and AW) and discrepancies were resolved by a fourth review author (MP) (Table of Included Studies). This description of the included trials provides a context for discussing the reliability, internal and external validity of results.

Outcome data for the primary and secondary outcomes were independently extracted by two review authors (SH and PA) and discrepancies were resolved by a third review author (JM).

We sought additional data from the principal authors of trials that appeared to meet the eligibility criteria when aspects of methodology were unclear, or where the data were missing, or were in a form unsuitable for meta-analysis. We contacted pharmaceutical companies or searched their web sites for additional information or data where the investigators did not have access to this.

Post hoc, we decided to extract suicide related outcomes from the Medicines and Healthcare Products Regulatory Agency (MHRA) report rather than from the individual trial reports retrieved in the search for the current review. The MHRA has produced a web based report (www.mhra.gov.uk/) that summarises the results of the SSRI trials (except two trials Wagner 2006; TADS 2004). They have also produced two additional reports, one on suicide related outcomes and one on trial characteristics (Hammad 2004; Dubitsky 2004). The report of suicide related outcomes includes outcomes for 25 SSRI trials for a range of disorders in children and adolescents. Suicide related outcomes were defined after a careful process of definition from an expert panel, where all suicide related adverse events (AEs) identified by the sponsors of SSRI trials, all serious AEs and all accidental injuries were independently blindly adjudicated by a group of ten suicidology experts. These experts were assembled by Columbia University and led by Dr Kelly Posner. Suicide related outcomes included 'definitive suicidal behaviour/ideation' (pg 8, Hammad 2004) and where more than one event was recorded for an individual, the most severe event was used. There was some discrepancy between the sponsors' classifications and the expert panel classification (with 22 new events added, and 26 old events removed). Overall there were no completed suicides in any of the trials. The results were pooled using meta-analysis and it was concluded that there was an increased suicide risk when groups were combined (although no individual trial showed statistically significant risks). The report highlighted the important point that none of these trials had adequate power for safety analysis.

Using the definition developed by the MHRA expert panel, we extracted suicide related outcomes from trials of depressive disorders from the MHRA report (Hammad 2004) for inclusion in the meta-analysis in this review. Using the data from the MHRA report allowed us to overcome inconsistent reporting of these outcomes across trial reports. Given the small number of events in the individual trials, and that there is no definitive evidence about a difference in effectiveness or safety profile for different compounds of SSRIs in adults (Cipriani 2005), a decision was made post hoc to pool the data across drug type to estimate the risk of a suicide related event for those receiving any SSRI.

For each drug, the relative risk of experiencing adverse events was estimated (where a count of any adverse event; was reported). However, given inconsistencies in data collection of these events between RCTs, the relative risks may not be comparable between drugs (Table 03).

Data Analysis
Statistical analysis was undertaken in accordance with the guidelines for statistical analysis in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Summary

statistics were pooled statistically using the meta-analytic methods implemented in Review Manager (RevMan 4.2).

For dichotomous outcomes, such as response rates and adverse effects, results from each trial were pooled using a fixed-effect meta-analysis (Mantel 1959) and expressed as Risk Ratios (RR) with 95% confidence intervals. For meta-analyses where there were adequate numbers of trials (e.g. all SSRIs versus placebo), random-effects models (DerSimonian 1986) were also fitted. When the pooled summary statistic differed clinically between models, this was reported. A post hoc decision was made not to calculate number needed to treat to benefit (NNTB) and number needed to treat to harm (NNTH) for several reasons. First, NNTB and NNTH are dependent on the prevalence of the condition in the population. Given the exclusion criteria applied in these trials, the prevalence observed in the placebo group is unlikely to be similar to that observed in the population presenting for treatment. The calculated NNTB and NNTH could therefore provide misleading results. Second, as is mentioned in the review, the outcome measure of 'response' is extremely difficult to interpret since it is defined variously between RCTs; and occasionally it is unclear if it is of clinical importance. Calculation of NNTB using this outcome would place undue importance on the result.

For continuous outcomes, such as depression symptom severity, the majority of trials reported estimates of treatment effects from multiple linear regression models. These models adjusted for varying factors such as age, sex, and baseline of the outcome. Treatment estimates from these trials were pooled using fixed-effect (inverse variance) meta-analysis.

P-values and confidence intervals for treatment effect were converted to standard errors and entered into RevMan using the generic inverse variance. When data was not available, authors were contacted (Characteristics of included studies).

We assessed heterogeneity of intervention estimates by visually inspecting the scatter on the forest plots and by the I^2 statistic (Higgins 2003).

We investigated the potential for publication bias using two funnel plots for the outcomes 'response' and suicide related behaviour. These outcomes were chosen since they were available for the majority of included trials.

There is evidence that children and adolescents may respond differently to pharmacological intervention e.g. oral tricyclic antidepressants versus placebo significantly reduce symptoms in adolescents but not in children (Hazell 2002). For this reason we conducted subgroup analyses by age, where children and adolescents were defined as those aged approximately 6-12 and 13-18 years respectively (Characteristics of Included Studies). For the majority of trials, estimates of treatment effect were presented for children and adolescents separately. When this did not occur, we created another subgroup which contained both children and adolescents.

We had planned a priori to undertake sub-group analyses based on depressive disorder (major versus dysthymic disorder and 'double depression'), sex and co-morbidity. However, due to limited data, analyses on these subgroups were not carried out.

Pre planned sensitivity analyses based on pharmaceutical funding and inclusion criteria (clinical diagnosis versus depression rating scales) were not carried out since the majority of trials were pharmaceutically funded, and no trials used rating scales as inclusion criteria. A pre-planned sensitivity analysis based on attrition rates was not undertaken since there were reasonably high attrition rates in all included RCTs (19% to 38% Table 04). Therefore, for all trials there was potential for bias in estimates of treatment effect. Deciding on a cut-off that would measure the degree of this bias would have been an arbitrary decision. Additionally, a cut-off would not have taken into account the potential disparity in attrition rates between treatment arms which could potentially be more predictive of bias than overall attrition rate.

All trials used the Last Observation Carried Forward (LOCF) method of data imputation, that is, the last observed value for a participant lost to follow-up is assigned as the follow-up value. Some trials also reported estimates of treatment effect from observed case (OC) data. Estimates of treatment effect calculated from both datasets can be either inflated or deflated when there is attrition. As a post-hoc analysis, where possible, we compared estimates of treatment effect calculated from pooling: firstly, estimates of treatment effect calculated from data sets where LOCF had been used; and secondly, estimates of treatment effect calculated from data sets with OC data.

Data that could not be pooled statistically, such as information on co-morbidity, were presented in tables and described in the results and discussion section.

Timeline

The update of the review will be submitted for editorial review within two years of publication of the review.

DESCRIPTION OF STUDIES

Of those studies retrieved in the search, 12 were eligible for inclusion. From 10 of these, data could be extracted and pooled in one or more meta-analyses. The web-based report of the Medicines and Healthcare Product Regulatory Agency (MHRA), summarising the majority of clinical trials on SSRIs for major depressive disorder in children and adolescents, was located in the search. Additional data was sought from investigators of the trials, although in many cases the pharmaceutical company who funded the trial had the only access to these data. SmithKline·Beecham had published their three trials on paroxetine (Keller 2001; Milin 2004; Paroxetine Study 3) on the web (http://www.gsk.com/media/paroxetine.htm). Eli Lilly provided additional data for a trial on fluoxetine

(Emslie 2002). Several trials were initially unpublished e.g. the trial on escitalopram was available only as a brief report on the Forest Pharmaceutical website, the Milin trial was unpublished, and one paroxetine trial was only available on the MHRA website. Subsequent to the initial search, the trial on Escitalopram was published by Wagner and her colleagues and the additional information from this trial report was included (Wagner 2006). The Milin trial was published by Beard and colleagues (2006) and the paroxetine 3 study was published by Emslie and colleagues (2006). Again, subsequent to the search, one trial previously only reported in the MHRA web-based report was published (Von Knorring 2006). However, the published report provided little additional information to the MHRA report and did not present any data that could be used in meta-analysis (Von Knorring 2006). One published trial report included the results of two trials (Wagner Study 1&2), with data for the individual trials only available from the MHRA report (Wagner Study 1&2). The trial by Simeon was discontinued early due to slow enrolment with some information about the trial from the written report and some from the MHRA report (Dubitsky 2004).

The trials were often multi centre, and included data from many countries (Denmark, Estonia, Germany, Norway, Sweden, Switzerland, Argentina, Belgium, Holland, Italy, Mexico, South Africa, Spain, United Arab Emirates, the UK, India, Costa Rica, USA, Canada). The trials all compared SSRIs to a placebo or included treatment arms with these comparisons (TADS). There were three trials of paroxetine (Keller 2001; Milin 2004; Paroxetine Study 3), four trials of fluoxetine (Emslie 1997; Emslie 2002; Simeon 1990; TADS 2004), two trials of citalopram (Von Knorring 2006; Wagner 2004), one of escitalopram oxalate (the therapeutically active component of citalopram) (Wagner 2006), and two trials of sertraline (Wagner Study 1&2).

Participants

Most of the trials, except those on fluoxetine, gave little information on their recruitment strategies. Of those that did, both Emslie 2002 and TADS 2004 used media advertising. Emslie 1997 stated that media recruitment was not used (Characteristics of Included Studies).

There were five trials in adolescents (Von Knorring 2006; Keller 2001; Milin 2004; Simeon 1990TADS 2004) with an age range of 12 or 13 to 17 or 18, and seven in children and adolescents (Emslie 1997; Emslie 2002; Wagner 2006; Paroxetine Study 3; Wagner 2004; Wagner Study 1&2) with a lower age limit of between 6-8 years. The mean age ranged from 14.6 -16.0 years and 11.9 - 12.7 years in the adolescent, and child and adolescent, trials respectively (Characteristics of Included Studies).

There were similar proportions of females and males in five trials (Emslie 1997, Emslie 2002, Simeon 1990, Wagner 2006, and Paroxetine Study 3) and nearly twice as many females in two trials (Keller 2001 and Milin 2004). In Wagner 2004 and Wagner Study 1&2 (two trials reported together), there was imbalance in the proportion of females between groups, with a greater proportion of females in the treatment group. The TADS 2004 study did not provide information on sex by treatment arm. One study provided no information on sex (Von Knorring 2006). There was no imbalance in sex between groups in the fluoxetine trials (Characteristics of Included Studies).

All trials were of major depressive disorder and all except Von Knorring 2006 stated that diagnoses were based on a structured clinical interview such as the K-SADS-P & L. Three trials based diagnoses on DSM-III or DSM-III-R criteria (Emslie 1997; Keller 2001; Simeon 1990) and the remainder on DSM-IV criteria. A final trial (Von Knorring 2006), in contrast to all the other trials, used only a five minute clinical interview with parents. In addition to a diagnostic interview, the majority of trials (except Paroxetine Study 3) used a cut-off score on a measure of depressive disorder symptom severity to establish eligibility. Emslie 1997; Emslie 2002; Wagner 2006;and Wagner 2004 used a cut-off of greater than 40 on the CDRS-R, while for TADS 2004 and Wagner Study 1&2 the cut-off was 45. In Von Knorring 2006 the Childrens Depression Inventory (CDI) was used with cut-offs greater than 21 and 16 for girls and boys respectively. A score greater than 12 or 20 on the HAM-D scale was used in Keller 2001 and Simeon 1990 respectively, and a score greater than 16 on the MADRS scale was used in Milin 2004. Some trials also used a measure of functioning to confirm diagnosis (Von Knorring 2006; Keller 2001; Milin 2004; Wagner Study 1&2).

Some trials included a screening process that was undertaken over a period of 1-3 weeks (Emslie 1997; Emslie 2002; Keller 2001; Paroxetine Study 3; TADS 2004; Wagner Study 1&2). A report by the MHRA described the process as more extensive for three of these trials (Emslie 1997; Emslie 2002; Keller 2001) but did not describe what this meant. However, further investigation revealed a screening process that included up to three independent diagnostic interviews, taking place over a period of up to three weeks. In six trials all participants were treated with placebo for a lead in period and those whose depressive disorder improved during this time were excluded (Emslie 1997; Emslie 2002; Milin 2004; Simeon 1990; Wagner 2004; Wagner 2006).

Authors of all reports, except one (Simeon 1990) describe depressive disorder symptom severity at baseline for the treatment and placebo groups. Mean severity scores at baseline from the individual trials range from 54.5 to 65.5 on the CDRS-R (range 17 - 113) and from 25.9 to 32.5 on the K-SADS 9 item depression score (range 9 - 56) (see Characteristics of Included Studies). For all trials, there was no clinically important imbalance between treatment groups in depressive disorder symptom severity at baseline.

In eight of the trials data was available on co-morbid conditions as well as major depressive disorder (Emslie 1997; Emslie 2002; Keller 2001; Milin 2004; Paroxetine Study 3; TADS 2004; Wagner 2004; Wagner 2006) (see Table 05). Comorbidity may affect clinical outcome (Birmaher 1996; Kovacs 1989). Some trials

(Keller 2001 and TADS 2004) presented data on the proportion of young people having any co-morbid condition. In other trials, the percentage of young people experiencing the different types of co-morbid conditions was presented. In these trials it was shown that anxiety disorders were the most common co-morbid conditions, followed by dysthymic disorders and disruptive behaviour disorders (disruptive behaviour disorder, ODD/CD), and ADHD.

Some co-morbid disorders were excluded in a number of trials. In all trials exclusion criteria included psychotic features or disorder, and substance abuse or dependence. In all but three trials (Paroxetine Study 3; Simeon 1990; TADS 2004) anorexia nervosa and bulimia nervosa were excluded; in all but three trials (Emslie 1997; Emslie 2002; Simeon 1990) pervasive developmental disorder were excluded. Externalising disorders (disruptive behaviour disorder, ODD and CD) and ADHD were excluded in six trials (Von Knorring 2006; TADS 2004; Wagner 2004; Wagner Study 1&2; Wagner 2006). Participants who were considered at risk for suicide at baseline were specifically excluded in all but two trials (Von Knorring 2006; Emslie 1997) (Hammad 2004). Those who had made a previous suicide attempt were excluded in five trials (TADS 2004; Wagner 2004; Wagner Study 1&2; Wagner 2006) (Hammad 2004). There existed inconsistency between the MHRA report (Hammad 2004) and the trial reports regarding suicidal ideation as an exclusion criterion. The MHRA report (Hammad 2004) states that a history of suicidal ideation was not an exclusion criteria in any of the trials included in its report, however, the SmithKline Beecham on-line report of Milin 2004 states that those with serious suicidal ideation were excluded and Keller 2001 states those with serious suicidal ideation with intent or a specific plan were excluded. In many of the trials "suicide risk" was an exclusion criteria, however, there is no information on how this assessment was made nor on the criteria on which it was based. The MHRA carried out a stratified analysis based on history of suicide attempt or ideation to investigate if risk of suicide attempt or ideation for those receiving SSRIs varied by stratum. They concluded that there was no evidence of this (Hammad 2004).

Interventions

Half of the trials excluded those who had previously not responded to SSRI treatment (Emslie 2002; Paroxetine Study 3; TADS 2004; Wagner 2004; Wagner Study 1&2; Wagner 2006). Only two trials (Von Knorring 2006; Simeon 1990) stated that inpatients were included, although the MHRA report (Dubitsky 2004) states that Simeon 1990 only included outpatients.

The treatment period of the included trials was between 7 and 12 weeks. Efficacy measures were collected throughout the treatment period and at completion of the trial. Four trials (Emslie 1997; Emslie 2002; Keller 2001; Wagner 2004) described a continuation phase. Emslie 1997 stated that after the 8 weeks of acute treatment, treatment was not controlled and participants were followed up at 6 and 12 months. In a later report Emslie 2002 describes two additional phases, one for non-responders, and one for relapse prevention, both of which were blinded. Keller 2001 stated that at the end of acute treatment (8 weeks), responders continued on blinded treatment (paroxetine, imipramine or placebo) for a further six months and non-responders were tapered off medication and terminated from the study. Wagner 2004 stated that there was a 24 week open label extension study. With the exception of two trials (Emslie 1997; Emslie 2002), a flexible dosing scheme was used. One study included an additional comparison group receiving imipramine, as well as the placebo group (Keller 2001).

Outcomes

Remission of depressive disorder was the primary outcome of the review, however, few studies used diagnostic interviews to establish this. Where this outcome was published, it was defined by the trialists as a level of improvement in depression symptoms on clinician-rated scales. The scale and the cut-point used to define this level of improvement varied between trials. Response was reported in all trials, however, again, scale and the cut-point was variously defined between trials and usually, but not always, of a smaller magnitude compared to remission.

Commonly response was defined as a CGI score of 1 or 2 (Paroxetine Study 3; TADS 2004; Wagner 2006) or a decrease on the CDRS-R (30% - 50%) (Wagner, 2003, Emslie 1997; Emslie 2002) a decrease of 50% on the MADRS or change (the magnitude of which was not specified) on the K-SADS (Milin 2004), a score of 28 or less on the CDRS-R (Wagner 2004; Wagner 2006), a score of 8 on the HAM-D, or 50% reduction on the HAM-D (Keller 2001).

The definition of response in one of the citalopram studies (Wagner 2004) and in the escitalopram study (Wagner 2006) was equivalent to that of remission (CDRS-R = 28) in two of the fluoxetine trials (Emslie 1997; Emslie 2002). The other citalopram study (Von Knorring 2006) defined remission as a Montgomery Asperg Depression Rating Scale (Montgomery & Asberg, 1979) score less than 12. The paper publication of the sertraline studies (Wagner, 2003), did not include remission, however the MHRA reported this data using a definition of those who no longer met DSM-IV criteria for MDD. Given remission is in most cases a cut-point, different only in magnitude to response, it should be noted that these data are correlated and were not extracted or reported in this review, but are discussed to highlight how definition could potentially affect the outcome and as a result, the reporting of trials results

Depressive disorder symptom severity was measured in a variety of ways in the trials. Two primary measures were used: 1. The CDRS-R (Emslie 1997; Emslie 2002; Paroxetine Study 3; TADS 2004; Wagner 2004; Wagner Study 1&2; Wagner 2006); 2. K-SADS (Von Knorring 2006; Keller 2001; Milin 2004). The HAM-D was used in the Simeon trial.

Measures of function included the Global Assessment of Functioning (GAF) (Von Knorring 2006; Emslie 2002; Paroxetine Study

3), the Children's Global Assessment Scale (Emslie 1997; Milin 2004; TADS 2004; Wagner Study 1&2; Wagner 2006), and the Autonomous Functioning Checklist (Keller 2001). The CGI was also used in many trials.

Suicide related outcomes were classified and reported in various ways in each of the trials. As described in the methods section, a post hoc decision was made to use the data provided in an MHRA report (Hammad 2004), which was based on a re-analysis of outcomes reported in the trials by a team of experts in suicide related behaviours assembled by Columbia University.

Description of measures used in the trials

The Children's Depression Rating Scale (CDRS-R) assesses 17 symptom areas. The first 14 items are rated on the basis of responses to interview questions by the child or an adult informant who knows the child well and are rated for the past two weeks and currently. The remaining three symptom areas (depressed facial affect, listless speech and hypoactivity) are rated by the clinician on the basis of the child's non verbal behaviour in the room. Each symptom is graded on a 5 or 7 point scale. For items 1-14 the highest ratings from the child, parent or other caretaker are taken as the *item* scores. The total score, or CDRS-R score, is the sum of all 17 item scores and has a range of 17-113. In samples studied in the development of the scale (Poznanski 1996) mean CDRS-R T scores (standardised scores) were 71, 58 and 53 for those with a depressive disorder (based on DSM-III criteria), other psychiatric disorder (outpatient) and no disorder respectively. This scale is used widely, has adequate internal reliability, good test-retest reliability, good to excellent inter-rater reliability and is sensitive to treatment effects (Myers 2002).

The Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician-rated scale that assesses depressive disorder symptoms in the last week or the last three days. This scale is less commonly used compared to other depression rating scales. It consists of 10 items covering apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. Each of these items is scored between 0 and 6 based on severity. The possible range of scores is 0 to 60 with a higher score indicating more severe depression. This scale was specifically designed to assess treatment outcome, but its psychometric properties have not been specifically examined in adolescents (Brooks 2001).

The Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present Episode Version (K-SADS-P) depression module has nine items on an ordinal scale, four of which consist of two -three sub items. Each of the items or sub items is rated from zero to either four or six with higher numbers corresponding to greater severity. The score range is 9-56. The various items rated are for the last two weeks in order to enable diagnosis according to DSM-IV criteria. It has reasonable reliability but isn't often used to assess treatment outcome (Brooks 2001).

The Hamilton Psychiatric Rating Scale for Depression (HAM-D) consists of 17 multiple choice questions each of which is numerically scored on a scale of zero to two or four. The score can range from 0 to 42 with a higher score indicating more severe depression. The various items refer to depressive disorder severity over the last week. Reliability is reported as excellent with studies suggesting sensitivity to treatment effects although further research is required (Myers 2002).

The Clinical Global Impression of Improvement (CGI-I) is a clinician rated seven -point scale that assesses global improvement from baseline to the current state. The scale is:

1. very much improved
2. much improved
3. minimally improved
4. no change
5. minimally worse
6. much worse
7. very much worse

The Global Assessment of Functioning (GAF) measure is a clinician rated scale that assesses the patients current level of functioning. Scores range from 1 to 90 (90 indicates good functioning in all areas). There are few studies of its psychometric properties in child and adolescent populations, however, a recent review suggests it is likely to be reliable when used in research given the training and motivation of raters (Schorre 2004).

The Children's Global Assessment Scale (CGAS) measures a child's current social functioning and is completed by the clinician. The range is from 1- 100 with a score of 1-10 indicating a need for constant supervision and a 90 - 100 indicating superior functioning. The CGAS has adequate reliability and is sensitive to change (Myers 2002).

The Autonomous Functioning Checklist is completed by the parent, and assesses the child's autonomy in performing daily activities. It consists of 78 questions grouped into 4 categories; twenty-two questions on self and family care; 20 questions on management; 16 questions on recreational activities; and 20 questions on social and vocational activities. The first three categories are rated on an ordinal scale ranging from 0 ("does not do") to 4 ("does every time there is an opportunity"). While the last categories consist of "yes" (coded 1) and "no" (coded 0) questions. A total score and a sub score for each of the 4 categories are calculated, with higher values indicating a greater degree of autonomy. There has been little psychometric investigation of this measure.

METHODOLOGICAL QUALITY

The number of participants randomised in these trials was between 96 and 439. One study was discontinued early (Simeon 1990). The attrition rate for the 12 trials varied between 17% and 46% in the control groups and 17% and 40% in the intervention groups

(see Table 04). The disparity in attrition between treatment arms was of particular concern in the trials of fluoxetine (Table 04).

All authors stated that intention-to-treat analyses (ITT) had been undertaken. However, a full application of the intention-to-treat principle is only possible when complete outcome data are available for all randomised participants (Hollis 1999). Only two trials (Emslie 1997; TADS 2004) appear to include all patients randomised in their analyses. In the other trials, analyses are carried out on fewer patients than the number randomised. For the majority of trials, only those who received at least one dose of medication or placebo, or had at least one post baseline efficacy or safety evaluation were included in the analyses.

There were no full reports of allocation concealment in any of the included trials.

All trials were described as being "double blind" or of having the relevant treatment arms double-blind (TADS). In two trials (Emslie 1997; Emslie 2002) the description of blinding indicates that the SSRI and placebo medications were identical. There is little description of the blinding in three trials, so that it is unclear what "double blind" refers to (Von Knorring 2006; Simeon 1990; Wagner 2004; Wagner 2006). TADS 2004 states that there were independent evaluators who were also "blind". Emslie 1997 mentions that the pharmacy staff were blind. There were no reports on the success of blinding in any of the trials. The possibility of clinicians or patients guessing the nature of the intervention from side-effects was not discussed. Given that outcomes were based on ratings by participants and clinicians, this is an important omission.

There is some evidence of reporting bias in some of the trials, though this is difficult to assess in most trials, since it is not always clear whether a full report has been given. The trial report by Emslie 2002 emphasises CDRS-R scores and remission rates rather than response rate, even although response rate was the primary outcome identified in the methods section. Additionally, the cut-off used for remission rate differed from that stated in the methods section. Emslie 1997 reports outcomes at five weeks rather than at the completion of the trial. In a letter to the editor, Keller 2001 was criticised for changing the definition of response post data analysis to a cut-off that showed treatment effectiveness (Jureidini 2003). In response, Keller 2001 changed their claim of finding a significant effect to stating that the findings showed a strong signal for efficacy (Keller 2003; Jureidini 2004). The report by Wagner et al 2003 (Wagner Study 1&2) combines the results of two trials and reports the overall outcomes. Wagner 2006 emphasises post hoc subgroup analyses.

The funnel plot for 'response' was suggestive of publication bias. However, this was not the case for suicide related behaviour. Explanations of the observed funnel plot symmetry for 'response' include publication bias, poor methodological quality of the smaller studies, true heterogeneity, and chance. It is not possible to know which of these, or in combination, explain the observed asymmetry. However, potential contributors could be poor methodological quality (for example, 'response' variously defined between trials), and chance, given that there were relatively few trials. Given that asymmetry was not observed for suicide related behaviour we are less concerned about the potential of publication bias.

Most trials, with the exception of Emslie 1997, were pharmaceutically funded. The TADS 2004 study was funded by an NIMH contract but had an 'unrestricted educational grant from Eli Lily' (pg 531 of the 2003 publication).

Five trials assessed the extent of non-compliance (Von Knorring 2006; Emslie 1997; Milin 2004; Paroxetine Study 3; TADS 2004). This was assessed differently between the trials. For example, Von Knorring 2006 and Wagner 2004 used blood levels of citalopram in those receiving the treatment, while pill counts were used in several trials (Emslie 1997; Emslie 2002; Keller 2001; Milin 2004; Paroxetine Study 3; Wagner Study 1&2), supplemented by direct questioning in two studies (Emslie 1997; Emslie 2002). No information was provided in two studies TADS 2004; Wagner 2006). The MHRA report (Dubitsky 2004) provides a description of compliance for most of the trials.

RESULTS

SSRIs (as a class)

Efficacy Outcomes

No trial reported on depressive disorder as an outcome, and there were no mortality events in any trial. Therefore, only secondary outcomes (as defined in the protocol of the review) were reported. These were response and a continuous measure of depressive disorder symptom severity. The definition of response varied between trials, but measured some level of improvement on a depressive symptom rating scale.

Overall, based on response, there was a significant increase in the percentage of those who improved when being treated with an SSRI compared to those in the placebo group (RR 1.28, 95% CI 1.17 to 1.41). While heterogeneity was quite large for this outcome (I^2 = 57.5%), the majority of estimates were in the same direction, favouring treatment with an SSRI (Figure 06.01). Similar results were obtained from a random-effects analysis (RR 1.31, 95% CI 1.13 to 1.51). Two factors potentially contributing to the heterogeneity include the use of different compounds of SSRIs and different age groups in the included trials.

Suicide Related Outcomes (definitive suicide behaviour and suicidal ideation)

Overall, the risk of experiencing a suicide related outcome while being treated with an SSRI was 80% greater than if treated with a placebo (RR 1.80, 95% CI 1.19 to 2.72). The estimate of risk was increased, although not statistically so, for each SSRI (Figure 06.02). There was no evidence of heterogeneity (I^2 = 0%).

In the TADS 2004 study, suicidal ideation was measured using the Suicidal Ideation Questionnaire - Junior High School Version (SIQ-Jr). The trial report stated that there was consistent improvement in suicidal ideation scores in all four groups in this study. Compared to placebo, however, fluoxetine alone did not significantly reduce scores on this measure (p = 0.36) (pg. 814 of the 2004 publication), however, no treatment effect was presented. From the MHRA report, it was stated that Wagner 2004 showed that citalopram was superior to placebo in reducing suicidal ideation based on item 13 of the CDRS-R, however, it did not state if this was significant or provide an estimate of the effect. Likewise, the MHRA report stated that for Von Knorring 2006 citalopram showed a slighter greater improvement in suicidal ideation than placebo, based on item nine of the K-SADS-P. It was not stated if this was significant and an estimate of effect was not provided. Suicidal ideation was not stated to be measured using either an item from a depressive disorder symptom severity scale or a suicidal ideation scale in any other trials.

SSRIs by compound

Paroxetine

Efficacy Outcomes

There were three trials on paroxetine that included a total of 646 children and adolescents.

When results from analyses using LOCF data were used, there was no statistically significant difference in the percentage of patients who improved (on the criteria of 'response' as defined within the trial) between those receiving paroxetine and those receiving placebo (RR 1.09, 95% CI 0.95 to 1.26) (Figure 01.01). The response rate in the treatment groups in the three trials varied between 49% and 67% and the response rates in the placebo groups varied between 46% and 58%. One trial had separate data for children and adolescents. From this trial there was no evidence to suggest that paroxetine was effective for children (RR 0.96, 95% CI 0.62 to 1.48). Combining the two trials of adolescents with the adolescent data from one trial of children and adolescents, showed no advantage of paroxetine over placebo (RR 1.11, 95% CI 0.96 to 1.29) for adolescents.

One trial reporting CDRS-R for children and adolescents separately showed no statistically significant differences on depressive disorder symptom severity scores overall (Treatment effect 1.60, 95% CI -2.24 to 5.44) (Figure 01.02), for children (Treatment effect 5.27, 95% CI 0.00 to 10.54) or for adolescents (Treatment effect -2.55,95% CI -8.16 to 3.06). The two trials on adolescents using the K-SADS 9-item subscale to measure depressive disorder symptom severity showed that there was no statistically significant difference between the groups (Treatment effect -0.96, 95% CI -2.26 to 0.34) (Figure 01.03).

Paroxetine Study 3 measured functioning using GAF. For both children and adolescents, there was no statistical evidence of a difference for those receiving paroxetine. Keller 2001 measured functioning using the Autonomous Functioning Checklist in adolescents and found no evidence of a treatment effect.

Meta-analysis of results from trials using OC data demonstrated a statistically significant treatment effect in the percentage of patients who responded (RR 1.15, 95% CI 1.02 to 1.30) (Figure 02.01). While statistical significance of the treatment estimate differed by the imputation method used in the component trials (OC or LOCF), the difference was of no clinical importance. However, it is clear that high attrition in the component trials impacts on the results. For children, the treatment effect differed considerably by imputation method used in the component trials. The RR for 'response' estimated from OC data was 1.32 (95% CI 0.90 to 1.92) compared to 0.96 (95% CI 0.62 to 1.48) from LOCF data. This was based on one study which included children and adolescents, and had 28% attrition. For adolescents, the treatment effect was similar when estimated from OC and LOCF data (RR 1.13, 95% CI 0.99 to 1.29) for OC data versus 1.11 (95% CI 0.96 to 1.29) for LOCF data.

Estimates of treatment effect for depressive disorder symptom severity (CDRS-R) for both children and adolescents varied considerably by the imputation method employed. Overall, from the OC data, those receiving paroxetine were -0.59 lower than those receiving placebo (95% CI -4.3 to 3.11) (Figure 02.02). This compared to an estimated increase of 1.60 (95% CI -2.24 to 5.44) when LOCF data were used. Two trials of adolescents used the K-SADS scale as an outcome. Pooling estimates of treatment from these trials using OC data resulted in an estimate of treatment effect similar to that of LOCF data. From both imputation methods there was no evidence of a statistically significant treatment effect (LOCF data treatment effect -0.96, 95% CI -2.26 to 0.34) and OC data treatment effect -0.79 (95% CI -2.05 to 0.46) (Figure 02.03).

Adverse outcomes

The percentage of participants completing a trial is sometimes considered a proxy measure of global adverse treatment effects. For paroxetine this percentage did not differ statistically between the treatment and placebo groups (RR 0.93, 95% CI 0.85 to 1.03) (Figure 01.07).

Adverse events were more common for those receiving paroxetine (RR 1.14, 95% CI 1.03 to 1.27) (Figure 01.08). Headaches were common side effects in both groups, as were nausea and dizziness. Somnolence, insomnia, and emotional lability were also noted. Side effects were reported differently in each trial, and a summary of the adverse events reported is in Table 03.

Fluoxetine

Efficacy Outcomes

Three of four trials investigating the effectiveness of fluoxetine provided outcome data. These three trials included a total of 527 children and adolescents. There was a statistically significant increase in the percentage of those who responded in the fluoxe-

tine group compared to the placebo group (RR 1.86, 95% CI 1.49 to 2.32) (Figure 03.01). The response rates in the fluoxetine groups in the three trials varied between 41% and 61% and in the placebo groups between 20% and 35%. Depressive disorder symptom severity scores on the CDRS-R in the fluoxetine group were also statistically significantly lower than scores in the placebo treated group at the end of treatment (Treatment effect -5.63, 95% CI -7.38 to -3.88) (Figure 03.02). Functioning was reported using the CGAS in Emslie 1997 and the GAF in Emslie 2002. Neither trial showed a statistically significant difference in functioning (Figure 03.03. & 03.04).

Data from the sub-group analysis of children showed a statistically significant greater percentage of children receiving fluoxetine responded compared to placebo (RR 2.43 95% CI (1.30 to 4.56)). In two trials depressive disorder symptom severity scores for children were statistically significantly lower in the fluoxetine group (Treatment effect -6.72, 95% CI -10.55 to -2.88 on the CDRS-R). Two trials investigating fluoxetine in adolescents provided some evidence of improved response for those receiving fluoxetine (RR 1.74, 95% CI 1.32 to 2.28). Pooled results of three trials showed statistically significantly lower depressive disorder symptom severity scores (CDRS-R) in adolescents treated with fluoxetine (Treatment effect -5.34, 95% CI -7.31 to -3.38). There was no statistically significant difference in functioning at the end of treatment in either children or adolescents (Figure 03.03. & 03.04).

There were no OC data reported.

Adverse outcomes
Based on one study, more young people on fluoxetine completed the treatment protocol compared with those on placebo (RR 1.34, 95% CI 1.13 to 1.58) (Figure 03.06), but there were statistically significantly more adverse events experienced by the group treated with fluoxetine (RR 1.19, 95% CI 1.03 to 1.36) (Figure 03.07).

Data on adverse outcomes could not be extracted for the Emslie trials. In the TADS trial, the following adverse events were reported: headaches, diarrhoea, somnolence, insomnia, emotional lability, and mania or hypomania. Headache was most commonly reported with 12% and 9% of those in the fluoxetine and placebo groups experiencing these respectively. All other adverse events were reported in less than 3% of the participants, with similar rates observed in both groups. Details can be found in Table 03.

Sertraline
Efficacy Outcomes
There were two trials of sertraline. These trials were combined and treated as a single trial in the publication (Wagner Study 1&2). The trialist states that 'data were pooled in a prospectively defined combined analysis' (Wagner Study 1&2, pg 1035). The author states that this pooling was planned a priori. The MHRA report, however, reported results for the two trials separately. The meta-analysis is based on these data. In total, 364 young people were included in the two trials. There was no statistical difference in the percentage of young people responding between treatment and placebo groups (RR 1.17, 95% CI 1.00 to 1.36) (Figure 04.01). The percentage of young people responding in the sertraline and placebo groups was 69% and 59% respectively. For this outcome, data were not provided separately for children and adolescents.

Data from the sub-group analysis of children on depressive disorder symptom severity scores on the CDRS-R showed no statistically significant differences in scores between the sertraline and placebo treated groups (Treatment effect -2.34, 95% CI -7.01 to 2.33) (Figure 04.02). For adolescents, depressive disorder symptom severity scores were statistically significantly lower in the group treated with sertraline (Treatment effect -4.56, 95% CI -8.79 to -0.32) (Figure 04.02). When these sub-groups were combined, depressive disorder symptom severity scores were statistically significantly lower in the group treated with sertraline (Treatment effect -3.56, 95% CI -6.69 to -0.42).

Functioning was measured using the CGAS scale and was reported for the combined group. Those in the sertraline group had improved functioning, but not statistically significantly so (Treatment effect 1.31, 95% CI -1.61 to 4.23) (Figure 04.03).

No OC data were reported.

Adverse outcomes
There was no statistically significant difference between the groups in the percentage who completed the treatment protocol (RR 0.91, 95% CI 0.82 to 1.01) (Figure 04.05). There were no data on overall adverse outcomes.

Nausea were commonly reported in both groups. Adverse effects that were reported relatively frequently included diarrhoea, vomiting and insomnia. Emotional lability but not mania/hypomania were reported (see Table 03).

Citalopram
Efficacy Outcomes
Two trials, including 435 young people, had data that could be extracted on the percentage of young people who responded. There was a statistically significant increase in the percentage of those who responded in the citalopram group compared to the placebo group (RR 1.30, 95% CI 1.02 to 1.67) (Figure 05.01). In the two trials, the percentage of participants responding in the citalopram groups varied between 36% and 46% and in the placebo groups between 24% and 38%. Depressive disorder symptom severity scores (CDRS-R) were not statistically significantly lower in the group treated with citalopram (Treatment effect -2.13, 95% CI -4.95 to 0.69) (Figure 05.02).

One trial reporting CDRS-R for children and adolescents separately showed no statistically significant difference on depressive disorder symptom severity scores for children (Treatment effect -0.05, 95% CI -6.02 to 5.92) or for adolescents (Treatment effect -2.60, 95% CI -6.86 to 1.66).

Data on improvement in functioning (CGAS) were available from one trial. Data from the sub-group analysis of children on the CGAS showed no statistically significant difference in scores between the citalopram and placebo treated groups (Treatment effect -1.80, 95% CI -6.89 to 3.29). For adolescents functioning scores on the CGAS were statistically significantly higher in the placebo group (Treatment effect 5.70, 95% CI 1.78 to 9.62). When these sub-groups were combined there was no significant difference between the groups in functioning (Figure 05.03).

No OC data were reported.

Adverse outcomes

A smaller percentage of participants receiving an SSRI completed the trial (RR 0.89, 95% CI 0.78 to 1.00) (Figure 05.05). The percentage of participants experiencing adverse events did not differ between groups (RR 1.09, 95% CI 0.97 to 1.22) (Figure 05.06).

Headache was a commonly reported adverse outcome, as well as nausea, diarrhoea and insomnia. Dizziness and respiratory adverse events were also recorded. Emotional lability and mania/hypomania were not reported (see Table 03).

DISCUSSION

In this review we have presented data on efficacy and on adverse outcomes, including suicide related outcomes, from all published and unpublished trials examining the use of SSRIs for child and adolescent depressive disorder. We have carefully reviewed the risk of bias although unclear reporting in a number of trials hampered this effort. The high drop out rates and issues regarding appropriate outcome measurement and the associated potential for reporting bias make it difficult to draw conclusions about the clinical benefit of SSRIs. The exclusion of young people at risk of suicide and the lack of power to examine suicide related outcomes are important factors that limit the assessment of the clinical implications of the findings. Conflicting data make it difficult to assess the relevance of the association between SSRIs and suicide related behaviours and suicide completion. How children and adolescents with a depressive disorder, co-morbid conditions, who are at risk of suicide (i.e. those more typical of the young people who present at health services) would respond to SSRIs is unknown. Overall, the data regarding the benefits of SSRIs for child and adolescent depression are far from compelling while the information on the risks is limited.

The results of this review present a dilemma for those treating young people with depressive disorders. Although there was a statistically significant reduction in depressive symptoms in children and adolescents taking fluoxetine, the results are inconsistent for sertraline and citalopram. Additionally, the trials are of young people not representative of those presenting for treatment in clinics and had some significant methodological shortcomings, making it difficult to draw firm conclusions. The reduction seen in symptoms was modest and the potential benefit must be balanced with the finding that SSRIs are associated with a statistically significant increased risk of suicide related behaviour (a combination of suicidal ideation and definitive suicidal behaviour). Counter to this, there are risks in not treating depressive disorder which has an increased risk of suicide completion, as well as impacts on academic and social functioning (Brent 2002; Ebmeier 2006; Fleming 1993; Lewinsohn 1998; NHMRC 1997; Rao 1995). Given the nature of this topic, and ambiguity of the data and population we have given a more lengthy discussion of the relevant issues.

Are SSRIs effective in treating depression?

When data are pooled across all SSRIs there is evidence of greater reduction in depressive symptoms to a predetermined level deemed a "response" on medication compared to placebo. While heterogeneity was present, the effect sizes were all in the same direction. However, the only individual SSRI that showed a significant "response" that was better than placebo as well as also showing an associated greater reduction in depression scores was fluoxetine. The difference in reduction of depressive disorder symptoms between those on fluoxetine and placebo was not large. Generally both those on fluoxetine and placebo improved over the treatment period (difference between baseline scores and endpoint ranged between 10 and 23 points), but those receiving fluoxetine had a greater improvement, scoring on average 5.63 lower on the CDRS-R scale (range 17-113) than those on placebo. It is unclear whether this is of clinical importance. Poznanski 1996 found a difference of 25 points on the CDRS-R scale between a clinically referred depressed group (n =60) and a non clinical group (n =223), and a difference of 19 points between clinically referred groups with (n =60) and without depressive disorder (n =18) (Poznanski 1996, p 53).

The impact of high attrition on treatment estimates is evident from the paroxetine results. The estimates of treatment effect vary, for some outcomes, quite considerably by the imputation method used in the component RCTs. This can make interpretation of the results difficult. However in this instance we do not believe that the differences in treatment estimates are of clinical importance.

Sertraline appeared effective for adolescents but not for children. However, there was considerable overlap in the respective confidence intervals suggesting no evidence of a difference in effectiveness by age with a small reduction overall on scores on the CDRS-R scale. The percentage of those responding on sertraline and citalopram compared to placebo was less than for fluoxetine. In citalopram, this difference in response rate was not born out by differences in the reduction of depression symptom.

The young people in the trials are not likely to be representative of the clinical population as most trials included recruitment using advertisement, excluded those at risk of suicide or with comorbidity and in some instances excluded those who responded to placebo in the lead-in stage of the trial. Suicide related behaviours and co-

morbidity are significant features of clinically referred young people with MDD (Birmaher 1996; Kovacs 1984; Marttunen 1998; Petersen 1993). The effectiveness of SSRIs in this group of young people with more severe disorders is therefore unknown.

These results regarding efficacy need to be considered within the context of outcomes related to adverse events, including suicide related behaviours. The ways trials were conducted and the potential for bias also need to be taken into account.

What was the effect of trial design and bias?
There was limited information on the conduct of trials in relation to allocation concealment, blinding and compliance. Blinding is an issue when clinician-rated scales are the main outcome, particularly in the context of an inactive placebo where it may be possible to guess the assigned treatment group given side and other physiological effects likely in this group (Moncrieff 2005b). The low level of response may be due to poor compliance rates, which conceivably could have contributed to the differential ability to show an effect with fluoxetine rather than the other compounds. The effect shown in the fluoxetine trials may also be due to exclusion of placebo responders in the lead in time to the start of the trial. The placebo response rate was higher in trials of other compounds and has previously been cited as a cause for concern regarding the efficacy of SSRIs (Newman 2004). Again, it is notable that only in the trials of fluoxetine was the drop out rate consistently higher in the placebo group compared to the fluoxetine group. There were generally very high attrition rates in all of the trials and it is unclear what effect this has on treatment estimates.

Reporting bias was difficult to assess given the conduct of a trial can be obscured in the write-up for publication. Full and explicit reporting of changes in outcome definition was only undertaken by one investigator, however the primary outcome was reported and findings discussed (Emslie 1997; Jureidini 2004). The possibility of reporting bias was highlighted in a letter to the editor regarding post hoc alterations of response definitions (Jureidini 2003).

What level of improvement constitutes a meaningful clinical outcome is uncertain given response was defined variously, with the noted possibility of alteration of this definition. In addition, remission was simply a level of improvement, again variously defined, and usually of a greater magnitude to response. A standard definition of response would have been ideal; however, to calculate this individual patient data would have been necessary. Moreover, remission was inconsistently reported, which may be an issue of reporting bias.

Outcome measurement deserves comment. Diagnosis of major depressive disorder on DSM criteria was an entry criterion for most of the trials and would have been desirable as an outcome measure; however, only data on cut-off points on rating scales were available. Many of these included scales psychometric properties or sensitivity are unknown in this age group, thus limiting conclusions that can be made.

Additionally, given symptom improvement or resolution does not necessarily correlate with improvements in functioning (see Winters 2005 for a review), the later would seem a more clinically important patient outcome to collect. However, this was inconsistently measured and reported on scales that often did not have established psychometric properties. Based on the most commonly used instruments in this field, there was no difference in functioning outcomes. Self-report data may also tap an outcome that is meaningful to the young person, however, no few individual trials reported this and of those that did few reported any significant differences between placebo and SSRI.

The trials are designed only to examine the short-term effects of SSRIs, however, this does not preclude the possibility that the effectiveness of treatment is only apparent over a longer period of time. For example, functioning may take longer to improve than do symptoms. Long term follow-up would be required to assess this.

There was evidence of inappropriate methods of imputation with trialists often using Last Observation Carried Forward data. Patients were often not analysed as randomised.

The methodological shortcomings of the trials make it difficult to interpret outcome data on the efficacy of SSRIs. This is a particularly unsatisfactory since large numbers of children and adolescents have participated in trials, and we are still unable to answer the important clinical question of whether SSRIs are effective in treating depressive disorders.

How were the trial data for the review sourced?
The majority of trials were pharmaceutically funded. Two of the three fluoxetine trials were not pharmaceutically funded (Emslie 1997; TADS 2004) (although the TADS trial had an unrestricted education grant from Eli Lily).

It should be noted that the review process included collection of data from various sources. There were more complete data for the trials on paroxetine due to publication of trial reports by SmithKline·Beecham on the Internet. Details of aspects of trial methodology were relatively brief even in this case. Information and data from other trials were taken variously from scientific journal publications, from the MHRA data and, in some cases, obtained directly from trialists and pharmaceutical companies. Additionally, a large number of analyses were undertaken in the review.

What are the risks from SSRIs?
Potential benefit from SSRIs must be balanced against risk from the medication. We have assessed two major domains of risk; suicide related outcomes (a combination of suicidal ideation and definitive suicidal behaviour) and adverse effects (a count of any adverse event reported by trialists) from medication.

There were no reports of completed suicide in a total sample of 2,240 young people. However, suicide is a rare event and much larger sample sizes with longer follow-up would be needed to assess

the risk fully. Research suggests that the best predictor of eventual suicide completion is previous suicidal ideation and suicidal behaviour so that an increase in these may increase the risk of future suicide completion (Andrews 1992; Brent 1986; Brent 1993; Lewinsohn 1996). In the FDA pooled analysis 4% on medication and 2% on placebo experienced suicidal ideation or definitive suicidal behaviour. In our meta-analysis the risk of suicide related behaviour is slightly higher; between 1 and 13% (a total of 63 events in 1,167 patients) in the SSRI group and between 0 and 7% (a total of 32 events in 1,073 patients) in the placebo group. Dubicka 2006, using data submitted to the Committee on Safety in Medicines in the UK, published similar results. Additionally he analysed the data by type of suicide related outcome showing suicidal ideation in 1.2% of those on SSRIs compared to 0.8% on placebo, self harm in 3.3% of those on SSRIs versus 2.6% on placebo, and attempts in 1.9% of those on an SSRI versus 1.2% on placebo (Dubicka 2006). The small differences between results in the review may be due to differing inclusion of various trials (e.g. Simeon 1990; Wagner 2006 not included in the FDA review).

It isn't clear whether a short term increase in risk of suicide related behaviours is followed by a longer term reduction (AACAP 2004). An increase in risk has been shown within one month of starting antidepressant use in one study (Jick 2004) but not in another (Simon 2006b). We did not have the data to examine this question in this review due to the short term follow-up of participants in the trials.

In all reviews the rates of suicide related behaviour are much lower than reports of suicidal ideation and behaviour in adolescents from the community. In some population based studies suicidal ideation is reported by as many as 12-23% of young people and suicide attempts by 4-8% of adolescents aged 13-18 years (AHRG 2003; Grunbaum 2002; Lewinsohn 1996; Sawyer 2001). This could be explained by exclusion of those at risk of suicide from all but two trials (Von Knorring 2006; Emslie 2002). Most trials also excluded those with co-morbid conditions (although in some trials children and adolescents with co-morbidity were included). Co-morbidity is related to an increased risk of suicidal ideation and suicidal behaviours (Andrews 1992; Asarnow 1992; Brent 1986; Esposito 2002; Kovacs 1993; Shaffer 1996; Wetzler 1996) so this may also help explain lower rates of suicide related behaviour in the trials included in this review. It is unclear what the effect of treatment with an SSRI would be on suicide related outcomes in a population of depressed children and adolescents at risk of suicide and with co-morbid conditions.

The TADS study highlights the difficulty in measuring suicide related outcomes. In this study suicidal ideation is measured by a tool specifically designed for this purpose, and a reduction was shown over the course of the trial for those on fluoxetine compared with placebo. However, there was a statistically significant increase in suicide related behaviours for those on fluoxetine compared to placebo in the FDA analysis (Hammand 2006).

With regard to other adverse outcomes, there was some evidence to suggest an increased risk of any adverse events (apart from suicide related outcomes) for those treated with fluoxetine, paroxetine, and citalopram. Equivalent data were not available in the sertraline trials.

Comparisons with other reviews on SSRIs

Healy was one of the first to publish regarding the possibility of an increased risk of suicide associated with SSRIs (Healy 2003). The current review is just one of many similar studies that investigate the link between suicide, as well as suicidal behaviour and ideation with SSRIs.

Olfson showed an association between use of antidepressants and those attempting suicide in adolescents who had been hospitalised for suicide attempt (Olfson 2006). The risk of suicide attempt was greater in children and adolescents compared with adults (Simon 2006b).

Meta-analyses based on FDA data (Hammand 2006) and data submitted to the Committee on Safety in Medicines in the UK (Dubicka 2006) showed similar results to the current review on suicide related outcomes. Differences in results are likely to be due inclusion of different trial data for different meta-analyses.

How results on suicide related outcomes (a combination of suicidal ideation and suicidal behaviours) relate to risk of suicide completion is unclear. There is evidence that suicide related outcomes are a significant risk for future behaviour and completion (Andrews 1992; Brent 1986; Brent 1993; Lewinsohn 1996). Counter to this, a range of studies have shown a relationship between increased SSRI prescribing and reduced suicide rates (Gibbons 2005, Isacsson 2000; Ludwig 2005; Olfson 2003, Tiihonen 2006). There have been criticisms of this data with the causal link contested, for example it could be that there are lower suicide rates in countries with less stigma associated with seeking intervention for mental health disorders (Gunnell 2004; Simon 2006).

Also important are comparisons between SSRIs and with other types of antidepressant medication, for example tricyclic antidepressants. Comparisons with other antidepressants have shown little difference in the risk of suicide (Fergusson 2005; Khan 2003; Martinez 2005) or suicide attempt (Jick 2004) again suggesting a tenuous relationship between SSRIs and suicide (Wessely 2004). For suicide attempts, however, there are conflicting findings for children and adolescents: Martinez 2005 showed a higher risk for those under 18 prescribed an SSRI compared to TCA; Jick 2004 found no difference in 10-19 year olds.

Some have suggested that the association between antidepressant use and adolescent suicide related behaviours may simply be highlighting that use of antidepressants is a marker of severity of depression, which is in turn associated with suicide related behaviours (Friedman 2007; Simon 2006). However, in RCT's comparisons are made between groups with similar severity, with those on SSRIs at greater risk of these outcomes.

The findings regarding an increased risk of suicide behaviour and suicidal ideation need to be balanced with concerns regarding the risk of untreated depression and the need to balance benefits and harms (AACAP 2004; Simon 2006; Ebmeier 2006).

Several reviews of the efficacy of SSRIs in children and adolescents with depression have previously been published. Some of these base their conclusions on narrative summaries of individual trial results (Brent 2004; Cheung 2005, Wagner 2005) not meta-analyses. Of these, the conclusions of Cheung 2005 are the most conservative, stating data are limited, commenting specifically on the appropriateness of the outcomes used and cautioning clinicians to consider the use of SSRIs carefully.

In earlier meta-analyses Jureidini 2004 highlighted methodological problems, particularly regarding reporting, and concluded cautiously that there is only a small benefit of SSRIs that should be balanced with the risks. In contrast Cohen 2004 concluded SSRIs are an effective treatment for adolescent depression based on published data. In the same year, a review by Whittington 2004, highlighted the change in risk-benefit profile when unpublished data are included, and found a favourable risk-benefit profile only for fluoxetine, with a NNTB of 6 (95% CI 4 to 15) for remission, and 5 (95% CI 4 to 13) for response.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for effectiveness of SSRIs compared with placebo in the treatment of depressive disorder in children and adolescents is far from compelling. The limitations in the trials carried out thus far mean that there are no definitive answers for those working with children and adolescents with depressive disorder.

Even when there is evidence that SSRIs reduce depressive symptoms, it is unclear whether the difference in effect between SSRIs and placebo reflects a difference that is of clinical importance to patients. As studies have largely been done in children and adolescents with no co-morbid conditions and with no significant suicidal ideation, it is unclear how children and adolescents with more serious difficulties and those at risk of suicide would respond. There is evidence to suggest an increased risk of suicide related behaviours (combined suicidal ideation and definitive suicidal behaviour) in those treated with SSRIs, but the importance of this is unclear as is the association between SSRIs and suicide completion. Untreated depressive disorder is associated with the risk of completed suicide and impacts on academic and social functioning. It is not clear that treatment with an SSRI will modify this risk in any significant way

For clinicians, results of the review may mean that the threshold of severity for treatment of a depressive disorder with SSRIs is raised. Clinicians should make every effort to present the information on the potential benefits and risks of SSRIs, including the risks of untreated depression, and together with the child or adolescent and their family, consider the various options for treatment. This should include consideration of psychological treatments such as cognitive behavioural therapy and other non medication options. The risk of suicide should be assessed and, if medication is used, this should be monitored particularly closely.

Given the evidence does not clearly answer questions about the effectiveness and harms of SSRIs there is a need for further research.

Implications for research

In the first instance a Cochrane Review should be undertaken comparing the effectiveness and risk of SSRIs with other treatments for child and adolescent depression. The NICE guidelines have presented this information in a format for clinicians, highlighting the paucity of research in this area. Individual patient data meta-analyses may be useful in examining whether the effect of treatment differs in particular subgroups.

A large long term pragmatic trial that includes young people who are representative of those who present for treatment is needed. Considerable care would be required in assessing and monitoring suicidal ideation and behaviour, and the trial would need to be powered to detect suicide related behaviours. Such a trial should have presence of a depressive disorder and functioning as the primary outcomes. Comparative intervention arms could include IPT and CBT.

POTENTIAL CONFLICT OF INTEREST

Per Sindahl works at Leo Pharm, however, their main areas are dermatology and critical care. They are not involved in psychiatric disorders.
There is no conflict of interest for any author.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Emslie 1997**
Methods	Study Design: Randomised Controlled Trial Randomisation type: table of random numbers. Restirction via stratification (age and sex) Concealment of Allocation: yes Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: not reported Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: assessed Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes Follow-up assessment points: post intervention No. eligible: 106 No. randomised: 96 No. started trial: 96 No. analysed: 96 Withdrawals: 36 No. crossed over: none Funded by: National Institute of Mental Health
Participants	Setting of care: outpatients Recruitment: self referred or referred to mood disorders program; none were recruited by media Mean age (intervention): 12.2 (SD 2.7) Mean age (control): 12.5 (SD 2.6) Age range: 7-17 Gender (intervention): female 22; male 26Gender (control): female 22; male 26 Methods used to diagnose: DSM-II-RK-SADS depressive items;CDSR-R>and=40; 3 independent diagnostic interviews and a one week placebo lead in Diagnosis: MDD Severity Intervention: CDRS-R 58.5 (10.5) Severity Control: CDRS-R 57.6 (10.4) Co-morbidity intervention: None 7; Dysthymia 20; Anxiety disorders 32; ADHD 16; ODD/CD 13 Co-morbidity control: None 11; Dysthymia 14; Anxiety disorders 22; ADHD 13; ODD/CD 16 Location: USA Inclusion criteria: Non psychotic MDD, single or recurrent; good general medical health; normal intelligence

Characteristics of included studies (*Continued*)

	Exclusion criteria: Bipolar I and II; psychotic depression; independent sleep-wake disorder; alcohol and other substance abuse; anorexia nervosa; bulimia nervosa; previous adequate treatment with fluoxetine; at least one first-degree relative with bipolar I disorder
Interventions	Intervention group Drug: Fluoxetine Dosage: 20 mg Regimen: taken daily Length of treatment: 8 weeks (following acute treatment, participants were given the option to continue treatment blindly or be treated openly). Control group: Placebo pill
Outcomes	Responders defined as CGI improvement rating of 1 or 2 Other outcomes: Clinical global Impressions Scale Improvement (CGI); Children's Depression Rating Scale - Revised (CDRS-R); Children's Depression Inventory (CDI); Beck Depression Inventory (BDI); Weinberg Screening Affective Scale (WSAS); Brief Psychiatry Rating Scale - Children's (BPRS-C); Children's Global Assessment Scale (CGAS)
Notes	Additional data were sought and supplied by the authors. Data in the MA for child, adolescent and total populations taken from paper publication and this additional data. Child and adolescent data from author. MHRA # X065 MHRA contacted for additional data some of which was provided.
Allocation concealment	A – Adequate

Study	**Emslie 2002**
Methods	Study Design: Randomised Controlled Trial Randomisation type: computer generated randomization sequence restriction via stratified (age, sex, site) Concealment of Allocation: not done or not reported Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: yes Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: not assessed Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes Follow-up assessment points: post assessment No. eligible: 219 No. randomised: 219 No. started trial: 219 No. analysed: 219 Withdrawals: 61 No. crossed over: none Funded by: Eli Lily
Participants	Setting of care: Outpatients Recruitment: academic hospitals and private research psychiatric clinics as well as newspaper and radio recruitment Mean age (intervention): 12.70 (2.46) Mean age (control): 12.69 (2.67) Age range: 8 - <18 Gender (intervention): female 54; male 55 Gender (control): female 54; male 56 Methods used to diagnose: DSM-IV using DICA interview, CDRS-R >and=40 and CGI=4

Characteristics of included studies (*Continued*)

	3 independent diagnostic interviews and a one week placebo lead in Diagnosis: MDD Severity (Intervention): CDRS-R 57.1 (9.9) Severity (Control): 55.1 (11.8) Co-morbidity intervention: ADHD 16; ODD 17; CD 3 Co-morbidity control:ADHD 15; ODD 17; CD 1 Location: USA Inclusion criteria: outpatients; aged 8 - <18; primary diagnosis of non psychotic major depressive disorder, single or recurrent; depressive symptoms of at least moderate severity; no clinically significant ECG abnormalities; able to keep appointments; normal intelligence as judged by investigator Exclusion criteria: serious illness that was not stabilized; abnormal thyroid function; seizure disorder; bipolar I or II; sleep-wake disorder; psychotic depression; anorexia nervosa; bulimia nervosa; borderline personality disorder; substance abuse disorder; one or more first degree relatives with bipolar I disorder; organic brain diseases; previous failed response to antidepressant medication; serious suicide risk; prior adequate treatment with fluoxetine; receipt of fluoxetine within 3 months prior to study entry; regular use of other psychotropic drugs
Interventions	Intervention group Drug: Fluoxetine Dosage: 20 mg Regimen: 1 week 10 mg daily, then 20 mg daily for 8 weeks Length of treatment: 9 weeks Control group: Placebo
Outcomes	Responders defined as CGI improvement rating of 1 or 2 or at least a 30% reduction on CDRS-R Children's Depression Rating Scale - Revised (CDRS-R) Clinical Global Impressions Scale Severity (CGI-Severity) Clinical Global Impressions Scale Improvement (CGI - Improvement) Hamilton Anxiety Rating Scale (HAMA) Beck Depression Inventory (BDI) Children's Depression Inventory (CDI) Global Assessment of Functioning Scale (GAF) Montgomery-Asberg Depression Rating Scale (MADRS) Adverse Events
Notes	Additional data were sought from authors. They did not have the additional data but gave a contact in Eli Lily. Eli Lily provided additional data. Data in the MA from the paper and from additional data supplied by Eli Lily. MHRA # HCJE. MHRA contacted for additional data some of which was provided. All data from paper (Table 3). Assume the p value (that goes with the adjusted treatment effect of 7.1; effect size 0.51; CI 3.3, 10.9) is adjusted but the means presented in table 3 and provided by the author are probably not. JM calculated SE from SDs (in stata file) for depression symptom outcome.
Allocation concealment	B – Unclear

Study	**Keller 2001**
Methods	Study Design: Randomised Controlled Trial Randomisation type: computer generated list. No details of any restriction Concealment of Allocation: not done or not reported Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: yes Use of diagnostic criteria (or clear specification of inclusion criteria): yes

Characteristics of included studies (*Continued*)

	Intervention integrity: not assessed Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes as defined by author Follow-up assessment points: post intervention No. eligible: 275 No. randomised: 275 No. started trial: 275 No. analysed: 190 Withdrawals: 85 No. crossed over: none Funded by: GlaxoSmithKline
Participants	Setting of care: outpatient Recruitment: no information Mean age (intervention): 14.8 (SD 1.6) Mean age (control): 15.1 (SD 1.6) Age range: 12-18 Sex (intervention): female 58; male 35 Sex (control): female 57; male 30 Methods used to diagnose: DSM-III-R using K-SADS-L, HAM-D >and= 12, CGAS >and= 60;7-14 day screen Diagnosis: MDD Severity (Intervention): CGAS 42.7 Severity (Control): CGAS 42.8 Co-morbidity (Intervention): Any diagnosis 41; Anxiety disorder 19; Externalising disorder 25 Co-morbidity (Control): Any diagnosis 50; Anxiety disorder 26; Externalising disorder 26 Location: USA and Canada Inclusion criteria: MDD of at least 8 weeks duration; at least 80 on the Peabody Picture Completion Task; Medically Healthy Exclusion criteria: Bipolar disorder; schizoaffective disorder; eating disorder; alcohol or substance abuse disorder; OCD; autism/pervasive developmental disorder; organic brain disorder; PTSD within 12 months of study entry; current suicidal ideation with intent or specific plan; history of suicide attempt by drug overdose; current psychotropic drug use; trial of antidepressant medication within 6 months of study entry
Interventions	Intervention group Drug: Paroxetine Dosage: 20-40 mg Regimen: 20 mg daily in week 1 to 4 with optional increase to 30 mg in week 5 and 40 mg in week 6 Length of treatment: 8 weeks Control group: Placebo Comparison group: Imipramine (gradual upward titration to 200-300mg)
Outcomes	Responders defined as = 8 or less on HAM-D or at least 50% decrease from baseline Other measures: HAM-D; Clinical Global Impressions Scale Improvement (CGI - Improvement); Depression items from K-SADS-L; Autonomous Function Checklist; Self Perception Profile; Sickness Impact Scale; Adverse Events
Notes	Addtional data were sought from the authors. They did not have the data required but provided a contact from GlaxoKleinSmith who responded to inform us of the trial information now published on the web. MHRA # 329 MHRA contacted for additional data some of which was provided. Data in MA taken from GlaxoKline Beecham web-based report. GlaxoSmithKlein web publication.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	Milin 2004
Methods	Study Design: Randomised Controlled Trial Randomisation type: not stated Concealment of Allocation: not done or not reported Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: yes Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: yes - returned pill pack Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes as defined by author Follow-up assessment points: post intervention No. eligible: 286 No. randomised: 286 No. started trial: 286 No. analysed: 275 Withdrawals: 90 No. crossed over: none Funded by: SmithKlineBeecham
Participants	Setting of care: not stated Recruitment: no information Mean age (intervention): 15.5 (SD 1.6) Mean age (control): 15.8 (SD 1.6) Age range: 13-18 Sex (intervention): female 122; male 65 Sex (control): female 61; male 38 Methods used to diagnose: DSM-IVC; GAS < 69; MADRS >and= 16; after screening 14 day single blind run-in period Diagnosis: MDD Severity (Intervention): MADRS score 25. 9 (SE0.5) (moderately to severely ill) Severity (Control): MADRS 25.9 (SE 0.6) (moderately to severely ill) Co-morbidity (Intervention): Specific Phobia 6; Separation Anxiety 5; Panic disorder 3; Social phobia 3; GAD 13; PTSD 1; ADHD 3; ODD 1; AN 1; BN 2; Substance abuse 0 Co-morbidity (Control): Specific Phobia 3; Separation Anxiety; Panic disorder 0; Social phobia 4; GAD 4; PTSD 3; ADHD 0; ODD 1; AN 0; BN 0; Substance abuse 1 Location: Argentina, Belgium, Canada, Holland, Italy, Mexico, South Afric, Spain, United Arab Emirates, United Kingdom Inclusion criteria: unipolar MDD for at least 8 weeks duration; negative pregnancy test Exclusion criteria: Prepubertal; diagnosis of CD, Autism, PDD, organis psychiatric disorder including schizophrenia and epilepsy; serious suicidal ideation; OCD, panic disorder, social phobia, PTSD that preceeded MDD; medical illness that contraindicated use of paroxetine; previous response to psychotherapy; planned long term psychotherapy; ECT in previous 3 months or planned for trial period; drug or alcohol dependency; concomitant psychotrophic medication or other drugs interfering with CNS activity; use of sumatriptan, oral anticoagulants or type 1C antiarrythmics, i.e. encainide, flecainide, lorcainide and propafenone; previous use of paroxetine or other SSRI; sensitivity to SSRI; sexually active and not using contraceptive or pregnant or lactating; use of other investigational drug
Interventions	Intervention group Drug: Paroxetine Dosage: 20-40 mg Regimen: daily Length of treatment: 12 weeks Control group: Placebo

Characteristics of included studies (*Continued*)

Outcomes	Responders defined as at least a 50% reduction on MADRS Other measures: change in the K-SADS-L depression subscale; Children's Global Assessment Scale (CGAS); Montgomery-Asberg Depression Rating Scale (MADRS); K-SADS-L; Clinical Global Impressions Scale Improvement (CGI - Improvement); Mood and Feeling Questionnaire; Adverse events
Notes	Additional data were sought and received from the authors. MHRA # 377 MHRA contacted for additional data some of which was provided. Data in MA taken from GlaxoKline Beecham web-based report.
Allocation concealment	B – Unclear

Study	**Paroxetine Study 3**
Methods	Study Design: Randomised Controlled Trial Randomisation type: not stated; restriction via stratified (age) Concealment of Allocation: yes Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: yes Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: yes Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes aa defined by author Follow-up assessment points: post intervention No. eligible: No. randomised: 206 No. started trial: 206 No. analysed: 203 Withdrawals: 57 No. crossed over: none Funded by: GlaxoSmithKline
Participants	Setting of care: outpatient Recruitment: no information Mean age (Intervention): 11.9 (SD 3.00) Mean age (Control): 12.1 (SD 2.95) Age range: 7-17 Sex (intervention) female 48; male 53 Sex (control): female 47; male 55 Methods used to diagnose: DSM-IV, K-SADS-PL using 1 week screening phase Diagnosis: MDD Severity (Intervention): CDRS-R 60.7 (9.37) Severity (Control): CDRS-R 62.6 (8.96) Co-morbidity (Intervention): ODD 5; GAD 4; Overanxious Disorder 3; Attention Deficit Disorder 3; Separation Anxiety Disorder 2; Simple phobia 1; PTSD 1; Enuresis 1; Adjustment Disorder with Depressed Mood 0 Co-morbidity (Control): ODD 4; GAD 1; Overanxious Disorder 1; Attention Deficit Disorder 1; Separation Anxiety Disorder 0; Simple phobia 0; PTSD 0; Enuresis 0; Adjustment Disorder with Depressed Mood 1 Location: USA and Canada Inclusion criteria: 7-17 years; MDD Exclusion criteria: clinically predominant Axis I disorder other than MDD; history of psychotic episode or disorder; bipolar disorder; mental retardation or PDD; substance abuse or dependence within 3 months of screening or current positive test on drug screen; suicidal or homocidal risk; epilepsy; ECT within 3 months of screening; lactating or pregnant; sexually active female and not using contraception; requirement of concurrent psychotherapy; clear history of non response to SSRIs

Characteristics of included studies (*Continued*)

Interventions	Intervention group Drug: Paroxetine Dosage: 10-50 mg Regimen: week one 10 mg daily with option to increase up to 10 mg weekly to a maximum of 50 mg; reduction/tapering over 4 weeks post 8 week treatment Length of treatment: 8 weeks Control group: Placebo pill
Outcomes	Response defined as CGI Improvement of 1 or 2 Other outcomes: Children's Depression Rating Scale - Revised (CDRS-R); Clinical Global Impressions Scale Severity (CGI-Severity); Clinical Global Impressions Scale Improvement (CGI-Improvement); Global Assessment of Functioning (GAF); Kutcher Adolescent Depression Rating Scale (KADS); Adverse outcomes
Notes	MHRA #701 MHRA contacted for additional data some of which was provided. Data in MA taken from GlaxoKline Beecham web-based report.
Allocation concealment	A – Adequate

Study	**Simeon 1990**
Methods	Study Design: Randomised Controlled Trial Randomisation type: not stated Concealment of Allocation: not stated Blinding (participants): not clear states double blind (no test of blind) (assessors): not clear states double blind (no test of blind) Power calculation: not stated Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: yes Outcome measures described or validated measures used: yes Intent-to-treat analysis: not stated Follow-up assessment points: weekly visits, post intervention and long term follow-up on average 24 months post study termination No. eligible: No. randomised: 40 No. started trial: 40 No. analysed: unclear for 32 Withdrawals: 8 No. crossed over: none Funded by: not stated
Participants	Setting of care: outpatient Recruitment: no information Mean age (total) 16 Mean age (Intervention): not stated Mean age (Control): not stated Age range: actual range not stated Sex (total) female 22; male 18 Methods used to diagnose: DSM III criteria with HAM-D score of 20 or more, one week placebo run-in period Diagnosis: MDD Severity (Intervention): not stated Severity (Control): not stated Co-morbidity (Intervention): not stated Co-morbidity (Control): not stated Location: Canada Inclusion criteria: 13-18 years; MDD

Characteristics of included studies (*Continued*)

	HAM-D score >20 Raskin Depression Scale >8 Raskin Depression Score must exceed the Covi Anxiety Scale Score Outpatients Exclusion criteria: history of seizures, schizophrenia, or other psychotic illnesses, girls who were sexually active and not using medically accepted means of contraception, patients with a recent drug or alcohol abuse and those who presented with serious suicidal risk
Interventions	Intervention group Drug: Fluoxetine Dosage: 20 - 60 mg Regimen: initial dose 20 mg daily increased to 40mg after 4 to 7 days, and up to 60mg in the second week; Length of treatment: 7 weeks Control group: Placebo pill
Outcomes	HAM-D; Clinical Global Impressions Scale (CGI) ; Raskin Depression Scale; Covi Anxiety Scale; Hopkins Symptom Checklist Follow-up assessment included semi-structured interviews by a nurse to obtain treatment subsequent to the study, current activities and funcitoning with family and peers, and follow-up interview with parents using the HAM-D, Raskin, Covi and a DSM-III checklist for MDD and an adaptive functioning scale
Notes	Letter requesting additional data sent. Data has not been received.
Allocation concealment	B – Unclear

Study	**TADS 2004**
Methods	Study Design: Randomised Controlled Trial Randomisation type: Sequence generated by computer program; restriction via strateification (age and sex) and blocking Concealment of Allocation: not done or not reported Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: yes Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: assessed for some treatments Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes Follow-up assessment points: post intervention No. eligible: 1088 No. randomised: 439 No. started trial: 439 No. analysed: 439 Withdrawals: 90 No. crossed over: none Funded by: NIMH
Participants	Setting of care: outpatient Recruitment: included newspaper, TV and radio advertising Mean age (total): 14.6 (SD 1.5) Age range (actual): 12-18 Sex (total): female 239; male 200 Methods used to diagnose: DSM-IV using K-SADS-PL, CDRS-R > and = 45; Assessment (not interview) at consent and baseline Diagnosis: MDD Severity (Intervention): raw score CDRS-R 58.96 (10.16) T-score CDRS-R 74.73 (6.74)

Characteristics of included studies (*Continued*)

	Severity (Control): raw score CDRS-R 61.11 (10.50) T-score CDRS-R 76.14 (6.11) Co-morbidity (Intervention): Any 47 ; Dysthymia 6; Anxiety 26; OCD/Tic 2; ADHD 13; Substance use 3; Disruptive behaviour 25 Co-morbidity (Control): Any 57; Dysthymia 12; Anxiety 28; OCD/Tic 4; ADHD 19; Substance use 0; Disruptive behaviour 28 Location: USA Inclusion criteria: outpatient; age 12-17; FSIQ > 80; antidepressant-free before study Exclusion criteria: bipolar disorder; severe CD; substance abuse; pervasive developmental disorder; thought disorder; suicidality or homocidality; use of psychotropic medication or psychotherapy (stable stimulants permitted for ADHD); two previous failed SSRI trials or a failed trial of CBT; confounding medical condition; non-English speaking
Interventions	Intervention group Drug: Fluoxetine Dosage: 20- 40 mg Regimen: 10 mg daily to start; increase to 20 mg daily in week 1 with increase to a maximum of 40mg daily thereafter Length of treatment: 12 weeks Control group: Placebo Comparison group 1: CBT Comparison group 2: CBT plus fluoxetine
Outcomes	Response defined as a CGI improvement of 1 or 2 Other outcomes: Children's Depression Rating Scale - Revised (CDRS-R); Clinical Global Impressions Scale Improvement (CGI-Improvement); Reynolds Adolescent Depression Scale (RADS); The Suicidal Ideation Questionnaire-Junior High School Version (SIQ-Jr)
Notes	Additional trial information was sought and received from the author. Data in the MA from the paper. All young people in the trial were included as adolescents.
Allocation concealment	B – Unclear

Study	**Von Knorring 2006**
Methods	Study Design: Randomised Controlled Trial Randomisation type: no information on method used to generate sequence; restriction via blocking with blocks of size 4 Concealment of Allocation: not done or not stated Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: not stated Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: non compliance assessed by blood levels of citalopram Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes Follow-up assessment points: post intervention No. eligible: not stated No. randomised: 244 No. started trial: 233 No. analysed: 233 Withdrawals: 91 Funded by: pharmaceutical company not stated
Participants	Setting of care: in and outpatient (14% of participatns hospitalised at entry to study) Recruitment: no information Mean age (total): 16 (SD 1) Age range: 13-18 Sex (intervention): percentage female not stated; percentage male not stated

Characteristics of included studies (*Continued*)

	Sex (control): female not stated; male not stated Methods used to diagnose: DSM-IV including 5 minute interview with parents Global assessment of functioning less than 60 on either symptoms, activities, relationships or personal care, BDI less than 21 for girls and less than 16 for boys Diagnosis: MDD Severity (total): Kiddie-SADS-P 32 (SD5), MADRS 30 (SD 5/6), GAF 55 (SD 7) Co-morbidity (Intervention): not stated Co-morbidity (Control): not stated Location: Denmark, Estonia, Finland, Germany, Norway, Sweden, Switzerland Inclusion criteria: DSM-IV MDD current episode of greater than 4 weeks but less than 1 year duration; in or outpatient plus score of at least 21 or 16 on BDI and at least 60 on the GAF; 13-18 years inclusive; Tanner Stage III (commencement of puberty) Exclusion criteria: Bipolar disorder including hypermania; ongoing DSM-IV ADD or disruptive behaviour disorder; DSM-IV psychotic disorder; progressive neurological disorder; drug or alcohol abuse that influences daily functioning; primary anorexia nervosa or bulimia nervosa; attends special school for mentally retarted; pervasive developmental disorders
Interventions	Intervention group Drug: Citalopram Dosage: 10-40 mg Regimen: 10 mg for the first week with dose increases at the end of the week 1, 2, 5 or 9 weeks of 10 mg if GAF decreased by 10 points or unchanged to a maximum of 40mg Length of treatment: 12 weeks Control group: placebo pill
Outcomes	Responders defined as those with a score of 2 or less on the Kiddie-SADS-P depression and anhedonia items or with a reduction of at least 50% from baseline of the MADRS total score Other outcomes: K-SADS-P total score; Montgomery-Asberg Depression Rating Scale (MADRS); Beck Depression Inventory; Global Assessment of Functioning Adverse outcomes
Notes	MHRA #94404 MHRA contacted for additional data some of which was provided. Data in the MA from the MHRA publication. Subsequent to the final search the vonKnorring 2006 paper was retrieved and details of the study as well as outcome data checked against the MHRA reports.
Allocation concealment	B – Unclear

Study	**Wagner 2004**
Methods	Study Design: Randomised Controlled Trial Randomisation type: not stated Concealment of Allocation: not done or not reported Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: not reported Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: not assessed Outcome measures described or validated measures used: yes Intent-to-treat analysis: yes, as defined by authors Follow-up assessment points: post intervention No. eligible: 178 No. randomised: 178 No. started trial: 178

Characteristics of included studies (*Continued*)

	No. analysed: 174 Withdrawals: 36 No. crossed over: none Funded by: Forest Pharmaceuticals
Participants	Setting of care: outpatients Recruitment: no information Mean age (intervention): 12.1 (SD 2.8) Mean age (control): 12.1 (SD 3.1) Age range: 7-17 Sex (intervention): female 54; male 39 Sex (control): female 43; male 42 Methods used to diagnose: DSM-IV using K-SADS-P & LT, CDRS-R > and = 40 Diagnosis: MDD Severity (Intervention): CDRS-R 58.8 (10.9) Severity (Control): CDRS-R 57.8 (11.1) Co-morbidity (Intervention): Dysthymia 5; enuresis 4; previous ADHD 4 Co-morbidity (Control): Dysthymia 1; enuresis 3; previous ADHD 1 Location: USA Inclusion criteria: MDD of at least 4 week duration; normal physical exam, laboratory tests and ECG; parent available to accompany child Exclusion criteria: primary psychiatric diagnosis other than MDD; ADHD; PTSD; bipolar disorder; pervasive developmental disorder; mental retardation; CD; ODD; any psychotic features; any personality disorder that would interfere with treatment; alcohol or substance abuse; anorexia or bulimia nervosa; initiation of psychotherapy or behaviour therapy 3 months prior to study entry; suicide risk or previous active attempt in previous year or hospitalised due to attempt; and antidepressant or anxiolytic medication in two weeks prior to study entry; neuroleptic or stimulant medication within 6 months of study entry
Interventions	Intervention group Drug: Citalopram Dosage: 20 mg -40 mg Regimen: 20 mg daily for 4 weeks with option to increase to 40 mg daily Length of treatment: 8 weeks Control group: Placebo
Outcomes	Responders defined as at least =28 on Children's Depression Rating Scale - Revised (CDRS-R) Other outcomes: CDRS-R; Clinical Global Impressions Scale Improvement (CGI - Improvement); Clinical Global Impressions Scale Severity (CGI - Severity); Adverse events
Notes	Additional data were sought from authors. No response was received. MHRA # CIT-MD-18 MHRA contacted for additional data some of which was provided.
Allocation concealment	B – Unclear

Study	**Wagner 2006**
Methods	Study Design: Randomised Controlled Trial Randomisation type: sequence generated by computer program; stratification via centre using blocks of size 4 Concealment of Allocation: not done or not reported Blinding (participants): double-blind with tablets identical incdicating participants may be blinded Blinding (assessors): not clear Power calculation: not stated Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: not stated Outcome measures described or validated measures used: yes

Characteristics of included studies (*Continued*)

	Intent-to-treat analysis: yes Follow-up assessment points: post assessment No. eligible: 268 No. randomised: 268 No. started trial: 264 No. analysed: 264 Withdrawals: 18 in the placebo group and 29 in the treatment group No. crossed over: none Funded by: Forest Laboratories, Inc
Participants	Setting of Care: outpatients Recruitment: no information Mean age (intervention): 12.2 Mean age (control): 12.4 Age range: 6 - 17 Sex (intervention): female 68, male 63 Sex (control): female 69, male 64 Methods used to diagnose: DSM-IV diagnosis of MDD of at least 4 week duration using K-SADS-PL, CDRS-R >and=40; one week placebo run-in period Diagnosis: MDD Severity (Intervention): CDRS-R 54.5 Severity (Control): CDRS-R 56.6 Co-morbidity intervention: 6 had an ongoing anxiety disorder; none had ADHD Co-morbidity control: 10 had an ongoing anxiety disorder; none had ADHD Location: 25 centres in the USA Inclusion criteria: normal results at screening from physical examination, laboratory tests and electrocardiography Exclusion criteria: any primary psychiatric diagnosis apart from MDD; any psychotic features; any severe personality disorder; met DSM-IV criteria for ADHD, PTSD, bipolar disorder, PDD, mental retardation, conduct or oppositional defiant disorder; females not practicing or willing to practice a reliable method of birth control; history of AN, BN, substance abuse; suicide risk based on clinicial judgement of investigator or ever hospitalised for suicide attempt or had made a suicide attempt within the past year; initiation of psychotherapy was not allowed during the study of within three months before the screening visit; previous treatment failure on SSRI
Interventions	Intervention group Drug: escitalopram oxalate Dosage: fixed dose of 10 mg for the first 4 weeks; thereafter flexibly dosed from 10 to 20 mg based on clinicial response Regimen: taken daily Length of treatment: 8 weeks Control group: Placebo pill Evaluations at end of 1, 2, 4, 6, and 8 weeks
Outcomes	Two separate analyses of response data were undertaken using two different definitions of response: CDRS-R score of less than or equal to 28; or CGI-I of less than or equal to 2. The data used in the review was response based on the CDRS-R criteria Other outcomes: Children's Depression Rating Scale - Revised (CDRS-R); Clinical Global Impressions Scale Severity (CGI-Severity); Clinical Global Impressions Scale Improvement (CGI-Improvement); Children's Global Assessment Scale (CGAS); Adverse outcomes
Notes	Forest pharmaceutical ID is SCT MD 15 Data in the MA from the web-based publication. Subsequent to this Wagner 2006 was published and data checked against this publication with child and adolescent data added to the MA.

Characteristics of included studies (*Continued*)

Allocation concealment	D – Not used

Study	**Wagner Study 1**
Methods	See Wagner Study 1 & 2 entry
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	B – Unclear

Study	**Wagner Study 1&2**
Methods	Study Design: Randomised Controlled Trial Randomisation type: computer generated randomisation; restriction via stratification (age) Concealment of Allocation: not done or not reported Blinding (participants): yes (no test of blind) Blinding (assessors): yes (no test of blind) Power calculation: yes Use of diagnostic criteria (or clear specification of inclusion criteria): yes Intervention integrity: completers mean in intervention 131 mg per day; completers mean in control 144 mg per day Outcome measures described or validated measures used: yes Intent-to-treat analysis: not stated Follow-up assessment points: post intervention No. eligible: 376 No. randomised: 376 No. started trial: 376 No. analysed: 364 Withdrawals: 77 No. crossed over: none Funded by: Pfizer Study 1 No. randomised 188 No. analysed: 142 Withdrawals: 46 Study 2 No. randomised 188 No. analysed: 157 Withdrawals: 31
Participants	Setting of care: outpatient Recruitment: no information Mean age (intervention): not stated Mean age (control): not stated Age range: 6-17 Sex (intervention): female 108; male 81 Sex (control): female 84; male 103 Methods used to diagnose: DSM-IV using K-SADS-PL, CDRS-R >and= 45 and CGI-S > and= 4 During two week screen had to meet these criteria at first and third visit Diagnosis: MDD Severity (Intervention): 64.3 (11.0) Severity (Control): 64.6 (11.0)

	Co-morbidity intervention and control: 40% of participants had at least one co-morbid condition; the conditions that occurred in at least 5% of patients included Anxiety; phobic disorder; adjustment reaction; ODD Location: USA, India, Canada, Costa Rica, Mexico Inclusion criteria: outpatient; aged 6 - 17; MDD at the first and third visits during a two week screen and current episode had to be of at least 6 weeks duration; illness of at least moderate severity Exclusion criteria: ADHD; CD; OCD; panic disorder; history of bipolar or current psychotic features; history of psychotic disorders or autistic spectrum disorders; current anorexia nervosa or bulimia nervosa; drug or alcohol abuse/dependence within 6 months or current positive drug screen; pregnant or breast feeding; previous suicide attempt or current significant suicidal or homicidal risk; abnormal ECG, laboratory test results, vital signs or body weight; current use of other psychotropic medication; intention to commence psychotherapy; requirement of concomitant psychotropic therpay; previous failed response to an SSRI; additionally Study 2 stated it excluded those requiring inpatient admission
Interventions	Intervention group Drug: Sertraline Dosage: flexible dosage 25-200 mg Regimen: 25 mg for 3 days; 50 mg till the end of the second week; increases as indicated by 50 mg per day to a maximum of 200mg Length of treatment: 10 weeks Control group: Placebo pill
Outcomes	Responders defined as at least 40% decrease on Children's Depression Rating Scale - Revised (CDRS-R) Other outcomes: Clinical Global Impressions Scale Severity (CGI-Severity); Clinical Global Impressions Scale Improvement (CGI - Improvement); Clinician rated severity; Multidimensional Anxiety Scale for Children (MASC); Children's Global Assessment Scale (CGAS); Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q); Adverse Events
Notes	Additional data were sought from authors. No response was received. MHRA contacted for additional data for #1001 and 1017, some of which was provided. MHRA data used in MA as it gave data for each separate trial and separately for child and adolescent.
Allocation concealment	B – Unclear

Study	**Wagner Study 2**
Methods	See Wagner Study 1 & 2 entry
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	**Reason for exclusion**
Braconnier 2003	Comparison is not placebo; Paroxetine is compared with clomipramine
Cosgrove 1994	Case study design
Emslie Study 1	Intervention is venlafaxine which is not an inclusion criteria drug. Venlafaxine is a new antidepressant with a novel chemical structure and it acts on the norepinephrine as well as serotonin.
Emslie Study 1&2	Intervention is venlafaxine which is not an inclusion criteria drug. Venlafaxine is a new antidepressant with a novel chemical structure and it acts on the norepinephrine as well as serotonin.

Characteristics of excluded studies (*Continued*)

Emslie Study 2	Intervention is venlafaxine which is not an inclusion criteria drug. Venlafaxine is a new antidepressant with a novel chemical structure and it acts on the norepinephrine as well as serotonin.
Mandoki 1997	Comparison of venlafaxine plus psychotherapy with placebo and psychotherapy.
Mirtazapine Study 1	Intervention is mirtazapine which is not an inclusion criteria drug. Mirtazapine is a presynaptic alpha-2 antagonist that has dual action by increasing noradrenergic and serotonergic neurotransmission.
Mirtazapine Study 2	Intervention is mirtazapine which is not an inclusion criteria drug. Mirtazapine is a presynaptic alpha-2 antagonist that has dual action by increasing noradrenergic and serotonergic neurotransmission.
NIMH 2000	Primary diagnosis of bipolar disorder. Study discontinued.

ADDITIONAL TABLES

Table 01. Search Strings

PsychINFO

1. exp serotonin reuptake inhibitors/
2. (serotonin adj (uptake or reuptake or re-uptake)).mp.
3. ssri$.mp.
4. (Alaproclat$ or Citalopram or Escitalopram or Femoxetin$ or Fluoxetin$ or Fluvoxamin$ or Paroxetin$ or Sertralin$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
5. or/1-4
6. (trial$ or random$ or rct$).mp. [mp= title, abstract, cas registry/ec number word, mesh subject heading]
7. (child$ or adolescen$ or teenage$).mp.
8. (young adj (person$ or people or adult$)).mp.
9. or/7-8
10. and/5-6,9

CENTRAL

1.ssri
2.ssris
3.(selective next serotonin next reuptake)
4.(serotonin next reuptake next inhibitors)
5.Alaproclat* or Citalopram or Escitalopram or Femoxetin* or Fluoxetin* or Fluvoxamin* or Paroxetin* or Sertralin*
6.# 1 or #2 or #3 or #4 or #5
7.Depress* or Dysthymi*
8.child* or adolescent*
9.# 6 and #7 and #8

EMBASE

1. exp Serotonin Uptake Inhibitors/
2. (serotonin adj (uptake or reuptake or re-uptake)).mp.
3. ssri$.mp.
4. alaproclat$.mp.
5. citalopram.mp.
6. escitalopram.mp.
7. femoxetin$.mp.
8. fluvoxamin$.mp.
9. paroxetin$.mp.
10. sertralin$.mp.
11. or/1-10
12. Controlled study/ or randomized controlled trial/
13. double blind procedure/
14. single blind procedure/
15. crossover procedure/
16. drug comparison/
17. placebo/
18. random$.ti,ab,hw,tn,mf.
19. latin square.ti,ab,hw,tn,mf.
20. crossover.ti,ab,hw,tn,mf.
21. cross-over.ti,ab,hw,tn,mf.
22. placebo$.ti,ab,hw,tn,mf.
23. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
24. (comparative adj5 trial$).ti,ab,hw,tn,mf.
25. (clinical adj5 trial$).ti,ab,hw,tn,mf.
26. or/12-25
27. nonhuman/
28. animal/ not (human/ and animal/)
29. or/27-28
30. 26 not 29
31. 11 and 30

Table 01. Search Strings (*Continued*)

PsychINFO	CENTRAL	EMBASE
		32. limit 31 to (child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)

Table 02. Assessment of risk of bias

Study ID	Random sequence	Concealed allocation	Intervention blinded	Blinded outcome	Dropouts/exclusions
Emslie 2002	"computer generated random sequence" pg 1206	no statement	"both groups took three capsules daily" pg 1209	No complete statement "clinicians who were blinded to treatment group" pg 1209 plus patient and parent report pg 1206	full list of number of drop outs and reasons for drop out given; Last Observation Carried Forward (LCOF); Intention-to-Treat (ITT), however, "analysis of response and remission included only those patients treatment at least two weeks with study drug" pg 1208
Emslie 1997	"randomisation was by a table of random numbers" pg 1032	"randomisation was conducted by the pharmacy and clinicians who remained blind to assignment until the end of the study" pg 1032; "pharmacy provided blinded medication" pg 1033; MHRA report states that an interactive voice response system was used to maintain blinding through follow-up phase	"clinicians who remained blind to assignment" pg 1032; "pharmacy provided blinded medication"; "results of blood chemistry levels not provided to clinicians" pg 1033	No complete statement "clinicians who remained blind to assignment" pg 1032	numbers of drop outs and reasons for drop out described in Table 2; all those randomised completed and were included in responder outcome and Last Observation Carried Forward (LOCF) used for all 96 subjects randomised for Child Depression Rating Scale-Revised (CDRS-R) outcome
Citalopram 2	"randomized"; pharmaceutically funded so likely to have been done	no statement	"double blind";	no statement	full table of number of drops but no reasons for drop outs given; "all patients randomised who received at least one dose of double blind study medication and at least one post baseline efficacy assessment" therefore not true Intention-to-Treat (ITT) analysis; primary analysis based on observed case data with secondary analysis using

Table 02. Assessment of risk of bias (*Continued*)

Study ID	Random sequence	Concealed allocation	Intervention blinded	Blinded outcome	Dropouts/exclusions
					ANCOVA (Analysis of Covariance)
Wagner 06/Forest	pg 282 computergenerated randomization sequence. Patient randomization numbers were allocated to each site in ascending sequence in blocks of four. Randomization was not stratified by age.	no statement	stated to be "double blind" with tablets identical indicating participants may be blinded	no statement but clinicians and subjects completed measures and both of these were probably blind	pg 282 " Safety analyses were based on the safety population, which included all patients who received at least one dose of double-blind study medication. Efficacy analyses were performed on the intent-to-treat population who had at least one postbaseline Child Depression Rating Scale-Revised (CDRS-R) assessment" therefore not a true Intention-to-Treat (ITT)analysis; Numbers and reasons for drop out were reported with both Last Observation Carried Forward (LOCF) and Observed Case analyses undertaken
Keller 2001	"computer generated list" pg 764	no statement GlaxoKline Beecham states randomization codes were stored at SB clinical safety department pg 35	tablets overencapsulated in matching supro B locking capsules to preserve medication blinding"; " number of capsules...identical for each...group during forced titration" pg 764	no statement	"efficacy analysis based on patients who were randomised and had at least one postbaseline efficacy analysis evaluation" pg 764 therefore not a true Intention-to-Treat (ITT) analysis; numbers of drop outs and reasons for drop out were reported and Last Observation Carried Forward (LOCF) and

Table 02. Assessment of risk of bias (*Continued*)

Study ID	Random sequence	Concealed allocation	Intervention blinded	Blinded outcome	Dropouts/exclusions
					Observed Case (OC) data analysis undertaken
Milin	"a computer generated randomization list" GlaxoKline Beecham	"masterlist held by SB...individual sealed code breaks held by investigators...could be broken in case of emergency" GlaxoKline Beecham	"paroxetine and placebo capsules were identical and all packaging maintained the double blind nature of the study" GlaxoKline Beecham pg 32	no statement	Intention-to-Treat (ITT) population was : all patients randomised who received at least one dose of double blind medication and at least one treatment assessment was available" GlaxoKline Beecham therefore not a true Intention-to-Treat (ITT). Last Observation Carried Forward (LOCF) analysis was used.
Paroxetine 3	"a computer generated randomisation list was generated...stratified by age subgroup and performed in blocks" GlaxoKlineBeecham report	"individual sealed envelopes indicating treatment assigned to each patient at a particular visit were lodged with the investigators/ pharmacist....the master randomisation list was held by the sponsor" The investigators were blind to the study medication except in the instance of a serious adverse event. GlaxoKlineBeecham report	"double blind. GlaxoKlineBeecham report...paroxetine and placebo...identical in size shape and colour...blinding of study medication was maintained by referring to daily medication dose as dose level" pg 33	no statement	"the Intention-to-Treat (ITT) population...was all patients...who received at least one dose of randomized double blind treatment, and for whom at least one valid post-baseline evaluation was available" GlaxoKlineBeecham pg55 therefore not a true Intention-to-Treat (ITT) analysis; numbers of drop outs and reasons for drop out were reported and Last Observation Carried Forward (LOCF) and Observed Case (OC) data analysis undertaken.
TADS 2004	"computer stratified randomisation" pg 808 in	"centralized ivrs service. eligibility was assessed by	"except in emergencies participants and clinicians	"as rated by an independent evaluator pg 535 in the 2003	" full table of number of drop outs and reason for

Table 02. Assessment of risk of bias (*Continued*)

Study ID	Random sequence	Concealed allocation	Intervention blinded	Blinded outcome	Dropouts/exclusions
	2004 publication	same ie as did dependent variable assessments. Study coordinator not IE interfaced with IVRS and primary clinician for that patient revealed randomization status at Gate C2 after having first confirmed that patient/ parent understood and were willing to accept randomization to any TADS treatment“ from personal correspondence	remained blind in fluoxetine alone and placebo“ groups pg 808 in 2004 publication	publication; “independent evaluators blind to treatment assignment” pg 808 in the 2004 publication	drop outs given pg 811; all analyses were conducted using an intent-to-treat analysis”; “primary intent to treat, all patients regardless of treatment status return for all scheduled assessments” pg 535 in the 2003 publication
Wagner 2003	“using a computer generated randomisation code” pg 1034	no statement	“study drug was packaged in identical blister packs...both patients and clinicians were blinded to group assignment” pg. 1035	no statement	intention to treat population was modified... post randomisation efficacy data collected...problems with data collection pg 1036; full list of drop outs and reasons for drop out figure 1 pg 1036; Last Observation Carried Forward (LOCF) analysis for responder outcome but not clear for Child Depression Rating Scale-Revised (CDRS-R)
Wagner 2004	”randomly assigned“ but no statement how	no statement	”in a double-blind fashion“ pg 1080; different colour coating was used for placebo and citalopram pills with 9 patients were dispensed medication that potentially unblinded treatment	no statement	four patients all randomly assigned to citalopram group were lost to follow-up and did not receive study medication. These patients were not included in the Intention-to-Treat (ITT)

Table 02. Assessment of risk of bias (*Continued*)

Study ID	Random sequence	Concealed allocation	Intervention blinded	Blinded outcome	Dropouts/exclusions
			assignment		analysis"...of these (ITT population) 18 patients from each group discontinued double-blind treatment prematurely
Simeon 1990	"randomly assigned" pg 792 no other statement	no statement	"double-blind" pg 792	no statement	unclear how many dropped out during treatment phase, no statement regarding Intention-to-Treat (ITT) analysis; 8 patients not contacted for follow-up

Table 03. Adverse Outcomes

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
Body as a whole	Abdominal pain treatment	6	10	4		6	CITALOPRAM 2 (Von Knorring 2006)= 11; ESCITALOPRAM (Wagner 2006)=14	10	
	Abdominal pain placebo	9	10	3		2	CITALOPRAM 2 (Von Knorring 2006)=6; ESCITALOPRAM (Wagner 2006)=7	6	
	Asthenia treatment	12	10	7					
	Asthenia placebo	9	10	9					
	Headache treatment	34	32	20			CITALOPRAM 2 (Von Knorring 2006)= 32; ESCITALOPRAM (Wagner 2006)=30		
	Headache placebo	21	34	20			CITALOPRAM 2 (Von Knorring 2006)= 28; ESCITALOPRAM		

Table 03. Adverse Outcomes (*Continued*)

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
							(Wagner 2006)=29		
	Infection treatment	14	10	7					
	Infection placebo	6	9	6					
	Trauma treatment		2	13					
	Trauma placebo		6	8					
	Fatigue treatment					1	CITALO-PRAM 2 (Von Knorring 2006)=7	5	
	Fatigue placebo					2	CITALO-PRAM 2 (Von Knorring 2006)=1	1	
Digestive System	Constipation treatment		5						
	Constipation placebo		4						
	Decreased appetite treatment	14	7						10
	Decreased appetite placebo	3	4						2
	Diarrhea treatment	4	7			2	CITALO-PRAM 2 (Von	5	18

Table 03. Adverse Outcomes (*Continued*)

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
							Knorring 2006)=7; ESC-ITALOPRAM (Wagner 2006)=5		
	Diarrhea placebo	3	7			1	CITALO-PRAM 2 (Von Knorring 2006)=3; ESC-ITALOPRAM (Wagner 2006)=8	1	3
	Dry mouth treatment		19						
	Dry mouth placebo		12						
	Dyspepsia treatment		6	6					
	Dyspepsia placebo		4	3					
	Nausea treatment	44	22	13			CITALO-PRAM 2 (Von Knorring 2006)= 23; ESCI-TALOPRAM (Wagner 2006)=10	12	27
	Nausea placebo	14	17	9			CITALO-PRAM 2 (Von Knorring 2006)=	3	3

Table 03. Adverse Outcomes (*Continued*)

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
							17; ESCI-TALOPRAM (Wagner 2006)=6		
	Vomiting treatment	7	3	6		2	ESCITALO-PRAM (Wagner 2006)=7		8
	Vomiting placebo	3	6	2		1	ESCITALO-PRAM (Wagner 2006)=5		4
Nervous system	Dizziness treatment	19	22	5			CITALO-PRAM 2 (Von Knorring 2006)= 10; ESCI-TALOPRAM (Wagner 2006)=6		
	Dizziness placebo	7	16	1			CITALO-PRAM 2 (Von Knorring 2006)=6; ESC-ITALOPRAM (Wagner 2006)=3		
	Emotional lability treatment	8	6			0			12
	Emotional lability placebo	3	3			1			2

Table 03. Adverse Outcomes (*Continued*)

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
	Hostility/anger treatment		7			1			
	Hostility/anger placebo		0			0			
	Mania/ Hypermania treatment					3			
	Mania/ hypermania placebo					2			
	Nervousness treatment	2	8	6		0			
	Nervousness placebo	3	5	4		1			
	Somnolance treatment	17	8	10		0			
	Somnolance placebo	6	5	7		1			
	Tremor treatment	6	10			2			
	Tremor placebo	1	2			0			
	Insomnia treatment	9	14	11		3			26
	Insomnia placebo	3	4	7		1			18
Respiratory System	Pharyngitis treatment	2	5	8			ESCITALO-PRAM (Wagner 2006)=7		

Table 03. Adverse Outcomes (*Continued*)

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
	Pharyngitis placebo	5	8	6			ESCITALO-PRAM (Wagner 2006)=8		
	Respiratory disorder treatment	5	10	11					
	Respiratory disorder placebo	3	11	11					
	Rhinitis treatment	3	7	5			CITALO-PRAM 2 (Von Knorring 2006)= 12; ESCI-TALOPRAM (Wagner 2006)=8		
	Rhinitis placebo	3	5	3			CITALO-PRAM 2 (Von Knorring 2006)=9; ESC-ITALOPRAM (Wagner 2006)=8		
	Sinusitis Treatment		6	6		4			
	Sinusitis Placebo		7	4		2			
	Cough increased treatment		5	6					

Table 03. Adverse Outcomes (*Continued*)

Body Group	Specific outcome	Paroxetine (Milin)	Paroxetine (Kelle	Paroxetine (Emslie)	Fluoxetine (Emslies)	Fluoxetine (TADS)	Cit 2 & Forest	Citalopram (Wagner)	Sertraline (Wagner)
	Cough increased placebo		6	3					
	Influenza type symptoms treatment			7			CITALO-PRAM 2 (Von Knorring 2006)=7; ESC-ITALOPRAM (Wagner 2006)=3	5	
	Influenza type symptoms control			4			CITALO-PRAM 2 (Von Knorring 2006)=3; ESC-ITALOPRAM (Wagner 2006)=8	1	
	Total particpants per group	Treatment= 183/Placebo= 93	Treatment= 93/Placebo=87	Treatment= 101/Placebo= 102		Treatment= 109/Placebo= 112	CITALO-PRAM 2 (Von Knorring 2006) Treatment= 121/Placebo= 112; ESCI-TALOPRAM (Wagner 2006)Treat-ment= 131/Placebo= 133	Treatment= 89/Placebo=85	Treatment= 189/Placebo= 184

Table 04. Attrition (drop out) rates

Study ID	Total attrition	Total randomised	Percentage attrition	Attrition SSRI group	SSRI total N	% attrition SSRI	Attrition placebo gp	Placebo total N	% attrition placebo
Von Knorring 2006	91	242	38%	50	124	40%	41	120	34%
Emslie 1997	36	96	38%	14	48	29%	22	48	46%
Emslie 2002	61	219	28%	19	109	17%	42	110	38%
Keller 2001	47	180	26%	26	93	28%	21	87	24%
Milin 2004	90	286	31%	60	187	32%	30	99	30%
Paroxetine Study 3	57	206	28%	34	104	33%	23	102	23%
TADS 2004	41	221	19%	18	109	17%	23	112	21%
Wagner (Study 1 & 2) 2003	77	376	20%	46	189	24%	31	187	17%
Wagner 2004	40	178	22%	22	93	24%	18	85	21%
Wagner 2006	91	244	37%	45	124	36%	46	120	38%
Simeon	8	40	20%						

Table 05. Concurrent Comorbid Conditions in the Treatment or Control Groups

	Emslie 1997	Emslie 2002	TADS	Paroxetine trial 3	Milin	Keller	Wagner 1 & 2	Wagner 2004	Wagner 2006
Presence of dysthymia (treatment group)	41.7%		5.5%	2%					5.6%
Presence of dysthymia (control group)	29.2%		10.7%	0%				1.2%	
Presence of anxiety (treatment group)	66.7%		25.7%	10.9%	17.0%	20.4%			4.5%

Table 05. Concurrent Comorbid Conditions in the Treatment or Control Groups (*Continued*)

	Emslie 1997	Emslie 2002	TADS	Paroxetine trial 3	Milin	Keller	Wagner 1 & 2	Wagner 2004	Wagner 2006
Presence of anxiety (control group)	45.8%		28.6%	2%	18.3%	32.2%			7.5%
Presence of ADHD (treatment group)	33.3%	14.7%	11.9%	3%	1.6%			4.5%	
Presence of ADHD (control group)	27.1%	13.6%	16.7%	1%	0%			1.2%	
Presence of ODD/CD (treatment group)	27.1%	20.2%	22.9%	4.9%	0.5%	26.9%			
Presence of ODD/CD (control group)	33.3%	16.4%	25.0%	3.9%	1.1%	23.0%			
Presence of 'Any' diagnosis (treatment group)	85.4%		56.9%	27.7%		44.1%			
Presence of 'Any' diagnosis (control group)	77.1%		48.7%	17.6%		51.7%			

ANALYSES

Comparison 01. Paroxetine versus placebo (LOCF)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Response (by predefined criteria)	4	646	Relative Risk (Fixed) 95% CI	1.09 [0.95, 1.26]
02 Depression symptom severity CDRS-R	2		Mean Difference (Fixed) 95% CI	1.60 [-2.24, 5.44]
03 Depression symptom severity K-SADS 9 item subscale	2		Mean difference (Fixed) 95% CI	-0.96 [-2.26, 0.34]
04 Functioning GAF	2		Mean difference (Fixed) 95% CI	1.55 [-1.96, 5.05]
05 Functioning Autonomous Functioning Checklist	1		Mean difference (Fixed) 95% CI	5.40 [-2.29, 13.09]

06 Suicide related outcomes (ideation and attempt)	4	646	Relative Risk (Fixed) 95% CI	2.34 [0.99, 5.51]
07 Completion of study protocol	3	672	Relative Risk (Fixed) 95% CI	0.93 [0.85, 1.03]
08 Adverse events	4	658	Relative Risk (Fixed) 95% CI	1.14 [1.03, 1.27]

Comparison 02. Paroxetine versus placebo (OC)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Response (by predefined criteria)	4	473	Relative Risk (Fixed) 95% CI	1.15 [1.02, 1.30]
02 Depressive symptom severity CDRS-R	2		Mean difference (Fixed) 95% CI	-0.59 [-4.30, 3.11]
03 Depressive symptom severity K-SADS 9 item subscale	2		Mean difference (Fixed) 95% CI	-0.79 [-2.05, 0.46]
04 Functioning GAF	2		Mean difference (Fixed) 95% CI	2.30 [-1.51, 6.11]
05 Functioning Autonomous Functioning Checklist	1		Mean difference (Fixed) 95% CI	5.05 [-2.75, 12.85]

Comparison 03. Fluoxetine versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Response (by predefined criteria)	4	527	Relative Risk (Fixed) 95% CI	1.86 [1.49, 2.32]
02 Depression symptom severity CDRS-R	5		Mean difference (Fixed) 95% CI	-5.63 [-7.38, -3.88]
03 Functioning CGAS (LOCF)	2		Mean difference (Fixed) 95% CI	3.76 [-3.19, 10.71]
04 Functioning GAF (LOCF)	2		Mean difference (Fixed) 95% CI	1.11 [-2.09, 4.32]
05 Suicide related outcomes (ideation and attempt)	4	479	Relative Risk (Fixed) 95% CI	1.55 [0.77, 3.11]
06 Completion of study protocol	1	219	Relative Risk (Fixed) 95% CI	1.34 [1.13, 1.58]
07 Adverse events	1	219	Relative Risk (Fixed) 95% CI	1.19 [1.03, 1.36]

Comparison 04. Sertraline versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Response (by predefined criteria)	1	364	Relative Risk (Fixed) 95% CI	1.17 [1.00, 1.36]
02 Depression symptom severity (CDRS-R)	4		Mean difference (Fixed) 95% CI	-3.56 [-6.69, -0.42]
03 Functioning CGAS (LOCF)	1		Mean difference (Fixed) 95% CI	1.31 [-1.61, 4.23]
04 Suicide related outcomes (ideation and attempt)	4	376	Relative Risk (Fixed) 95% CI	2.36 [0.62, 8.95]
05 Completion of study protocol	1	376	Relative Risk (Fixed) 95% CI	0.91 [0.82, 1.01]

Comparison 05. Citalopram versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Response (by predefined criteria)	2	435	Relative Risk (Fixed) 95% CI	1.30 [1.02, 1.67]
02 Depressive symptom severity (CDRS-R)	3		Mean difference (Fixed) 95% CI	-2.13 [-4.95, 0.69]
03 Functioning CGAS (LOCF)	2		Mean difference (Fixed) 95% CI	2.91 [-0.20, 6.01]
04 Suicide related outcomes (ideation and attempt)	3	682	Relative Risk (Fixed) 95% CI	1.46 [0.72, 2.95]
05 Completion of study protocol	2	422	Relative Risk (Fixed) 95% CI	0.89 [0.78, 1.00]
06 Adverse events	2	436	Relative Risk (Fixed) 95% CI	1.09 [0.97, 1.22]

Comparison 06. SSRI versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Response (by predefined criteria)	9	1972	Relative Risk (Fixed) 95% CI	1.28 [1.17, 1.41]
02 Suicide related outcome	9	1864	Relative Risk (Fixed) 95% CI	1.73 [1.13, 2.67]

COVER SHEET

Title

Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

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Contribution of author(s)

Sarah Hetrick
Conceived the review
Coordinated preparation of the protocol and the review.
Contributed to the search strategy, extraction of information about the trials and outcome data, preparation of the text of the review.
Sally Merry
Help to conceive the review
Provided general advice on the protocol
Helped prepare the text of the review, with a significant contribution to the discussion and conclusion of the review.
Jo McKenzie
Assisted with the assessment of risk of bias of the included trials. Advised on the analysis of the data and made a significant contribution to writing the results, including input to the discussion and conclusions.
Per Sindahl
Provided general advice on the protocol.
Contributed to extraction of information about the trials and outcome data and preparation of the text of the review.
Michelle Proctor
Assisted with preparation of the protocol and made significant contribution to running the search strategy, contributed to extraction of information about the trials and outcome data, and commented on the text of the review.
Alison Ward
Provided with general advice on the protocol, contributed to extraction of information about the trials and outcome data and commented on the text of the review.

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Date new studies found but not yet included/excluded	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 01 Response (by predefined criteria)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 01 Response (by predefined criteria)

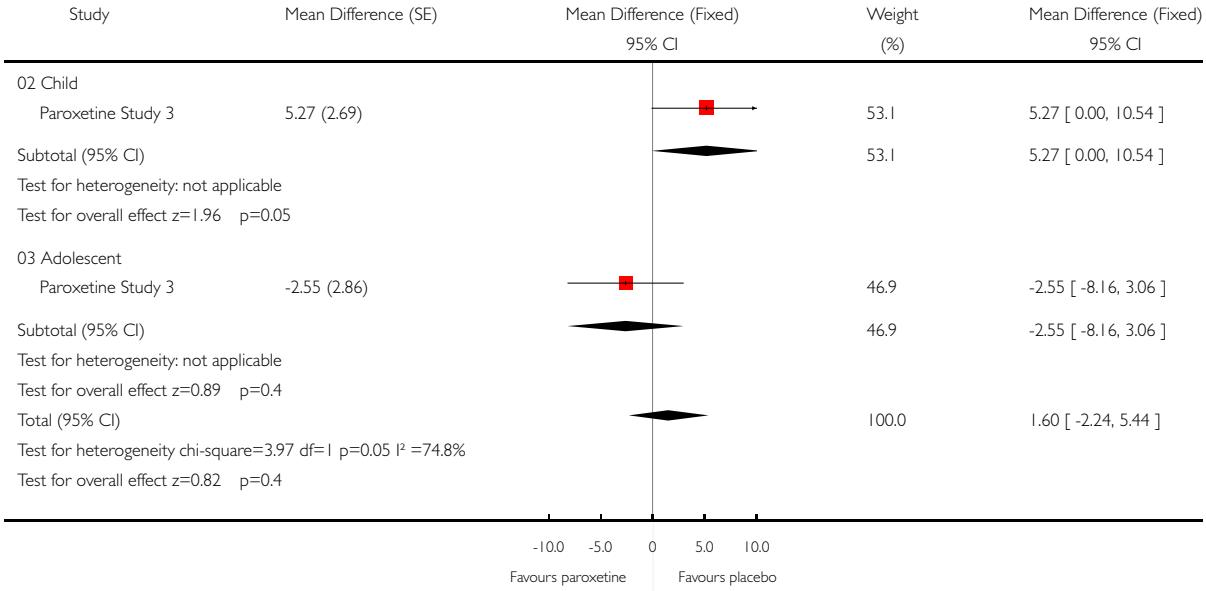
Study	Paroxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Children (LOCF)					
Paroxetine Study 3	22/49	22/47		13.6	0.96 [0.62, 1.48]
Subtotal (95% CI)	49	47		13.6	0.96 [0.62, 1.48]
Total events: 22 (Paroxetine), 22 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.19 p=0.9					
02 Adolescents (LOCF)					
Keller 2001	60/90	48/87		29.6	1.21 [0.95, 1.53]
Milin 2004	107/177	53/91		42.4	1.04 [0.84, 1.28]
Paroxetine Study 3	27/52	24/53		14.4	1.15 [0.77, 1.70]
Subtotal (95% CI)	319	231		86.4	1.11 [0.96, 1.29]
Total events: 194 (Paroxetine), 125 (Placebo)					
Test for heterogeneity chi-square=0.90 df=2 p=0.64 I^2 =0.0%					
Test for overall effect z=1.44 p=0.1					
Total (95% CI)	368	278		100.0	1.09 [0.95, 1.26]
Total events: 216 (Paroxetine), 147 (Placebo)					
Test for heterogeneity chi-square=1.31 df=3 p=0.73 I^2 =0.0%					
Test for overall effect z=1.25 p=0.2					

Analysis 01.02. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 02 Depression symptom severity CDRS-R

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 02 Depression symptom severity CDRS-R

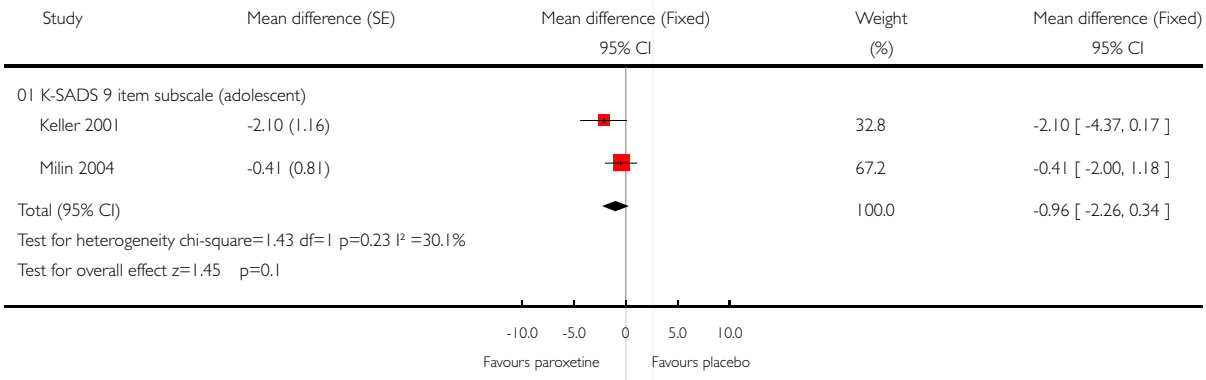


Analysis 01.03. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 03 Depression symptom severity K-SADS 9 item subscale

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 03 Depression symptom severity K-SADS 9 item subscale

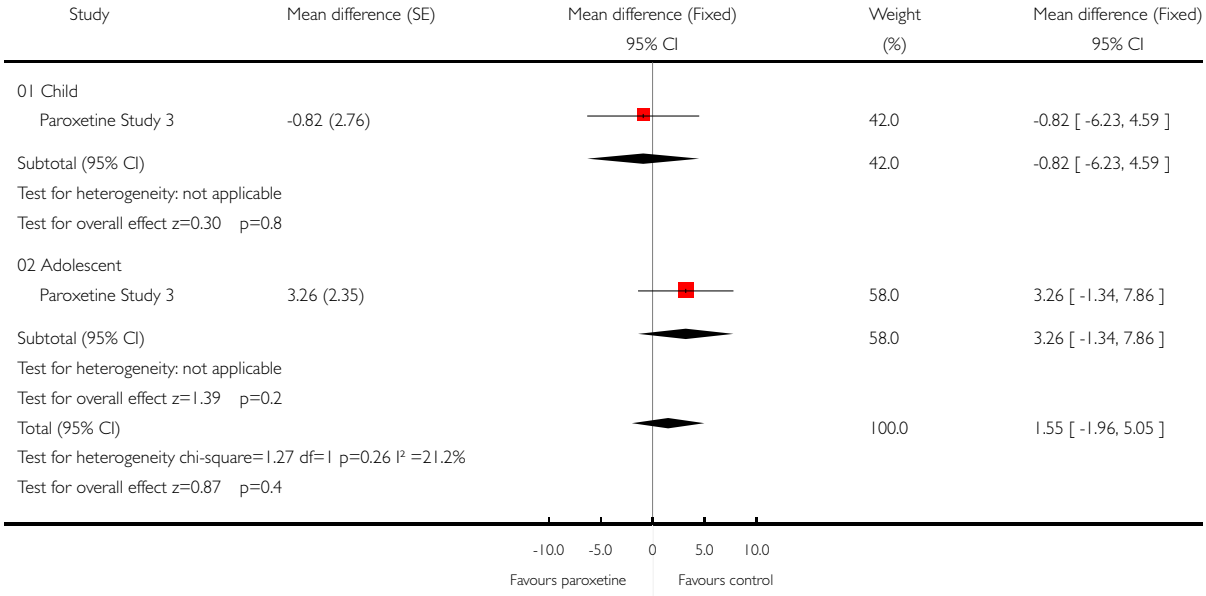


Analysis 01.04. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 04 Functioning GAF

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 04 Functioning GAF

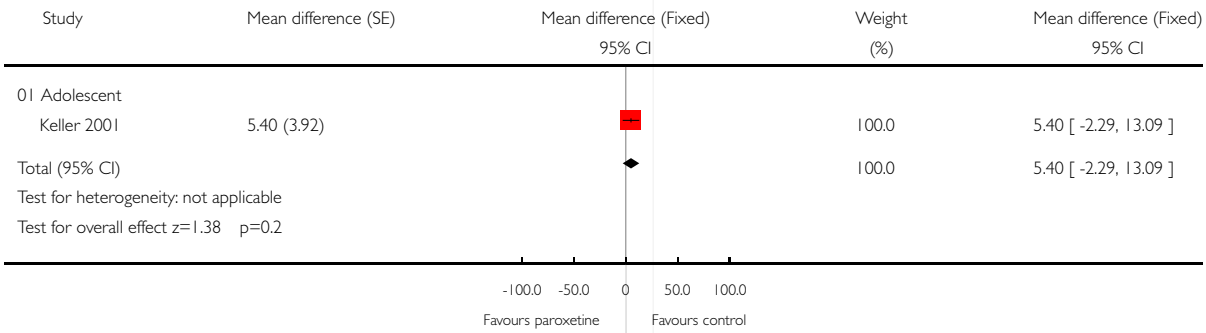


Analysis 01.05. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 05 Functioning Autonomous Functioning Checklist

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 05 Functioning Autonomous Functioning Checklist



Analysis 01.06. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 06 Suicide related outcomes (ideation and attempt)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 06 Suicide related outcomes (ideation and attempt)

Study	Paroxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Children					
Paroxetine Study 3	1/49	0/47		6.8	2.88 [0.12, 68.98]
Subtotal (95% CI)	49	47		6.8	2.88 [0.12, 68.98]
Total events: 1 (Paroxetine), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.65 p=0.5					
02 Adolescents					
Keller 2001	8/90	1/87		13.6	7.73 [0.99, 60.55]
Milin 2004	9/177	3/91		53.0	1.54 [0.43, 5.56]
Paroxetine Study 3	2/52	2/53		26.5	1.02 [0.15, 6.97]
Subtotal (95% CI)	319	231		93.2	2.30 [0.94, 5.60]
Total events: 19 (Paroxetine), 6 (Placebo)					
Test for heterogeneity chi-square=2.39 df=2 p=0.30 I^2 =16.5%					
Test for overall effect z=1.83 p=0.07					
Total (95% CI)	368	278		100.0	2.34 [0.99, 5.51]
Total events: 20 (Paroxetine), 6 (Placebo)					
Test for heterogeneity chi-square=2.44 df=3 p=0.49 I^2 =0.0%					
Test for overall effect z=1.94 p=0.05					

Analysis 01.07. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 07 Completion of study protocol

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 07 Completion of study protocol

Study	Paroxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Adolescents					
Keller 2001	67/93	66/87		28.6	0.95 [0.80, 1.13]
Milin 2004	127/187	69/99		37.9	0.97 [0.83, 1.15]
Subtotal (95% CI)	280	186		66.5	0.96 [0.86, 1.09]
Total events: 194 (Paroxetine), 135 (Placebo)					
Test for heterogeneity chi-square=0.05 df=1 p=0.83 I^2 =0.0%					
Test for overall effect z=0.61 p=0.5					
03 Children and Adolescents					
Paroxetine Study 3	70/104	79/102		33.5	0.87 [0.73, 1.03]
Subtotal (95% CI)	104	102		33.5	0.87 [0.73, 1.03]
Total events: 70 (Paroxetine), 79 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.62 p=0.1					
Total (95% CI)	384	288		100.0	0.93 [0.85, 1.03]
Total events: 264 (Paroxetine), 214 (Placebo)					
Test for heterogeneity chi-square=0.98 df=2 p=0.61 I^2 =0.0%					
Test for overall effect z=1.41 p=0.2					

Analysis 01.08. Comparison 01 Paroxetine versus placebo (LOCF), Outcome 08 Adverse events

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 01 Paroxetine versus placebo (LOCF)

Outcome: 08 Adverse events

Study	Paroxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Children					
Paroxetine Study 3	34/49	30/47		14.9	1.09 [0.82, 1.44]
Subtotal (95% CI)	49	47		14.9	1.09 [0.82, 1.44]
Total events: 34 (Paroxetine), 30 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.58 p=0.6					
02 Adolescents					
Keller 2001	86/93	69/87		34.6	1.17 [1.03, 1.32]
Milin 2004	120/182	55/93		35.4	1.11 [0.91, 1.36]
Paroxetine Study 3	37/52	32/55		15.1	1.22 [0.92, 1.62]
Subtotal (95% CI)	327	235		85.1	1.15 [1.04, 1.29]
Total events: 243 (Paroxetine), 156 (Placebo)					
Test for heterogeneity chi-square=0.30 df=2 p=0.86 I^2 =0.0%					
Test for overall effect z=2.60 p=0.009					
Total (95% CI)	376	282		100.0	1.14 [1.03, 1.27]
Total events: 277 (Paroxetine), 186 (Placebo)					
Test for heterogeneity chi-square=0.49 df=3 p=0.92 I^2 =0.0%					
Test for overall effect z=2.61 p=0.009					

Analysis 02.01. Comparison 02 Paroxetine versus placebo (OC), Outcome 01 Response (by predefined criteria)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 02 Paroxetine versus placebo (OC)

Outcome: 01 Response (by predefined criteria)

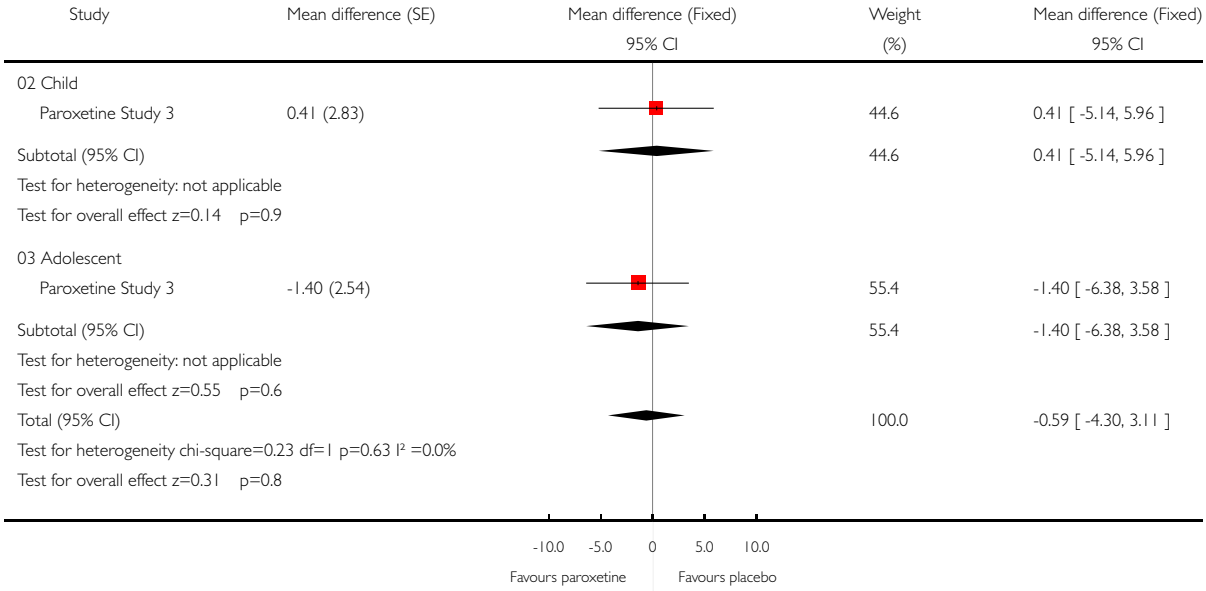
Study	Paroxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
04 Children (OC)					
Paroxetine Study 3	20/29	22/42		12.4	1.32 [0.90, 1.92]
Subtotal (95% CI)	29	42		12.4	1.32 [0.90, 1.92]
Total events: 20 (Paroxetine), 22 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.43 p=0.2					
05 Adolecents (OC)					
Keller 2001	54/67	43/66		29.8	1.24 [1.00, 1.53]
Milin 2004	94/126	47/66		42.5	1.05 [0.87, 1.26]
Paroxetine Study 3	26/39	22/38		15.3	1.15 [0.81, 1.63]
Subtotal (95% CI)	232	170		87.6	1.13 [0.99, 1.29]
Total events: 174 (Paroxetine), 112 (Placebo)					
Test for heterogeneity chi-square=1.36 df=2 p=0.51 I^2 =0.0%					
Test for overall effect z=1.85 p=0.06					
Total (95% CI)	261	212		100.0	1.15 [1.02, 1.30]
Total events: 194 (Paroxetine), 134 (Placebo)					
Test for heterogeneity chi-square=1.94 df=3 p=0.59 I^2 =0.0%					
Test for overall effect z=2.27 p=0.02					

Analysis 02.02. Comparison 02 Paroxetine versus placebo (OC), Outcome 02 Depressive symptom severity CDRS-R

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 02 Paroxetine versus placebo (OC)

Outcome: 02 Depressive symptom severity CDRS-R

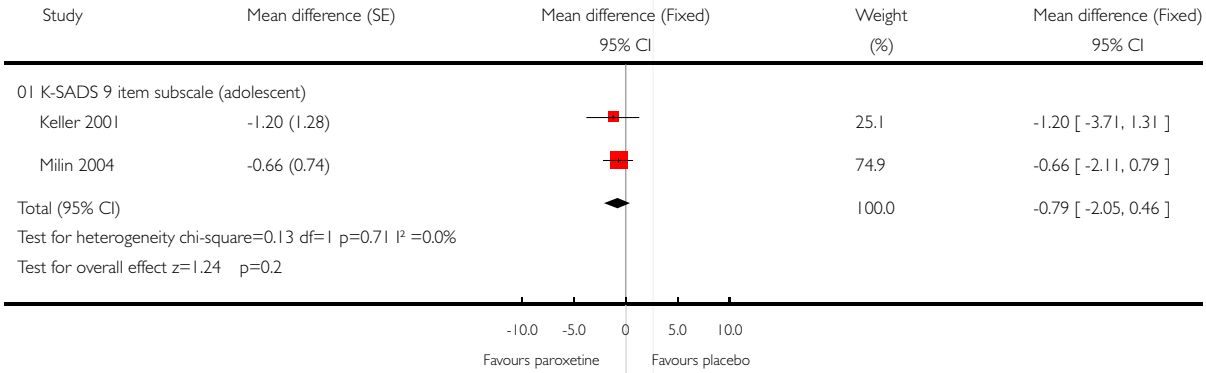


Analysis 02.03. Comparison 02 Paroxetine versus placebo (OC), Outcome 03 Depressive symptom severity K-SADS 9 item subscale

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 02 Paroxetine versus placebo (OC)

Outcome: 03 Depressive symptom severity K-SADS 9 item subscale

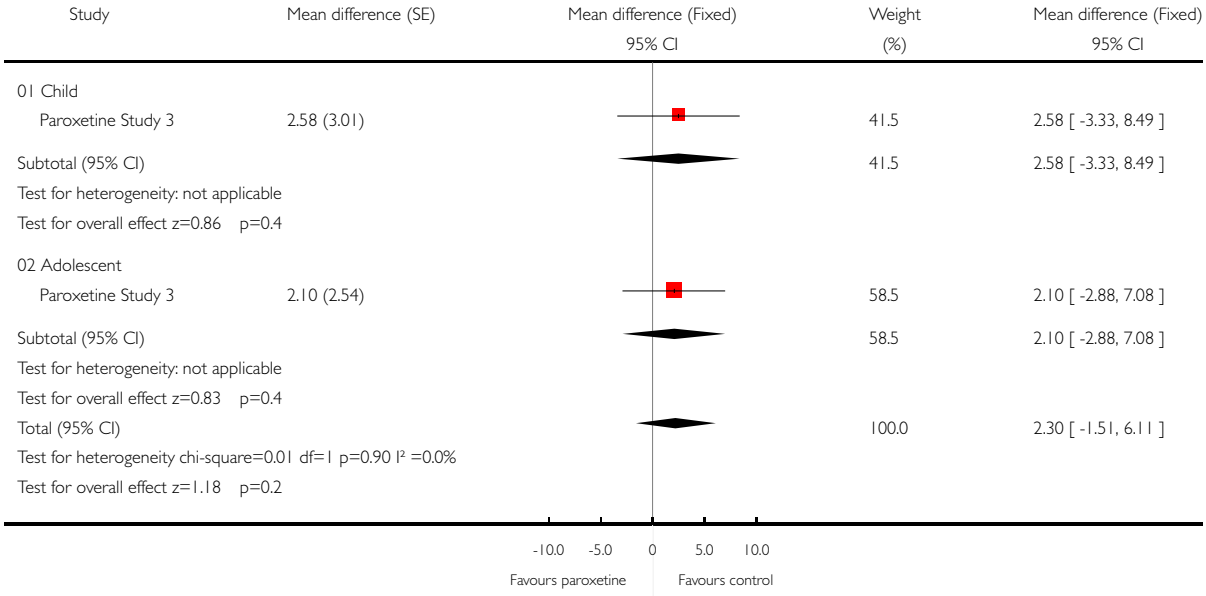


Analysis 02.04. Comparison 02 Paroxetine versus placebo (OC), Outcome 04 Functioning GAF

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 02 Paroxetine versus placebo (OC)

Outcome: 04 Functioning GAF

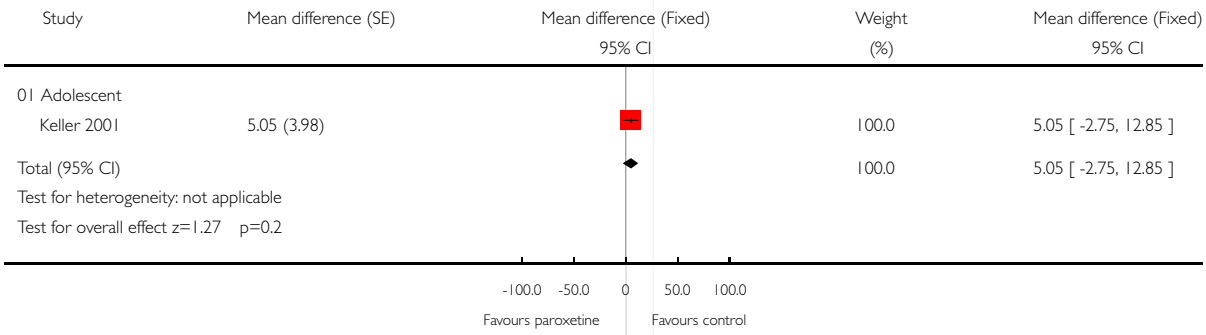


Analysis 02.05. Comparison 02 Paroxetine versus placebo (OC), Outcome 05 Functioning Autonomous Functioning Checklist

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 02 Paroxetine versus placebo (OC)

Outcome: 05 Functioning Autonomous Functioning Checklist



Analysis 03.01. Comparison 03 Fluoxetine versus placebo, Outcome 01 Response (by predefined criteria)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 01 Response (by predefined criteria)

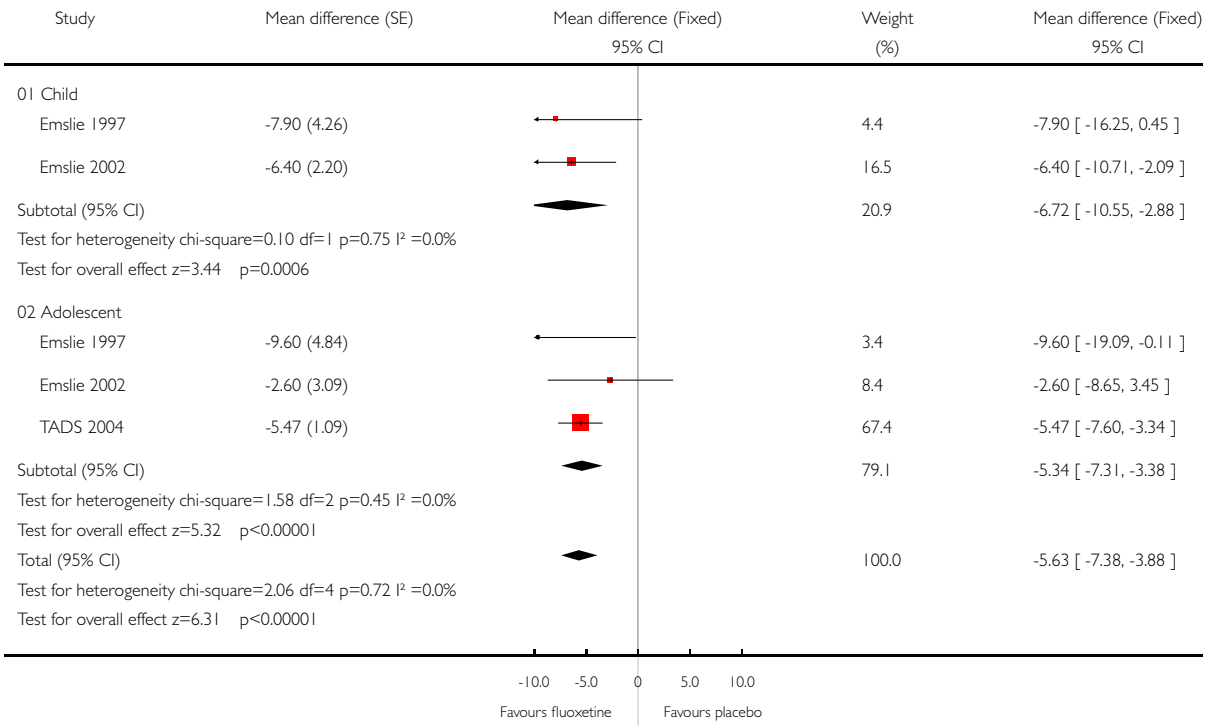
Study	Fluoxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Children (LOCF)					
Emslie 2002	27/61	10/55		14.2	2.43 [1.30, 4.56]
Subtotal (95% CI)	61	55		14.2	2.43 [1.30, 4.56]
Total events: 27 (Fluoxetine), 10 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.78 p=0.005					
02 Adolescents (LOCF)					
Emslie 2002	18/48	10/46		13.8	1.73 [0.89, 3.33]
TADS 2004	66/109	39/112		51.8	1.74 [1.29, 2.34]
Subtotal (95% CI)	157	158		65.6	1.74 [1.32, 2.28]
Total events: 84 (Fluoxetine), 49 (Placebo)					
Test for heterogeneity chi-square=0.00 df=1 p=0.98 I^2 =0.0%					
Test for overall effect z=3.99 p=0.00007					
03 Children and Adolescents (LOCF)					
Emslie 1997	28/48	15/48		20.2	1.87 [1.15, 3.03]
Subtotal (95% CI)	48	48		20.2	1.87 [1.15, 3.03]
Total events: 28 (Fluoxetine), 15 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.53 p=0.01					
Total (95% CI)	266	261		100.0	1.86 [1.49, 2.32]
Total events: 139 (Fluoxetine), 74 (Placebo)					
Test for heterogeneity chi-square=0.96 df=3 p=0.81 I^2 =0.0%					
Test for overall effect z=5.48 p<0.00001					

Analysis 03.02. Comparison 03 Fluoxetine versus placebo, Outcome 02 Depression symptom severity CDRS-R

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 02 Depression symptom severity CDRS-R

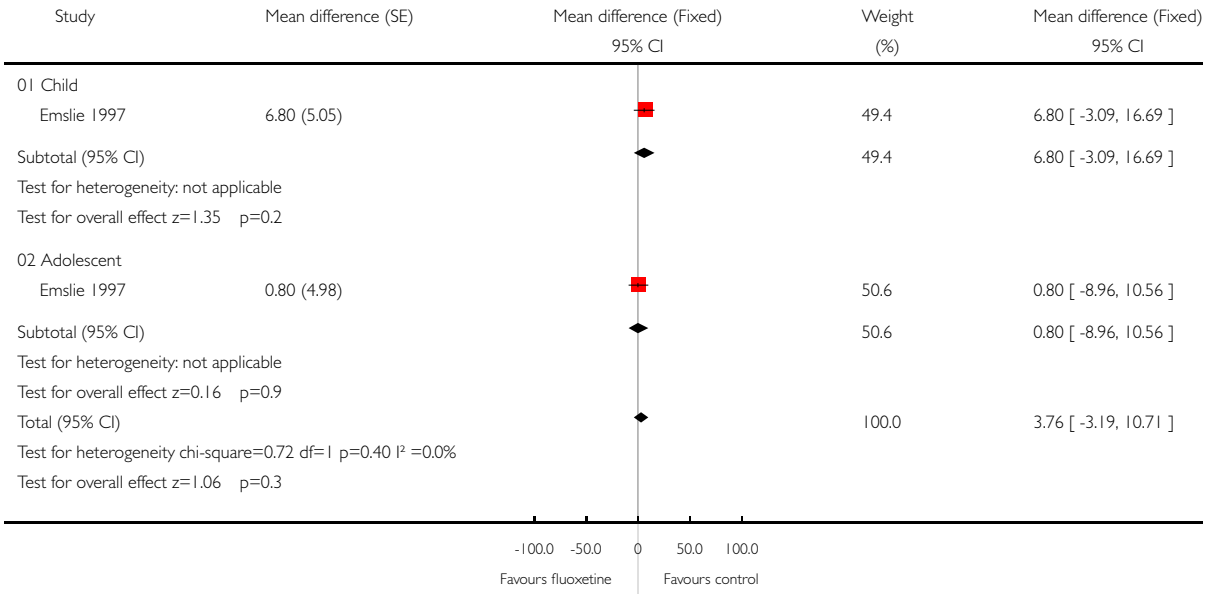


Analysis 03.03. Comparison 03 Fluoxetine versus placebo, Outcome 03 Functioning CGAS (LOCF)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 03 Functioning CGAS (LOCF)

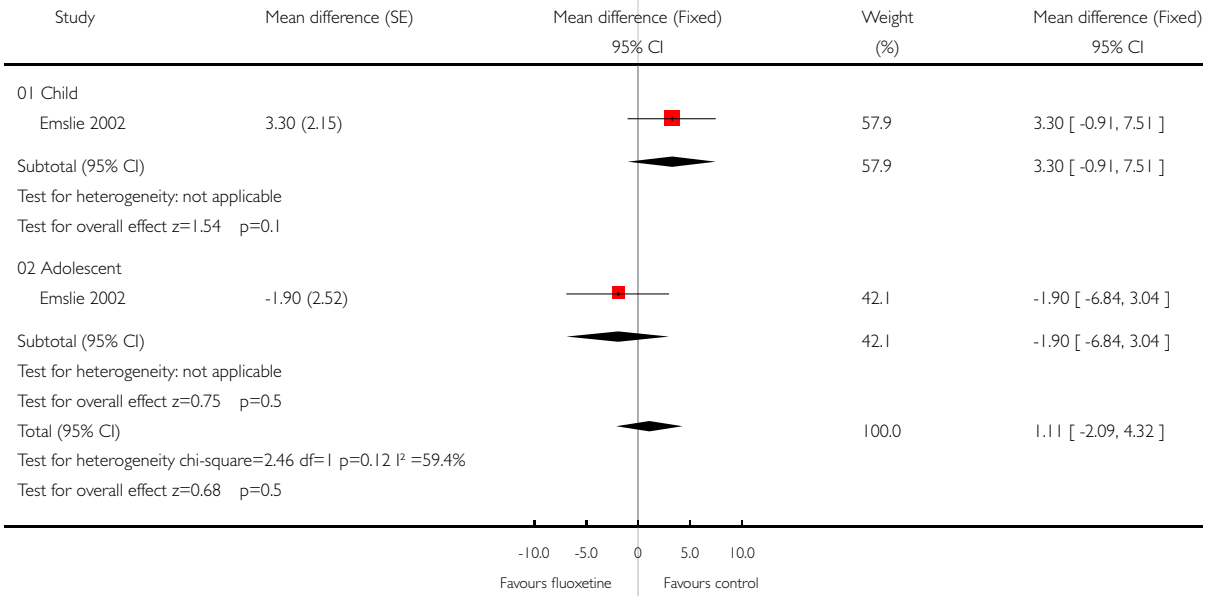


Analysis 03.04. Comparison 03 Fluoxetine versus placebo, Outcome 04 Functioning GAF (LOCF)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 04 Functioning GAF (LOCF)



Analysis 03.05. Comparison 03 Fluoxetine versus placebo, Outcome 05 Suicide related outcomes (ideation and attempt)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 05 Suicide related outcomes (ideation and attempt)

Study	Fluoxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Children					
Emslie 2002	4/61	3/55		25.9	1.20 [0.28, 5.13]
Subtotal (95% CI)	61	55		25.9	1.20 [0.28, 5.13]
Total events: 4 (Fluoxetine), 3 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.25 p=0.8					
02 Adolescents					
Emslie 1997	2/24	2/24		16.4	1.00 [0.15, 6.53]
Emslie 2002	4/48	3/46		25.2	1.28 [0.30, 5.40]
TADS 2004	9/109	4/112		32.4	2.31 [0.73, 7.29]
Subtotal (95% CI)	181	182		74.1	1.67 [0.75, 3.71]
Total events: 15 (Fluoxetine), 9 (Placebo)					
Test for heterogeneity chi-square=0.73 df=2 p=0.69 I^2 =0.0%					
Test for overall effect z=1.26 p=0.2					
Total (95% CI)	242	237		100.0	1.55 [0.77, 3.11]
Total events: 19 (Fluoxetine), 12 (Placebo)					
Test for heterogeneity chi-square=0.86 df=3 p=0.83 I^2 =0.0%					
Test for overall effect z=1.23 p=0.2					

Analysis 03.06. Comparison 03 Fluoxetine versus placebo, Outcome 06 Completion of study protocol

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 06 Completion of study protocol

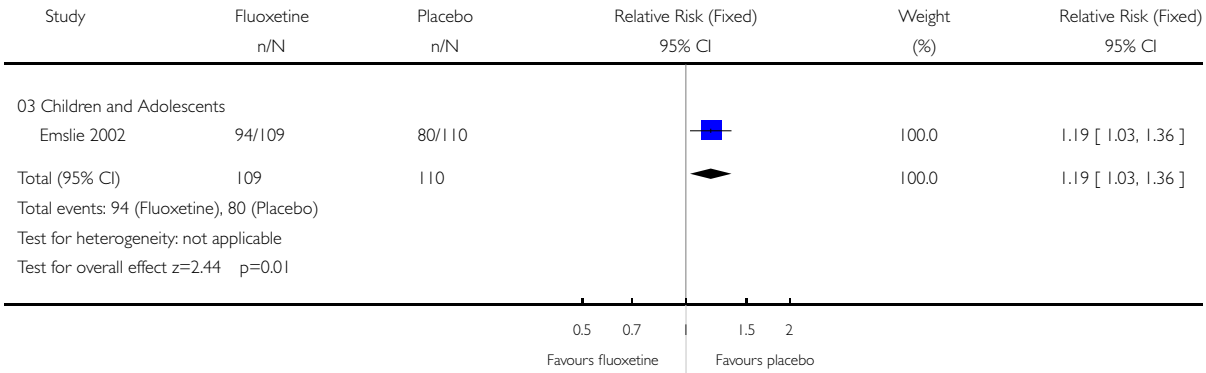
Study	Fluoxetine n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 Children and Adolescents					
Emslie 2002	90/109	68/110		100.0	1.34 [1.13, 1.58]
Total (95% CI)	109	110		100.0	1.34 [1.13, 1.58]
Total events: 90 (Fluoxetine), 68 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.33 p=0.0009					

Analysis 03.07. Comparison 03 Fluoxetine versus placebo, Outcome 07 Adverse events

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 03 Fluoxetine versus placebo

Outcome: 07 Adverse events

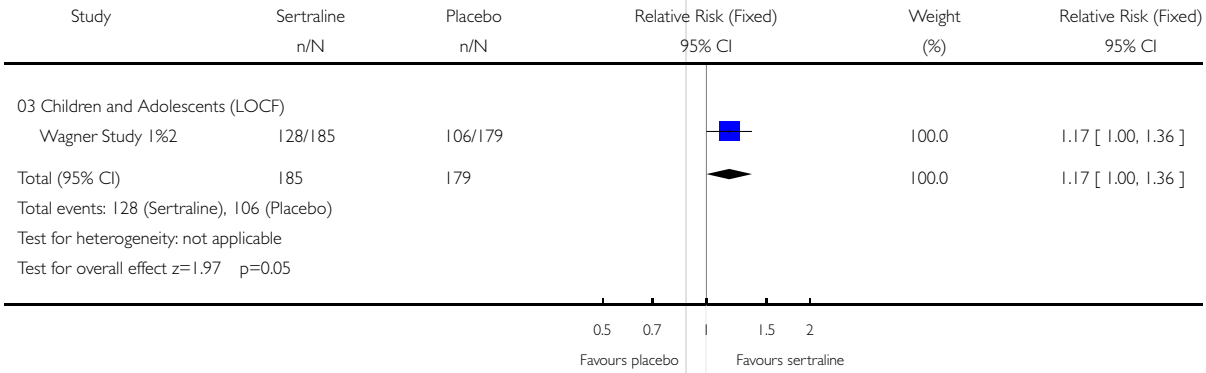


Analysis 04.01. Comparison 04 Sertraline versus placebo, Outcome 01 Response (by predefined criteria)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 04 Sertraline versus placebo

Outcome: 01 Response (by predefined criteria)

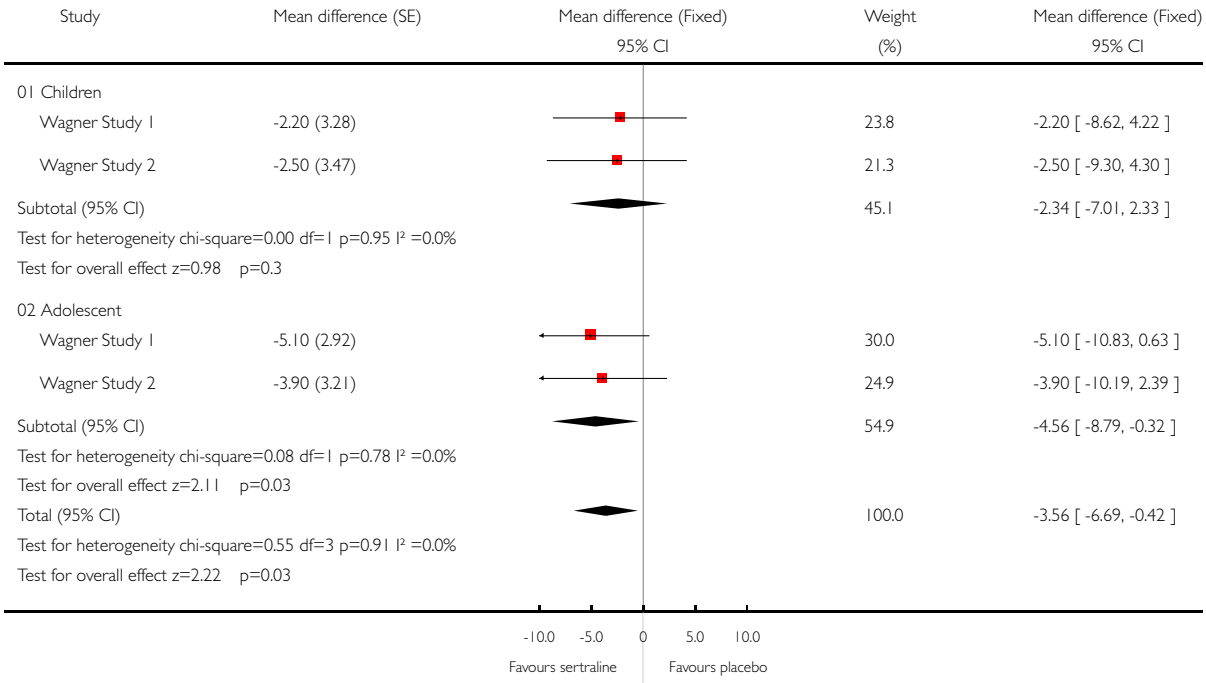


Analysis 04.02. Comparison 04 Sertraline versus placebo, Outcome 02 Depression symptom severity (CDRS-R)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 04 Sertraline versus placebo

Outcome: 02 Depression symptom severity (CDRS-R)

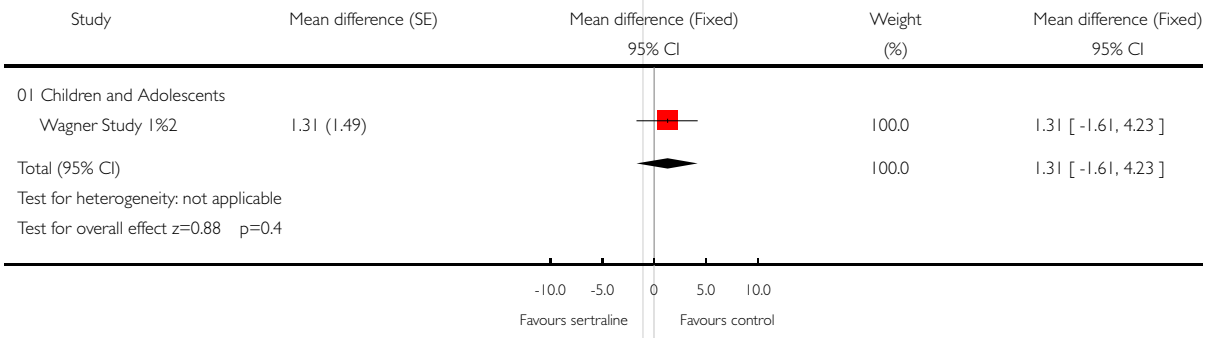


Analysis 04.03. Comparison 04 Sertraline versus placebo, Outcome 03 Functioning CGAS (LOCF)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 04 Sertraline versus placebo

Outcome: 03 Functioning CGAS (LOCF)

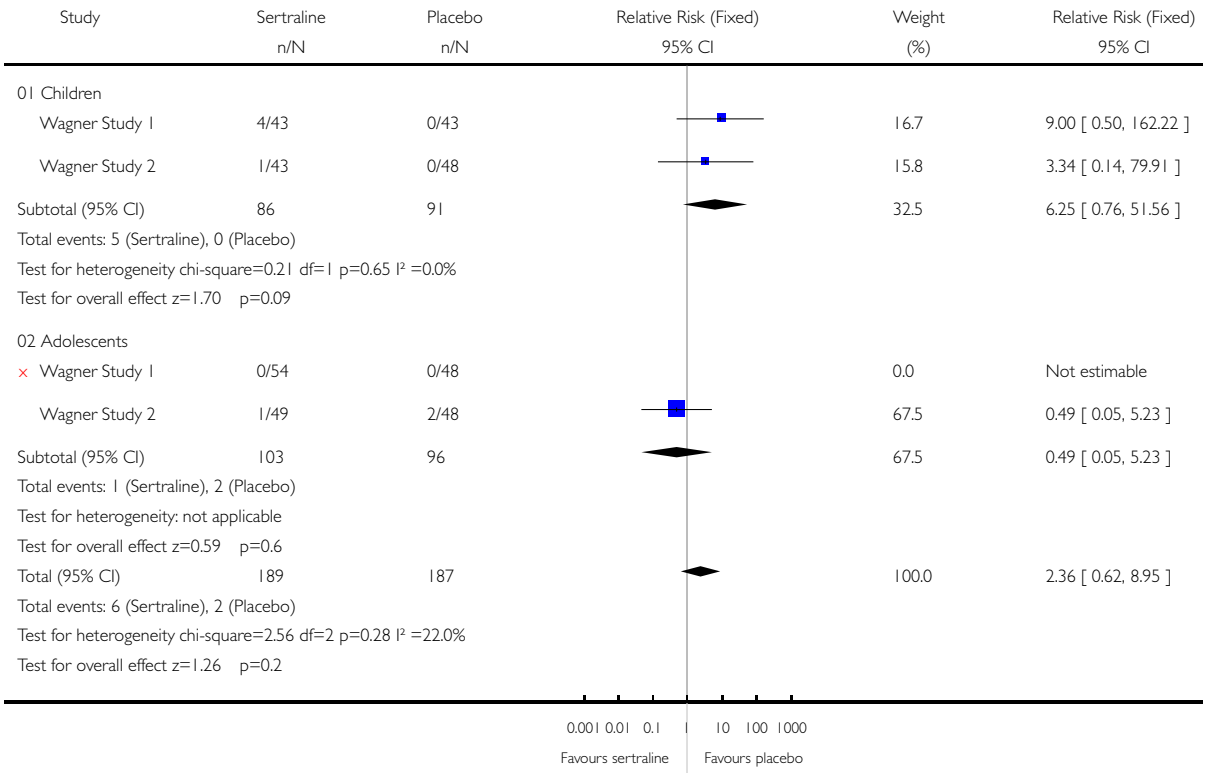


Analysis 04.04. Comparison 04 Sertraline versus placebo, Outcome 04 Suicide related outcomes (ideation and attempt)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 04 Sertraline versus placebo

Outcome: 04 Suicide related outcomes (ideation and attempt)

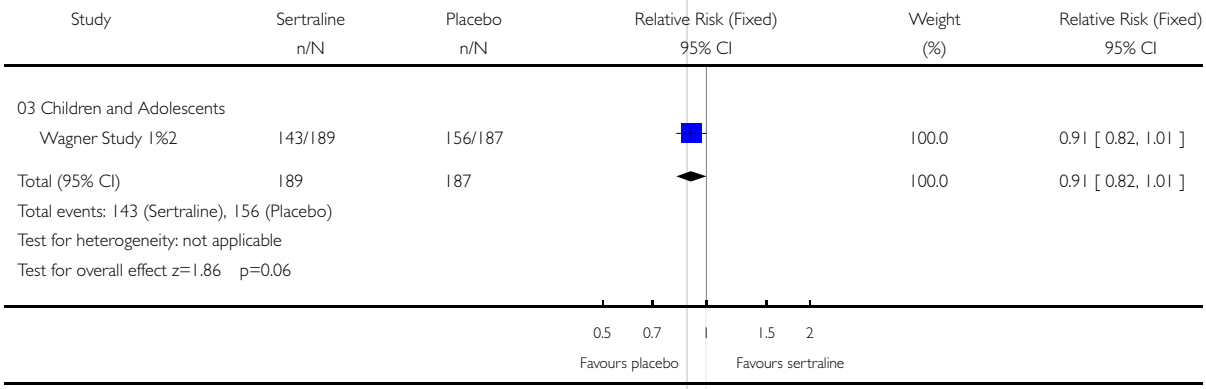


Analysis 04.05. Comparison 04 Sertraline versus placebo, Outcome 05 Completion of study protocol

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 04 Sertraline versus placebo

Outcome: 05 Completion of study protocol



Analysis 05.01. Comparison 05 Citalopram versus placebo, Outcome 01 Response (by predefined criteria)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 05 Citalopram versus placebo

Outcome: 01 Response (by predefined criteria)

Study	Citalopram n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 Children and Adolescents (LOCF)					
Wagner 2004	32/89	20/85		29.3	1.53 [0.95, 2.45]
Wagner 2006	59/129	50/132		70.7	1.21 [0.91, 1.61]
Total (95% CI)	218	217		100.0	1.30 [1.02, 1.67]
Total events: 91 (Citalopram), 70 (Placebo)					
Test for heterogeneity chi-square=0.70 df=1 p=0.40 I^2 =0.0%					
Test for overall effect z=2.09 p=0.04					

Analysis 05.02. Comparison 05 Citalopram versus placebo, Outcome 02 Depressive symptom severity (CDRS-R)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 05 Citalopram versus placebo

Outcome: 02 Depressive symptom severity (CDRS-R)

Study	Mean difference (SE)	Mean difference (Fixed) 95% CI	Weight (%)	Mean difference (Fixed) 95% CI
01 Children (LOCF)				
Wagner 2006	-0.05 (3.05)		22.4	-0.05 [-6.02, 5.92]
Subtotal (95% CI)			22.4	-0.05 [-6.02, 5.92]
Test for heterogeneity: not applicable				
Test for overall effect z=0.02 p=1				
02 Adolescents (LOCF)				
Wagner 2006	-2.60 (2.17)		44.1	-2.60 [-6.86, 1.66]
Subtotal (95% CI)			44.1	-2.60 [-6.86, 1.66]
Test for heterogeneity: not applicable				
Test for overall effect z=1.20 p=0.2				
03 Children and Adolescents				
Wagner 2004	-2.90 (2.49)		33.6	-2.90 [-7.77, 1.97]
Subtotal (95% CI)			33.6	-2.90 [-7.77, 1.97]
Test for heterogeneity: not applicable				
Test for overall effect z=1.17 p=0.2				

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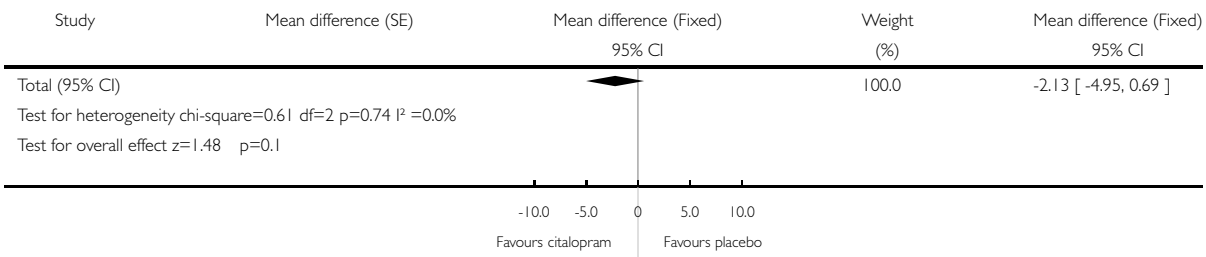
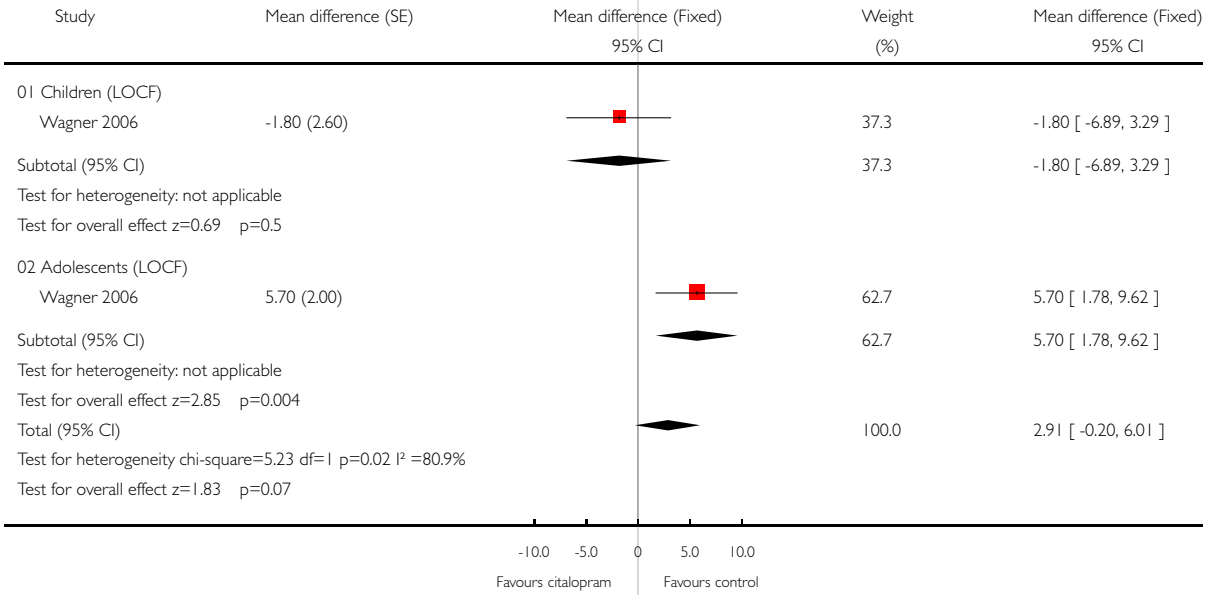


Analysis 05.03. Comparison 05 Citalopram versus placebo, Outcome 03 Functioning CGAS (LOCF)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 05 Citalopram versus placebo

Outcome: 03 Functioning CGAS (LOCF)



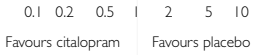
Analysis 05.04. Comparison 05 Citalopram versus placebo, Outcome 04 Suicide related outcomes (ideation and attempt)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 05 Citalopram versus placebo

Outcome: 04 Suicide related outcomes (ideation and attempt)

Study	Citalopram n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Adolescents					
Von Knorring 2006	16/124	8/120		66.9	1.94 [0.86, 4.35]
Subtotal (95% CI)	124	120		66.9	1.94 [0.86, 4.35]
Total events: 16 (Citalopram), 8 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.60 p=0.1					
03 Children and Adolescents					
Wagner 2004	1/89	2/85		16.8	0.48 [0.04, 5.17]
Wagner 2006	1/131	2/133		16.3	0.51 [0.05, 5.53]
Subtotal (95% CI)	220	218		33.1	0.49 [0.09, 2.66]
Total events: 2 (Citalopram), 4 (Placebo)					
Test for heterogeneity chi-square=0.00 df=1 p=0.97 I^2 =0.0%					
Test for overall effect z=0.82 p=0.4					
Total (95% CI)	344	338		100.0	1.46 [0.72, 2.95]
Total events: 18 (Citalopram), 12 (Placebo)					
Test for heterogeneity chi-square=2.06 df=2 p=0.36 I^2 =3.0%					
Test for overall effect z=1.05 p=0.3					



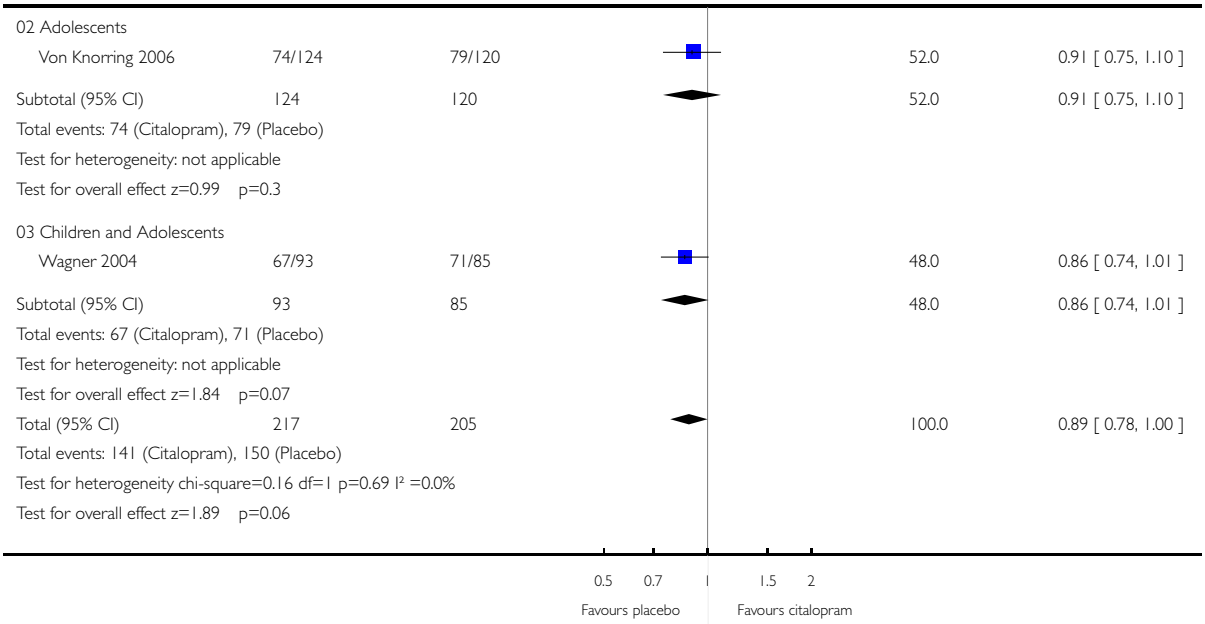
Analysis 05.05. Comparison 05 Citalopram versus placebo, Outcome 05 Completion of study protocol

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 05 Citalopram versus placebo

Outcome: 05 Completion of study protocol

Study	Citalopram n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 Adolescents					
Von Knorring 2006	74/124	79/120		52.0	0.91 [0.75, 1.10]
Subtotal (95% CI)	124	120		52.0	0.91 [0.75, 1.10]
Total events: 74 (Citalopram), 79 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.99 p=0.3					
03 Children and Adolescents					
Wagner 2004	67/93	71/85		48.0	0.86 [0.74, 1.01]
Subtotal (95% CI)	93	85		48.0	0.86 [0.74, 1.01]
Total events: 67 (Citalopram), 71 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.84 p=0.07					
Total (95% CI)	217	205		100.0	0.89 [0.78, 1.00]
Total events: 141 (Citalopram), 150 (Placebo)					
Test for heterogeneity chi-square=0.16 df=1 p=0.69 I^2 =0.0%					
Test for overall effect z=1.89 p=0.06					



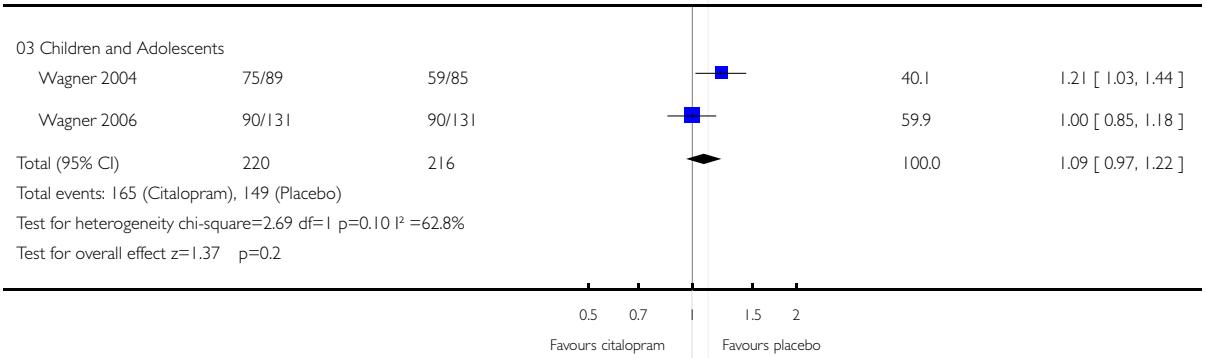
Analysis 05.06. Comparison 05 Citalopram versus placebo, Outcome 06 Adverse events

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 05 Citalopram versus placebo

Outcome: 06 Adverse events

Study	Citalopram n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 Children and Adolescents					
Wagner 2004	75/89	59/85		40.1	1.21 [1.03, 1.44]
Wagner 2006	90/131	90/131		59.9	1.00 [0.85, 1.18]
Total (95% CI)	220	216		100.0	1.09 [0.97, 1.22]
Total events: 165 (Citalopram), 149 (Placebo)					
Test for heterogeneity chi-square=2.69 df=1 p=0.10 I^2 =62.8%					
Test for overall effect z=1.37 p=0.2					



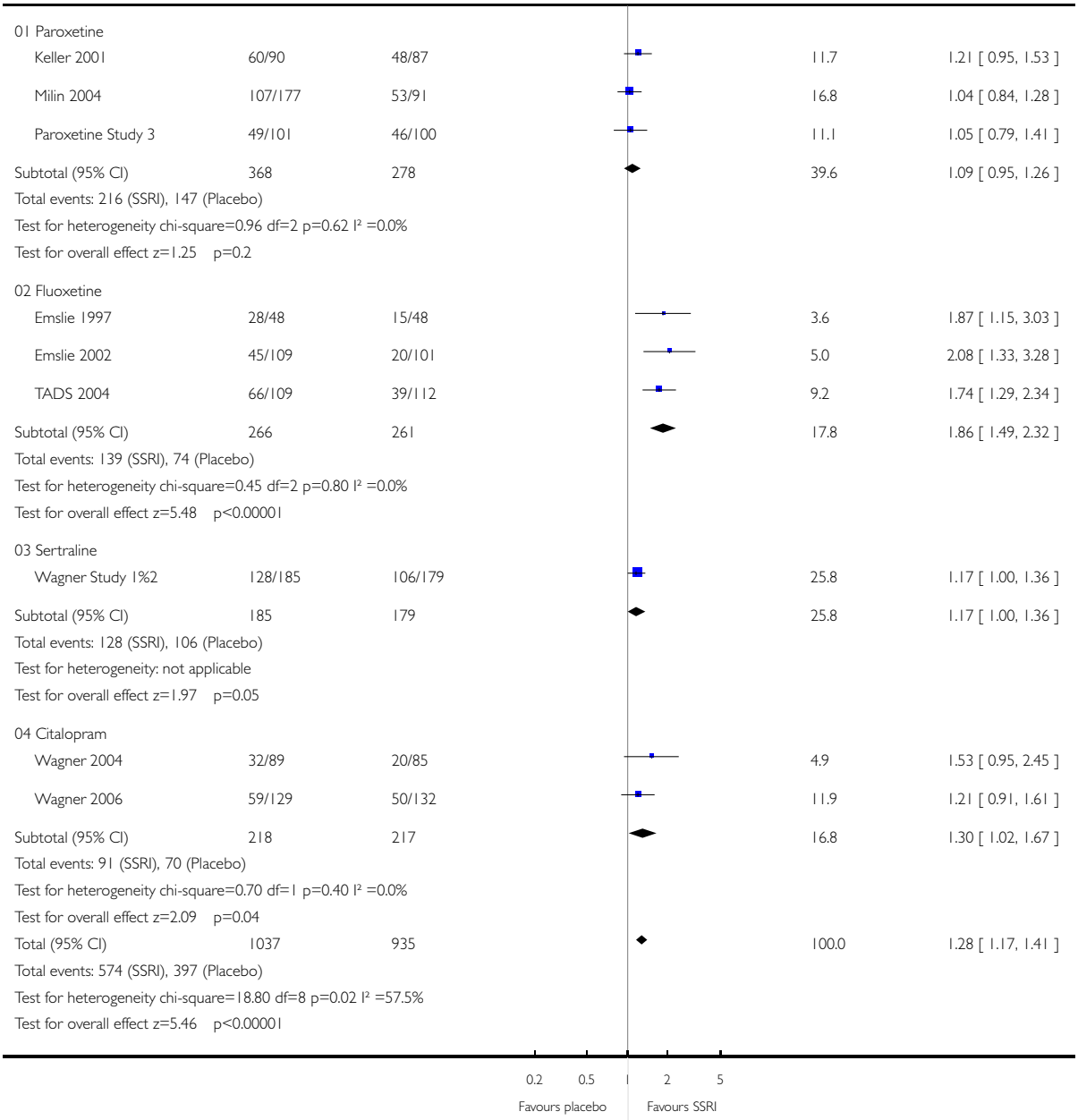
Analysis 06.01. Comparison 06 SSRI versus placebo, Outcome 01 Response (by predefined criteria)

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 06 SSRI versus placebo

Outcome: 01 Response (by predefined criteria)

Study	SSRI n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Paroxetine					
Keller 2001	60/90	48/87		11.7	1.21 [0.95, 1.53]
Milin 2004	107/177	53/91		16.8	1.04 [0.84, 1.28]
Paroxetine Study 3	49/101	46/100		11.1	1.05 [0.79, 1.41]
Subtotal (95% CI)	368	278		39.6	1.09 [0.95, 1.26]
Total events: 216 (SSRI), 147 (Placebo)					
Test for heterogeneity chi-square=0.96 df=2 p=0.62 I^2 =0.0%					
Test for overall effect z=1.25 p=0.2					
02 Fluoxetine					
Emslie 1997	28/48	15/48		3.6	1.87 [1.15, 3.03]
Emslie 2002	45/109	20/101		5.0	2.08 [1.33, 3.28]
TADS 2004	66/109	39/112		9.2	1.74 [1.29, 2.34]
Subtotal (95% CI)	266	261		17.8	1.86 [1.49, 2.32]
Total events: 139 (SSRI), 74 (Placebo)					
Test for heterogeneity chi-square=0.45 df=2 p=0.80 I^2 =0.0%					
Test for overall effect z=5.48 p<0.00001					
03 Sertraline					
Wagner Study 1%2	128/185	106/179		25.8	1.17 [1.00, 1.36]
Subtotal (95% CI)	185	179		25.8	1.17 [1.00, 1.36]
Total events: 128 (SSRI), 106 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					
04 Citalopram					
Wagner 2004	32/89	20/85		4.9	1.53 [0.95, 2.45]
Wagner 2006	59/129	50/132		11.9	1.21 [0.91, 1.61]
Subtotal (95% CI)	218	217		16.8	1.30 [1.02, 1.67]
Total events: 91 (SSRI), 70 (Placebo)					
Test for heterogeneity chi-square=0.70 df=1 p=0.40 I^2 =0.0%					
Test for overall effect z=2.09 p=0.04					
Total (95% CI)	1037	935		100.0	1.28 [1.17, 1.41]
Total events: 574 (SSRI), 397 (Placebo)					
Test for heterogeneity chi-square=18.80 df=8 p=0.02 I^2 =57.5%					
Test for overall effect z=5.46 p<0.00001					



Analysis 06.02. Comparison 06 SSRI versus placebo, Outcome 02 Suicide related outcome

Review: Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents

Comparison: 06 SSRI versus placebo

Outcome: 02 Suicide related outcome