Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents (Review)

Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE

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[Intervention Review]

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ABSTRACT

Background

Depressive disorders are common in children and adolescents and, if left untreated, are likely to recur in adulthood. Depression is highly debilitating, affecting psychosocial, family and academic functioning.

Objectives

To evaluate the effectiveness of psychological therapies and antidepressant medication, alone and in combination, for the treatment of depressive disorder in children and adolescents. We have examined clinical outcomes including remission, clinician and self reported depression measures, and suicide-related outcomes.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR) to 11 November 2011. This register contains reports of relevant randomised controlled trials (RCTs) from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to date), EMBASE (1974 to date), and PsycINFO (1967 to date).

Selection criteria

RCTs were eligible for inclusion if they compared i) any psychological therapy with any antidepressant medication, or ii) a combination of psychological therapy and antidepressant medication with a psychological therapy alone, or an antidepressant medication alone, or iii) a combination of psychological therapy and antidepressant medication with a placebo or 'treatment as usual', or (iv) a combination of psychological therapy and antidepressant medication with a psychological therapy or antidepressant medication plus a placebo.

We included studies if they involved participants aged between 6 and 18 years, diagnosed by a clinician as having Major Depressive Disorder (MDD) based on Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) criteria.

Data collection and analysis

Two review authors independently selected studies, extracted data and assessed the quality of the studies. We applied a random-effects meta-analysis, using the odds ratio (OR) to describe dichotomous outcomes, mean difference (MD) to describe continuous outcomes when the same measures were used, and standard mean difference (SMD) when outcomes were measured on different scales.

Main results

We included ten studies, involving 1235 participants in this review. Studies recruited participants with different severities of disorder and with a variety of comorbid disorders, including anxiety and substance use disorder, therefore limiting the comparability of the results. Regarding the risk of bias in studies, half the studies had adequate allocation concealment (there was insufficient information to determine allocation concealment in the remainder), outcome assessors were blind to the participants' intervention in six studies, and in general, studies reported on incomplete data analysis methods, mainly using intention-to-treat (ITT) analyses. For the majority of outcomes there were no statistically significant differences between the interventions compared. There was limited evidence (based on two studies involving 220 participants) that antidepressant medication was more effective than psychotherapy on measures of clinician defined remission immediately post-intervention (odds ratio (OR) 0.52, 95% confidence interval (CI) 0.27 to 0.98), with 67.8% of participants in the medication group and 53.7% in the psychotherapy group rated as being in remission. There was limited evidence (based on three studies involving 378 participants) that combination therapy was more effective than antidepressant medication alone in achieving higher remission from a depressive episode immediately post-intervention (OR 1.56, 95% CI 0.98 to 2.47), with 65.9% of participants treated with combination therapy and 57.8% of participants treated with medication, rated as being in remission. There was no evidence to suggest that combination therapy was more effective than psychological therapy alone, based on clinician rated remission immediately post-intervention (OR 1.82, 95% CI 0.38 to 8.68).

Suicide-related Serious Adverse Events (SAEs) were reported in various ways across studies and could not be combined in meta-analyses. However suicidal ideation specifically was generally measured and reported using standardised assessment tools suitable for meta-analysis. In one study involving 188 participants, rates of suicidal ideation were significantly higher in the antidepressant medication group (18.6%) compared with the psychological therapy group (5.4%) (OR 0.26, 95% CI 0.09 to 0.72) and this effect appeared to remain at six to nine months (OR 1.27, 95% CI 0.68 to 2.36), with 13.6% of participants in the medication group and 3.9% of participants in the psychological therapy group reporting suicidal ideation. It was unclear what the effect of combination therapy was compared with either antidepressant medication alone or psychological therapy alone on rates of suicidal ideation. The impact of any of the assigned treatment packages on drop out was also mostly unclear across the various comparisons in the review.

Limited data and conflicting results based on other outcome measures make it difficult to draw conclusions regarding the effectiveness of any specific intervention based on these outcomes.

Authors' conclusions

There is very limited evidence upon which to base conclusions about the relative effectiveness of psychological interventions, antidepressant medication and a combination of these interventions. On the basis of the available evidence, the effectiveness of these interventions for treating depressive disorders in children and adolescents cannot be established. Further appropriately powered RCTs are required.

PLAIN LANGUAGE SUMMARY

Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Depressive disorders are common in children and adolescents, with suggested overall prevalence rates for adolescents (13 to 18 years) being 5.7% and for children (under 13 years) 2.8%. Common symptoms of depression in children and adolescents include low mood, a loss of interest in once enjoyed activities, difficulties with concentration and motivation, changes in appetite and sleep, irritability, physical symptoms such as headaches or stomach aches and in some cases thoughts of suicide. If left untreated, depressive disorders in the younger years are likely to continue into adulthood, and can be increasingly difficult to treat as time goes on. Both psychological therapies and antidepressant medication can be used to treat depression in children and adolescents. Psychological therapies, sometimes called 'talking therapies', involve working with a qualified therapist to treat the depression. Psychological therapies in common use are cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT) and psychodynamic therapy. There are many different types of antidepressant medication, all of which have been developed specifically to work on chemicals in the brain that are believed to be linked to depression. Research has been undertaken on psychological therapies and antidepressant medication, alone and in combination, to asses the effects of these interventions on depression in children and adolescents.

In order to asses whether either intervention or a combination of both is most effective, we included studies that compared: (1) any psychological therapy with any antidepressant medication; (2) any combination of these therapies (a psychological therapy plus antidepressant medication) with either psychotherapy alone or antidepressant medication alone; (3) any combination of these therapies (a psychological therapy plus antidepressant medication) with a placebo or 'treatment as usual'; (4) any combination of these therapies (a psychological therapy plus antidepressant medication) with either therapy plus a placebo.

We included 10 randomised controlled trials (RCTs) involving 1235 participants in this review. These trials made a variety of different comparisons and only a small number of trials contributed information about each of the comparisons made in the review. Although most analyses included more than one trial, the results of these trials sometimes differed considerably or were even contradictory. In terms of adverse effects of treatment, in one trial, rates of suicidal thoughts were higher in those taking antidepressant medication, compared with those delivered psychological therapy. Overall, it was not possible to draw robust conclusions from the meta-analyses, nor to establish which intervention strategy was most effective.

In summary, on the basis of the available evidence, we do not know whether psychological therapy, antidepressant medication or a combination of the two is most effective to treat depressive disorders in children and adolescents.

BACKGROUND

Description of the condition

As recently as the 1970s, it was widely believed that depressive disorder in young people was very rare (Baker 2006). However, it is now well established that depression is a common disorder in this population. A 2006 meta-analysis suggested overall prevalence rates for adolescents (13 to 18 years) to be 5.7% and for children (under 13 years) to be 2.8% (Costello 2006), born between 1965 and 1996. Lifetime estimates range between 15% and 20% (Birmaher 1996). Depressive disorder is debilitating and affects psychosocial, family and academic functioning (Lewinsohn 1998). Major depressive disorder (MDD) is one of the leading causes of disability, morbidity and mortality (WHO 2008) and is a major risk factor for suicide. Children and adolescents with MDD are seven times more likely to complete suicide than those without (Gould 1998). Furthermore, approximately 70% of adolescents with MDD will relapse within five years, and adolescents who experience depression are four times more likely to develop a depressive disorder in adulthood compared to adolescents who do not suffer from depression (Richmond 2005). Early onset depression is also associated with treatment resistant depression later in life (Hatcher-Kay 2003).

Diagnostic criteria for depressive disorders are essentially the same for adults and children, although specific signs and symptoms may differ in children and adolescents. In adults, a diagnosis is reached through a consultation between the patient and the clinician, while for children and adolescents a diagnosis is often made using information from multiple sources including parents, teachers, counsellors, healthcare professionals, as well as the child or young person themselves (Emslie 2005). Compared with adults, depressed children and adolescents may exhibit higher levels of anxiety and irritability, 'temper tantrums', behavioural problems, social withdrawal, phobias, and exaggerated somatic symptoms. Symptoms of melancholia, psychosis, suicide attempts, lethality of suicide attempt, and impairment of functioning appear to increase with age (Birmaher 1996), and it has been established that treatments are not uniformly effective across age groups (Emslie 2005).

Description of the intervention

A number of psychological therapies have been trialed as a treatment for MDD in children and adolescents. Cognitive behavioural therapy (CBT) has been the most widely studied, and trials have also been conducted into the effectiveness of interpersonal therapy (IPT), behaviour therapy, and problem-solving therapy. A recent systematic review (Watanabe 2007) indicated that overall, psychotherapy was more effective than control comparisons immediately post-intervention, although this benefit was no longer evident at six months and 12 months follow-up. Subgroup analysis suggested that psychotherapy might be more effective than control for adolescents (13 to 19 years) but not for younger children (six to 12 years), and might be more beneficial than wait-list control, but no more effective than attention/placebo.

The majority of guidelines on the treatment of depressive disorders in young people recommend the judicious use of medication, specifically selective serotonin reuptake inhibitors (SSRIs), in the context of careful monitoring of symptoms and side effects (AACAP 2007; Cheung 2008a; NICE 2005; Zuckerbrot 2007). The SSRI for which there is the most consistent evidence of a statistically significant reduction in depressive symptoms compared with placebo is fluoxetine (Hetrick 2007; Richmond 2005;

Whittington 2004). The Committee on the Safety of Medicines (CSM) (CSM 2004) and the Food and Drug Administration (FDA) (FDA 2004) recommend it as the preferred SSRI for use in young people, and the National Institute for Health and Clinical Excellence (NICE) guidelines state specifically that fluoxetine should be the first antidepressant medication option (NICE 2005).

How the intervention might work

In psychological therapies the aim is to build a relationship with the client through a structured and purposeful encounter, and although a range of specific techniques are employed, life issues and problems can be discussed and addressed. Just as there are many approaches to psychological therapies, the assumed mechanism of action for each varies. However, common to most is the aim to increase awareness, with the implicit or explicit aim of changing thoughts, behaviours or emotions to improve the mental health well-being of the client.

Antidepressant medications are postulated to work via their effect on neurotransmitters. Each type of medication has a slightly different effect on various neurotransmitters. For example, tricyclic antidepressants (TCAs) prevent the reuptake by nerve cells of the neurotransmitters norepinephrine (noradrenaline), serotonin (5-hydroxytryptimine, or 5-HT) and to a lesser extent, dopamine. SSRIs block the reuptake of serotonin into the presynaptic (brain) cell, increasing the level of serotonin available to bind to the postsynaptic receptor. SSRIs also affect the neurotransmitters norepinephrine and dopamine. Newer antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRIs), work on both norepinephrine as well as serotonin reuptake processes.

Why it is important to do this review

Given the prevalence and impact of depressive disorders in children and adolescents, it is essential that effective interventions are identified and implemented. A number of randomised controlled trials (RCTs) are available to guide treatment decisions for adult depressive disorder, but the evidence-base for the treatment of child and adolescent depressive disorder is much less established. Nevertheless, an increasing number of RCTs of psychological interventions and antidepressant medications are being undertaken in this population, and several Cochrane reviews of treatments for depressive disorders in children and adolescents are already available or underway (Hazell 2002; Hetrick 2007; Watanabe 2004).

Findings from RCTs have suggested that some psychological therapies might be more effective than a variety of control comparators. Cognitive behavioural therapy (CBT) has been shown to be more effective than wait-list control (Lewinsohn 1990; Stark 1987), 'no treatment' (Weisz 1997) and life-skills tutoring (Rhode 2004). Trial data also indicate the efficacy of cognitive therapy (CT), behavioural therapy (BT), interpersonal therapy (IPT) and problem-solving therapy when compared to delayed treatment (Ackerson 1998), wait-list control (Kahn 1990; Stark 1987), clinical monitoring only (Mufson 1999) and 'treatment as usual' (Mufson 2004).

Trials and reviews conducted into the effectiveness of antidepressant medication in this population have been mixed. Tricyclic antidepressants (TCAs) have been reported to be ineffective for depression in children and adolescents (Hazell 2002; Papanikolaou 2006; Weller 2000). Although there is evidence that selective serotonin reuptake inhibitors (SSRIs) might be more effective than placebo in this population (Papanikolaou 2006), high dropout rates, inappropriate outcome measurements, and various potential reporting biases, mean that these findings should be viewed with great caution (Dubicka 2006; Hetrick 2007; Whittington 2004). In addition, a recent review compared all classes of antidepressant medications with placebo (Tsapakis 2008) and meta-regression analyses indicated no evidence to support the hypothesis that SSRIs were more effective than TCAs. The lack of robust evidence for the effectiveness of medication continues to stimulate the debate around its use in treating depression in children and adolescents (Goodyer 2010; Hetrick 2010).

In the context of the FDA 'black box' warning on SSRIs about the increased risk of self injurious ideations and behaviour of young people on SSRIs (FDA 2004), some guidelines recommend initial intervention using psychological therapies, for depressive disorders of mild to moderate severity (NICE 2005). Medication is reserved for more severe disorders and the recommendations highlight that, when used, antidepressant medication should be used in conjunction with ongoing psychological intervention (NICE 2005). Two major studies have investigated this approach; the Treatment for Adolescents with Depression Study (TADS) (March 2004) and Adolescent Depression Antidepressant and Psychotherapy (ADAPT) (Goodyer 2007). In ADAPT, the addition of CBT to fluoxetine plus standard care did not appear to improve outcomes compared to fluoxetine plus standard care Goodyer 2007. In TADS, fluoxetine alone was superior to CBT alone, and the combination of fluoxetine and CBT was statistically significantly better than either alone in the short-term (March 2004). A recent meta-analysis of trials in adult populations found no difference in efficacy between psychological therapies and antidepressant medication (Bortolotti 2008). Data from the adult literature also suggest that combination therapy is superior to antidepressant medication alone (Pampallona 2004) and psychotherapy alone (de Maat 2007).

The recommendations for treatment of depressive disorders in children and adolescents exist in the context of relatively little high quality research, and there have been calls for large, well conducted studies to be undertaken (Hetrick 2007; NICE 2005). A Cochrane review is timely in providing a review of evidence to date, examining the potential benefits and harms of psychological therapies, antidepressant medication and their combination

for child and adolescent depressive disorders, and findings could inform the design and conduct of future trials.

OBJECTIVES

1. To determine the effectiveness of psychological therapies compared with antidepressant medication for treating depressive disorders in children and adolescents.

2. To determine the effectiveness of a combination of psychological therapy and antidepressant medication compared with antidepressant medication alone for treating depressive disorders in children and adolescents.

3. To determine the effectiveness of a combination of psychological therapy and antidepressant medication compared with psychological therapy alone for treating depressive disorders in children and adolescents.

4. To determine whether the effectiveness of these interventions differs between children and adolescents.

5. To determine whether the effectiveness of these interventions differs according to the severity of depressive disorder.

6. To determine whether there is an increased risk of suicide-related outcomes in children and adolescents treated with antidepressant medication alone, compared with psychological therapy alone, or a combination of treatments.

We added the final objective (6) to the review following the publication of the protocol. Given the concern that antidepressant medication may increase suicide-related behaviour in children and adolescents, we felt it was important to assess the degree of suicide-related behaviour related to antidepressant medication.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished RCTs, available in any language, that compared antidepressant medications, psychological therapies or their combination. We did not include quasi-RCTs, or cross-over trials. We included cluster-RCTs and cross-over trials as a post hoc amendment and we will consider them for inclusion in the update of the review.

Types of participants

We included children (six to 12 years) and adolescents (13 to 18 years) with a primary diagnosis of depressive disorder, diagnosed by a clinician using Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) categories (APA 2000; WHO 2007). We excluded studies including adults.

While subsyndromal depression can still have a severe impact on an individuals' social and educational functioning, because of heterogeneity, and because of the lack of data on this group, we did not include studies of participants with subthreshold depressive disorder, or studies where depressive disorder was not formally diagnosed.

Comorbid conditions are frequently neglected in reviews. We aimed to include studies where participants had comorbid secondary medical or other mental health conditions, including suicidal behaviours. It is often difficult to deduce which mental health condition is deemed primary in clinical practice, and trial authors did not give information regarding 'primary' or 'secondary' diagnoses as such. Thus, we included trials where all participants were diagnosed with depressive disorder regardless of the accompanying severity of the comorbid diagnosis.

Types of interventions

We included trials if they compared:

1. any psychological therapy with any antidepressant medication;
2. a combination of interventions (psychological therapy plus antidepressant medication) with either psychological therapies or antidepressant medication alone;
3. a combination of interventions (psychological therapy plus antidepressant medication) compared with either intervention (psychological therapy or antidepressants) plus a placebo; and
4. a combination of interventions (psychological therapy plus antidepressant medication) with a placebo or 'treatment as usual'.

Psychological therapies

- Cognitive behavioural therapy (CBT) uses cognitive restructuring training and teaching behavioural changes.
- Behavioural therapy (BT) focuses attention on increasing access to pleasant events and positive reinforcers through the use of activity scheduling and social skills development.
- Mindfulness training is a common feature of the newer 'third wave' CBT interventions and involves concentrating on and attending to, without judgement, whatever is being experienced at the time of intervention.
- Cognitive therapy (CT) uses cognitive restructuring training.
- Interpersonal therapy (IPT), whereby the relationship between mood and relationship problems is explored and the focus is on improving relationship skills.

- Problem-solving therapy (PST), focuses on current problems faced by the participant with evaluation and subsequent development of solutions to such problems.
- Play therapy (PT) refers to techniques used to engage participants in activities, such as playing, listening to music, or outdoor activities, to assist them in coping and dealing with their problems. It often has psychodynamic underpinnings (Lebo 1958).
- Humanistic therapy (HT) can be described as 'supportive' therapy, and offers an empathic, non-directive and non-judgemental approach, based on client-centred principles.
- Psychodynamic therapy (PDT) is where the therapeutic relationship is used to explore and resolve unconscious conflict through the use of interpretation and transference.

In order to simplify and reduce the number of categories, we aimed to group these therapies into four broader groups, based on their theoretical underpinning. The categories are as follows.

1. CBT (including BT, CT, PST as well as mindfulness training and other third wave psychotherapies).
2. Integrative therapy (including IPT and cognitive analytic therapy).
3. Humanistic therapy (including interventions described as supportive therapy).
4. Psychodynamic therapy (including play therapy).

Antidepressant medications

- Selective serotonin reuptake inhibitors (SSRIs).
- Selective serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Noradrenergic and specific serotonin antidepressants (NaSSAs).
- Norepinephrine (noradrenaline) reuptake inhibitors (NRIs).
- Norepinephrine-dopamine reuptake inhibitors (NDRIs).
- Selective serotonin reuptake enhancers (SSREs).
- Monoamine oxidase inhibitors (MAOIs).
- Tricyclic antidepressants (TCAs).

Given the potentially variable effects of different psychological therapies and antidepressant medications, we intended to conduct subgroup analyses where possible for the (aforementioned) psychological therapy categories and antidepressant medication classes listed above.

Combination interventions

We included combination interventions where antidepressant medication (of any class described above) was combined with psychological therapy (of any type described above).

'Treatment as usual' and placebo comparison groups

The 'treatment as usual' condition that was eligible for inclusion was standard care. We also planned to include wait-list control as a comparison condition, however there were no instances where this comparison was used.

Participants in 'treatment as usual' arms of studies may have been receiving a psychological therapy, taking antidepressant drugs naturalistically, or both. For this reason, it was our intention to obtain as much information as possible from the authors regarding the details of participants' 'treatment as usual'. Similarly, if details of the placebo control were not specified, we sought this information. Where possible, information on 'treatment as usual' and placebo control conditions was described and reported in conjunction with statistical analyses, as we believe variability in 'treatment as usual' groups may lead to unclear and potentially misleading results.

Follow-up

We searched for studies that examined acute effects of treatment with at least pre- and post-intervention assessments, and, where data were available, for longer-term follow-up (maximum of up to 12 months).

We also included trials where there was an a priori plan for ongoing treatment and follow-up, as well as those where there was no a priori plan, but in which there was a post-acute, naturalistic follow-up phase. We endeavoured to obtain as much information as possible about the treatments that were received by participants in the studies with naturalistic follow-up. Where planned post-acute phase treatments (continuation or maintenance phase) took place, such as formal booster sessions or augmentations, we documented the treatment.

Types of outcome measures

Primary outcomes

1. Remission from depressive disorder according to a clinical interview by a mental health professional, using DSM (APA 2000) or ICD (WHO 2007) criteria (dichotomous) for full remission (eight weeks asymptomatic or free from any significant mood symptoms respectively). Computerised diagnostic assessments such as the computerised Diagnostic Interview Schedule for Children (C-DISC) could also be included.
2. Acceptability of treatment measured by number of dropouts for any reason.
3. Suicide-related serious adverse events (SAEs). Any suicide-related SAE, encompassing ideation, attempted suicide including acts with unknown intent was recorded. However, due to the diversity of tools in which these data were presented, we did not combine them in a meta-analysis.

Secondary outcomes

1. Suicide-related outcomes; we considered these as both a dichotomous and continuous outcome. For the dichotomous outcome, we extracted the number of participants with suicidal ideation, as measured on a standardised, validated reliable scale such as the Suicidal Ideation Questionnaire-Junior High School version (SIQ-JR; Reynolds 1987). For the continuous outcome, we also extracted suicidal ideation, measured on a standardised, validated measure such as the SIQ-JR.
2. Remission, defined by a cut-off or percentage improvement on measures such as the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski 1996), Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Episode Version (K-SADS-P) (Brooks 2001), or the Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960).
3. Improvement in depressive symptoms on clinician rated and self rated symptom measures (standardised, validated, reliable scales such as the CDRS-R, MADRS, K-SADS-P, and HAM-D).
4. Level of function measured on clinician rated measures of general functioning, such as the Global Assessment of Functioning (GAF; Hilsenroth 2000) and the Children's Global Assessment Scale (C-GAS; Shaffer 1983).
5. Number of dropouts due to at least one adverse effect.

Hetrick 2007 provided a list of measures used in the studies that were included in their SSRI review. It was reasonable to assume the measures used in the current review would be similar to those commonly used in SSRI trials. Presented below is a brief overview of some of these scales.

The CDRS-R is a 17-item clinician interview-based tool to diagnose and establish severity of depression in six to 12 year olds. The first 14 questions are based on response from the child or a parent or guardian closely related to the child. The final three questions are rated by the clinician based on non-verbal observations. Questions are rated on a five or seven-point scale and a final score is produced by summation of all 17 items (range 17 to 113). This scale has well documented psychometric properties and has shown adequate to high reliability and validity across multiple studies (Brooks 2001).

The MADRS is a 10-item clinician rated scale assessing depressive symptoms from the past three or seven days. Each item is scored on a fixed seven-point scale with a total score ranging from 0 to 60. Psychometric properties for adolescent depression treatment outcomes have yet to be established (Jain 2007).

The K-SADS-P contains a nine-item depression module completed by the clinician on the basis of interview. Four of these items contain two subgroups, each with three questions. A final score can range from 9 to 56. It covers symptoms from the previous two weeks and specifically assesses symptoms against the Diagnostic and Statistical Manual for Mental Disorders (DSM; IIIR and IV) (Brooks 2001). The depression module shows high inter-rater reliability (Kaufman 1997).

The HAM-D is a clinician rated scale and contains 17 variables measured on a scale of between zero and two or four (Hamilton 1960). Not all items contain objective criteria for the interviewer and he or she must use subjective judgement to differentiate responses as "mild", "moderate", or "severe" (Brooks 2001). Items target depressive symptoms from the previous week. This scale shows excellent reliability (Myers 2002).

The SIQ-JR is a 15-item self report scale designed to assess the presence of suicidal ideation in school-aged adolescents.

The GAF is a robust measure of social and general functioning that exists as the Axis-V of the DSM IV.

The C-GAS is an amended version of the GAF for children and adolescents under the age of 18 years. It too has a scale of 1 to 100, with 10 levels of functioning, each numeric interval of 10.

If several scales were used to measure the same outcome in a trial, we chose the measure most commonly used across trials.

We analysed both short- and long-term outcomes, including post-treatment and follow-up data. We undertook follow-up examination to show if there were (a) treatments that provide short-term benefits in terms of response or remission; (b) treatments that provide short-term benefits that remain over long-term follow-up; and (c) treatments that do not show short-term improvement, however, where the participants' condition improves over time (delayed treatment onset). We defined 'long-term' in the current review as greater than six months post-intervention. Due to the variability in long-term follow-up points, and the fact that some studies assessed outcomes at multiple follow-up time points, we subcategorised follow-up data into those that were measured between six and nine months from baseline, and those that were measured at 12 months. This allowed us to included multiple data from single studies in order to assess the time course of depressive symptoms and remission rates more stringently.

Search methods for identification of studies

Electronic searches

CCDAN's Specialised Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK; a references register and a studies-based register. The CCDANCTR-References Register contains over 30,000 reports of RCTs for depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique study ID tags. Coding of trials is based on the EU-Psi coding manual. (Please contact the CCDAN Trials Search Co-

ordinator for further details). Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCDAN's generic search strategies can be found on the Group's website.

The Trials Search Co-ordinator searched the CCDANCTR to 11 November 2011, using the following terms:

CCDANCTR-Studies Register:

Diagnosis = Depression or Dysthymia or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Symptoms"

And

Age = Child or Adolescent

The Trials Search Co-ordinator searched the CCDANCTR-References Register using a more sensitive set of free-text terms to identify additional untagged/uncoded references:

((depress* or dysthymi* or "adjustment disorder*" or "mood disorder*" or "affective symptom*") and (child* or infant* or juvenil* or minors or pediatri* or paediatri* or adolesc* or pubescen* or puberty or teen* or young or youth* or school* or high-school or college or student* or undergrad*))

Additional searches

We performed complementary searches on the following bibliographic databases to April 2011 (after which we decided to rely on the CCDAN specialised register alone, given the regular, generic searches of these databases by the Trials Search Co-ordinator).

- MEDLINE (1996 to April 2011)
- EMBASE (1980 to April 2011)
- PsycINFO (1967 to April 2011)

Searching other resources

Reference list

We checked the reference lists of all included trials retrieved from the searches to identify additional published or unpublished research.

Personal communication

We contacted the authors of all included studies and recognised experts in the field to ensure no study was missed (published or unpublished).

Data collection and analysis

Selection of studies

Three review authors (PC, SH and GC) independently conducted the screening process of titles and abstracts. We noted the trials that appeared to fulfil the selection criterion and subsequently retrieved the full articles. The same review authors assessed full articles for adherence to selection criteria. We have provided justification for exclusion of trials for which full copies were retrieved. To be included in the initial screen, references had to pass the following simple criteria.

- It had to be a RCT.
- Include participants with a diagnosis of a depressive disorder using DSM or ICD criteria (as diagnosed by a clinician).
- At a minimum, compare an antidepressant medication with a psychological therapy.

If discrepancies arose, we reached consensus through discussion, with the aid of a fourth review author, if needed.

Data extraction and management

Two review authors (PC and GC) independently extracted primary and secondary outcome-related data from full articles and recorded data on hard copy data collection forms. When disagreement arose, consensus was reached following discussion, with the aid of a third review author (SH), where necessary. Where required data were not present or were in a form that was not compatible with our meta-analysis, we attempted to contact the authors to obtain or clarify data.

Main comparisons made in the review.

1. Psychological therapies alone versus antidepressant medication alone.
2. Combination therapy versus psychological therapies alone.
3. Combination therapy versus antidepressant medication alone.
4. Combination therapy versus psychological therapies plus pill placebo.

A further two comparisons were possible given the inclusion criteria (although no data were available for these comparisons).

1. Combination therapy versus antidepressant medication plus psychosocial/attention only placebo.
2. Combination therapy versus 'treatment as usual'.

Assessment of risk of bias in included studies

Two independent review authors (PC and GC) conducted 'Risk of bias' assessment based on Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We discussed discrepancies in rating and reached consensus, with the aid of a third review author (SH) where necessary. We assessed risk of bias as "low risk", "unclear risk", or "high risk", in accordance with the

updated guidance and software from The Cochrane Collaboration for the following domains.

1. Sequence Generation.
2. Allocation concealment.
3. Blinding of participants, personnel, and outcome assessors.
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Other sources of bias.

We included all studies meeting the inclusion criteria, regardless of the outcome of the assessment of risk of bias.

Measures of treatment effect

We entered data from collection forms into Review Manager 5 (RevMan 2011). We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes such as remission, and suicide-related outcomes. With regards to continuous scales, there were many types of depression measures utilised in trials and therefore we used the standardised mean difference (SMD) with 95% CIs to calculate treatment effects in comparisons containing different assessment scales. In some cases, the same scales were used across studies, and on these occasions, we used the mean difference (MD).

Unit of analysis issues

Where a study had more than one active treatment arm, we extracted data from the appropriate arm for each of our main comparisons.

For future updates where we will consider including cluster-RCTs and cross-over RCTS, given the potential for carry-over affects, particularly for psychological interventions, we will only include the first phase of data from cross-over trials in any analysis.

For studies using a clustered randomisation method, if not reported, we will contact trial authors to obtain the intracluster correlation coefficient (ICC) for the sample. If we are unable to obtain this information from the authors, we will use an ICC estimate based on the average of the ICCs obtained from the other studies included in the analysis, or if necessary from relevant external studies. We will then adjust the study population numbers to take into account the effect of the clustering. We will undertake sensitivity analysis to check the robustness of the data, and to make decisions about which ICC adjustment to include in the data.

Dealing with missing data

Missing statistics

We obtained missing data from trial authors wherever possible.

In some cases, dichotomous outcomes such as remission rates, were reported as percentages (Bernstein 2000; Clarke 2005). We converted these percentages into dichotomous outcomes using information regarding the total (N) in the analysis reported in the publication. Where applicable, we contacted authors to confirm we had calculated the raw numerator and denominator correctly. In one case (Riggs 2007), only the standard error was reported for continuous outcome measures. We calculated the standard deviation for each group mean based on the sample size and standard error and have documented this as appropriate.

Missing participants

For continuous outcomes, if available, we extracted intention-to-treat (ITT) data and noted the method used for imputing missing data in the 'Risk of bias' table for each individual trial.

For remission by clinical interview, data were often reported for 'observed cases' (OC) only (Melvin 2006; TADS 2004). In this case we used the numbers randomised in an ITT analysis (making the assumption that those who dropped out did not improve) and compared this with an analysis based on the OC data provided as a sensitivity analysis. In one case (Clarke 2005), remission rates based on a cut-off score were reported based on an ITT analysis. This study was the only one that contributed data to the comparison, and we included these data.

Assessment of heterogeneity

We assessed heterogeneity on the basis of the *Handbook's* recommendations (I^2 values of 0 to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: represents considerable heterogeneity). Because the importance of the observed I^2 statistic depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity, in addition to the I^2 value (Higgins 2003), we have presented the χ^2 and its P value and have considered the direction and magnitude of the treatment effects in assessing heterogeneity. Because the χ^2 test is underpowered to detect heterogeneity in meta-analysis that includes only a few studies, a P value of 0.10 is used as a threshold of statistical significance.

Assessment of reporting biases

We had planned to assess small study effects and potential publication bias using a funnel plot if 10 or more studies were included in the meta-analysis, however, given we had so few trials we did not do this. We assessed selective reporting of outcomes using the 'Risk of bias' tool and have reported this in the 'Risk of bias' tables.

Data synthesis

For all meta-analyses, we used a random-effects model (der Simonian 1986). The random-effects method incorporates an assumption that the different studies are estimating different, yet

related, intervention effects, (which we were anticipating, particularly given the inclusion of different psychotherapy and medication interventions).

Subgroup analysis and investigation of heterogeneity

It was our intention to conduct separate analyses on the subgroups below.

1. Children (six to 12 years) and adolescents (13 to 19 years).
2. Severity of illness (severe, moderate, or mild).

Sensitivity analysis

We intended to conduct the sensitivity analyses below to investigate the effect that different statistical analyses may have exerted on the effect size.

- Using observed case (OC) data (excluding studies which use Last Observation Carried Forward (LOCF)).
- Excluding trials with 'no' or 'unclear' ratings for allocation concealment.

Timeline

We will update this review in accordance with Cochrane Collaboration guidelines for updating.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We retrieved 10,413 references from electronic searches to April 2011. One review author (PC) screened the titles and abstracts of these references against inclusion and exclusion criteria. Of these, we retained 89 and retrieved the full-text of each study. Two authors (PC and SH) screened the full-text of 89 references. We included, excluded and consolidated references into studies. We included a total of nine studies in the review.

We conducted an updated search on the CCDANCTR (11 November 2011), retrieving 428 references. Two authors (PC and GC) screened these references and retrieved the full-text of 18 references, of which we included one in the review. We screened a total of 10,841 references, from which we retrieved 51 full-text articles, and included ten studies in the analyses.

Included studies

Eight of the ten trials were undertaken in the USA (Bernstein 2000; Clarke 2005; Cornelius 2009; Deas 2000; Mandoki 1997; Riggs 2007; TADS 2004; TASA 2009); one in the UK (ADAPT 2007) and one in Australia (Melvin 2006). There were eight trials of selective serotonin reuptake inhibitors (SSRIs) (ADAPT 2007; Clarke 2005; Cornelius 2009; Deas 2000; Melvin 2006; Riggs 2007; TADS 2004; TASA 2009), one of a tricyclic antidepressant (TCA) (Bernstein 2000) and one of a serotonin-norepinephrine reuptake inhibitor (SNRI) (Mandoki 1997). The majority of trials contained two comparison arms, two trials contained three arms (Melvin 2006; TASA 2009) and one contained four comparison arms (TADS 2004). The TADS 2004 trial implemented a placebo arm for the first stage of intervention (up to 12 weeks), after which the placebo group were unblinded to condition, and offered an alternative treatment. As a result, all follow-up data after 12 weeks are based on three comparison conditions.

Five trials compared combination therapy to psychological therapies with placebo medication (Bernstein 2000; Cornelius 2009; Deas 2000; Mandoki 1997; Riggs 2007); four trials compared combination therapies to antidepressant medication alone (ADAPT 2007; Melvin 2006; TADS 2004; TASA 2009); one trial compared combination therapy to a placebo condition (TADS 2004) and one compared combination therapy to 'treatment as usual', involving routine medication of SSRIs (Clarke 2005). In the three trials with more than two comparison arms, psychological therapy alone was compared to antidepressant medication alone and a combination of medication and psychological therapy (Melvin 2006; TADS 2004; TASA 2009).

Therefore for objective one there were three trials that had relevant psychological therapy alone and medication alone arms (Melvin 2006; TADS 2004; TASA 2009), although TASA 2009 did not contribute any data. For objective two there were four trials that included a combination therapy and medication alone arms (ADAPT 2007; Clarke 2005; Melvin 2006; TADS 2004), each of which contributed some data to some outcomes. For objective three, two studies included combination therapy and psychological therapy alone arms, and both contributed data (Melvin 2006; TADS 2004), and five studies included combination therapy and psychological therapy plus placebo arms (Bernstein 2000; Cornelius 2009; Deas 2000; Mandoki 1997; Riggs 2007); only Mandoki 1997 contributed no data to any outcome.

Participants

One trial involved children and adolescents aged eight to 17 years (Mandoki 1997), and nine contained adolescents over the age of 11 years. Five trials had an age range of between 11 or 12 to 17 or 18 years (ADAPT 2007; Bernstein 2000; Clarke 2005; Melvin 2006; TADS 2004 TASA 2009); one between 13 and 19 years (Riggs 2007); one between 15 and 18 years (Deas 2000) and one slightly older sample of 15 to 20 years (Cornelius 2009). The mean age

ranged from 12.7 years to 17.6 years. Three trials contained similar proportions of males and females (Bernstein 2000; Cornelius 2009; TADS 2004), three contained around three times as many females as males (ADAPT 2007; Clarke 2005; TASA 2009), and three contained around twice as many males as females (Deas 2000; Mandoki 1997; Riggs 2007).

Nine trials included participants with major depressive disorder (MDD), with diagnoses made on either DSM-III or DSM-IV criteria, deduced from structured interviews such as the K-SADS-PL. Deas 2000 used both the K-SADS and the HAM-D to measure baseline depression severity. Two trials used a cut-off score of 35 or 36 on the CDRS-R (Bernstein 2000; TASA 2009), and TADS 2004 used a higher cut-off score of 45 on the CDRS-R to determine eligibility. One trial used a cut-off of eight or more on the Health of the Nation Outcome scales for children and adolescents (HoNOSCA; ADAPT 2007). Baseline severity of depressive symptoms was measured using the CDRS-R in six trials (ADAPT 2007; Bernstein 2000; Mandoki 1997; Riggs 2007; TADS 2004; TASA 2009), the CES-D in one trial (Clarke 2005) and the HAM-D in two trials (Cornelius 2009; Deas 2000). Melvin 2006 reported baseline severity split by depressive diagnosis as determined by the K-SADS. Three of the six trials that measured baseline severity using the CDRS-R (ADAPT 2007; Riggs 2007; TASA 2009) reported mean t-scores that ranged from 73.03 to 76.14.

It should be noted that while studies of young people with treatment resistant depression were excluded, in the ADAPT 2007 trial, an early description of the study methodology described its aim as treating "persistent adolescent major depression" (Harrington 2002) with entry criteria being a failure to respond, in the initial phase of the trial, to two brief initial sessions of support and educational interventions with a psychiatrist. The sample included 34 adolescents with "proven non-response" in that they had failed a trial of psychosocial intervention before being referred to the trial. This was a pragmatic trial conducted in tertiary specialist mental health outpatient clinics and the authors note that "Most participants had already been treated and would have received psychosocial interventions before medication" (pg. 4 ADAPT 2007).

Four studies reported data on the proportion or percentage of young people who experienced any comorbid disorder (ADAPT 2007; Melvin 2006; TADS 2004; TASA 2009). In these trials, dysthymic disorders, anxiety disorders, and disruptive behavioural disorders (Oppositional Definant Disorder (ODD) / Conduct Disorder (CD)) were the most common comorbid conditions. Bernstein 2000 reported the rate of comorbid anxiety, as it was part of the trial's inclusion criteria that participants were experiencing a current anxiety disorder, and major depressive disorder based on DSM-III-R criteria. The study by Riggs 2007 included participants with comorbid substance use disorder, and lifetime conduct disorder, while all participants in Deas 2000 and Cornelius 2009 had a dual diagnosis of major depression and an alcohol use disorder; however, no other comorbid disorders were measured in either trial. The majority of trials excluded participants based on certain comorbid conditions; however, one trial did not report data on any excluded comorbid conditions (Deas 2000). All but one of the trials excluded participants on the basis of psychotic features or disorders (Bernstein 2000). Pervasive developmental disorders, general intellectual disabilities or mental retardation were excluded in seven trials, and bi-polar disorder, either past or present, in seven trials. Those with substance abuse or dependence were excluded in four trials (Bernstein 2000; Cornelius 2009; Melvin 2006; TASA 2009), those with conduct disorder in two trials (Bernstein 2000; TADS 2004), and those with attention deficit hyperactivity disorder (ADHD) or an eating disorder in one trial (Bernstein 2000).

Participants who were 'actively suicidal' were excluded in two trials (Mandoki 1997; TADS 2004). Three trials included participants who reported high levels of suicidal behaviour (Clarke 2005; Melvin 2006; Riggs 2007), however, these trials still excluded those who were 'actively suicidal' or likely to make a suicide attempt during the course of the trial. The ADAPT 2007 trial included participants who were actively suicidal, and a prerequisite of the TASA 2009 trial, was that participants had made a suicide attempt within the past 90 days. Five of these studies measured suicidal behaviour at baseline (ADAPT 2007; Melvin 2006; Riggs 2007; TADS 2004; TASA 2009).

Please see Characteristics of included studies for details by individual study.

Interventions

Treatment programmes ranged from six weeks (Clarke 2005) to 24 weeks in length (TASA 2009), and participants received between six and 24 sessions of psychological therapy. After an acute phase of treatment, four trials described a continuation or maintenance phase, or both. In two trials, participants were offered 'booster sessions', that were less frequent (ADAPT 2007; Melvin 2006). Clarke 2005 stated that proceeding onto the second module of their cognitive behavioural therapy (CBT) treatment was based on "the degree of youth recovery from depression, enduring youth problems other than depression, and/or to consolidate gains". The trial also contained a 'continuation phase', whereby young people received a brief telephone 'check-in' by their therapists at one, two, three, five, seven, and nine months after completing the acute phase. The TADS 2004 trial was divided into three stages; stage one: up to 12 weeks; stage 2: up to 18 weeks; and stage 3: up to 36 weeks. Participants in the placebo group were unblinded after stage one and offered either telephone follow-up, or their choice of treatment. Participants in the CBT alone, and CBT + fluoxetine groups received weekly CBT sessions up to stage one. In stage two participants were further defined as either 'partial responders' or 'full responders'. Partial responders received six additional CBT sessions and full responders, three (biweekly) sessions. At stage three, participants in both treatment arms received CBT once every six weeks.

All psychological therapies contained core elements of CBT, or behavioural therapy (BT), or both, such as cognitive restructuring, goal setting and pleasant events scheduling. The TASA 2009 study consisted of a CBT-suicide prevention (CBT-SP) programme, in which known risk factors for suicidal behaviour, such as depression were addressed. The CBT-SP programme included 'chain analysis of the index suicide attempt' and safety planning to reduce current suicide risk. Clarke 2005 allowed participants to choose one of two therapy approaches to try first; either cognitive restructuring or behavioural activation; 67.5% of participants chose behavioural activation. Some programmes had a primary focus on another disorder, with depression being addressed as a secondary aim. Bernstein 2000 employed a CBT programme based on a school refusal treatment programme by Last 1998, which centred around negative thoughts surrounding school, and 'behavioural contracting' to increase school attendance. Cornelius 2009 utilised CBT for the treatment of adolescent depression, described by Brent 1997 in addition to motivational enhancement therapy (MET) described in Miller 1992 for the treatment of alcohol use disorders. The trial by Riggs 2007 focused on substance abuse, and contained one module on the management of depression, and how the identification of negative mood states could trigger substance abuse. The majority of the studies were manualised; two trials did not give any information (Clarke 2005; Mandoki 1997) and one was non-manualised (Deas 2000).

In nine trials the therapy included individual CBT sessions, and in one trial there were group sessions (Deas 2000). Three trials formally included youth-parent sessions (Bernstein 2000; Melvin 2006; TADS 2004; TASA 2009), while others encouraged parental involvement outside of the therapy sessions themselves (ADAPT 2007). Clarke 2005 held parent meetings for reviewing the general topics given in therapy sessions. Three trials included fidelity checks on therapists' adherence to protocol by video/audio taping sessions rated by independent raters (ADAPT 2007; Clarke 2005; Riggs 2007). Adherence was high, at over 80%. CBT sessions were delivered by a variety of professionals including a psychiatrist (Deas 2000), a clinical psychologist (Bernstein 2000), masters level psychologists (Clarke 2005), a social worker with experience in CBT, a probationary psychologist and general medical practitioners (Melvin 2006), study therapists trained by the manuals' developers (Riggs 2007) and trained psychotherapists (TASA 2009).

Six trials administered SSRI treatment of either fluoxetine (ADAPT 2007; Cornelius 2009; Riggs 2007; TADS 2004) or sertraline (Deas 2000; Melvin 2006). Bernstein 2000 used a TCA (imipramine) and Mandoki 1997 used a SNRI (venlafaxine). Six trials employed a flexible dosing scheme (ADAPT 2007; Bernstein 2000; Deas 2000; Melvin 2006; TADS 2004; TASA 2009). The 'treatment as usual' condition in the Clarke 2005 study allowed participants to receive antidepressant medication prescribed either by the Health Maintenance Organisation or outside agencies; therefore dosage and medication type varied on an individual basis.

Please see Characteristics of included studies for details by individual study.

Outcomes

There were three primary outcomes of this review; remission of a depressive disorder according to a clinical interview by a mental health professional; acceptability of treatment as measured by dropouts; and suicide-related serious adverse outcomes. Remission in these three trials was determined by the K-SADS scale (Clarke 2005; Melvin 2006; TADS 2004). Only in Melvin 2006 was it clear that DSM-IV criteria for full remission were used.

Suicide-related SAEs were reported in the TADS 2004 trial as 'spontaneously reported suicide-related events', and were measured using the Columbia Classification Algorithm of Suicide Assessment. ADAPT 2007 measured suicidal acts using the K-SADS-PL depression section, and Melvin 2006 reported adverse outcomes from the trial but did not state the criteria they used. Riggs 2007 measured suicidality using question 13 on the CDRS-R.

In most trials remission from depressive disorder was defined as a drop below a predetermined cut-off on a continuous measure of symptoms. A cut-off score of $\leq$ 28 on the CDRS-R scale was used in three studies (Riggs 2007; TADS 2004; TASA 2009), while a more liberal cut-off of $\leq$ 35 was used by Bernstein 2000, and Clarke 2005 used a score of $\leq$ 15 on the Centre for Epidemiological Studies-Depression (CES-D) scale.

All six trials which included a clinician rating of depressive symptom severity, used the CDRS-R. A variety of tools were used to measure self rated depressive symptom severity, including the Beck Depression Inventory (BDI) (Bernstein 2000; Cornelius 2009; TASA 2009), Reynolds Adolescent Depression Scale (RADS) (Melvin 2006; TADS 2004), Mood and Feelings Questionnaire (MFQ) (ADAPT 2007), CES-D (Clarke 2005), and HAM-D (Deas 2000).

The most common measure of functioning was the C-GAS (ADAPT 2007; Clarke 2005; TASA 2009). The GAF (Melvin 2006) and Clinical Global Impression Improvement (CGI-I) scale (Riggs 2007) were also used.

Melvin 2006 and TADS 2004 reported suicidal ideation as a continuous outcome using the SIQ-JR scale. TADS 2004 also reported suicidal ideation as a dichotomous measure, defining participants who scored above 31 on the SIQ-JR scale as displaying the behaviour.

Missing outcome data

We successfully obtained further outcome data for the trials described in Melvin 2006 and Riggs 2007. The trial authors for the TADS 2004 study referred us to the National Institute of Mental Health (NIMH), from whom no further information could be obtained. The trial authors for Clarke 2005 and Cornelius 2009

wrote that they were unable to provide us with further data. We did not have any response from other trial authors.

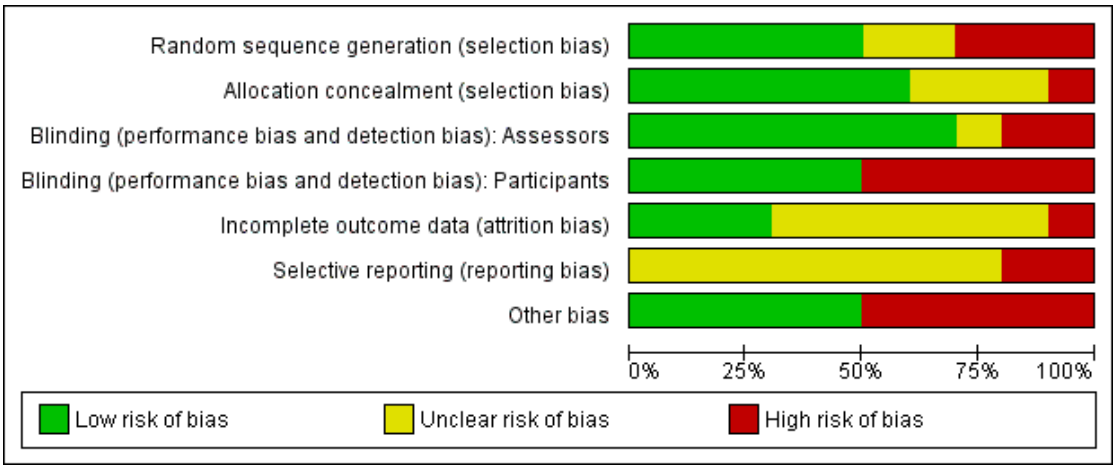
Excluded studies

Of the 51 full-text articles retrieved, references were consolidated into respective studies for which there were multiple references (ADAPT 2007; Bernstein 2000; TADS 2004; TASA 2009; TORDIA 2008), after which, we excluded 10 trials from the review. We excluded seven trials as they did not contain an appropriate comparison condition (Cheung 2008; Emslie 2002 (Eli 2002); Findling 2008; Fristad 2009; King 2009; Tang 2009; Wagner 2003); one was not a RCT (Emslie 2004); one implemented a cross-over design (Dujovne 1994); and we further excluded one study as it contained a 'treatment resistant' population (TORDIA 2008).

Risk of bias in included studies

The original intention was to conduct a sensitivity analysis on the primary outcome measures, excluding trials with 'high risk' or 'unclear risk' ratings for allocation concealment. However, only four trials were rated as such. One trial (TASA 2009) did not contain any data suitable for meta-analysis, and the remaining three were contained in comparisons with only limited data, therefore we did not conduct a sensitivity analysis. We have summarised and described all risk of bias items in Figure 1.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Of the 10 included studies, five reported sufficient information to determine that adequate methods of sequence generation were used (Clarke 2005; Cornelius 2009; Deas 2000; Melvin 2006; TADS 2004). There were three in which the sequence generation methods were rated as not being adequate (Bernstein 2000; Riggs 2007; TASA 2009). Adequate sequence generation was rated as 'unclear' in two trials (ADAPT 2007; Mandoki 1997).

The allocation of intervention arms were judged to be concealed in four trials (ADAPT 2007; Deas 2000; Riggs 2007; TADS 2004). TASA 2009 did not adequately conceal allocation, while the remaining five trials (Bernstein 2000; Clarke 2005; Cornelius 2009; Mandoki 1997; Melvin 2006) did not contain adequate information to determine whether allocation to intervention arms was concealed.

Blinding

Six trials contained sufficient information to determine that outcome assessors were blind to the intervention group of participants (ADAPT 2007; Bernstein 2000; Clarke 2005; Mandoki 1997; TADS 2004; TASA 2009). There was insufficient information to determine blinding of outcome assessors in two trials (Deas 2000; Riggs 2007), while the remaining two trials did not use blinded outcome assessors (Cornelius 2009; Melvin 2006).

Two studies tested psychotherapy alone against medication alone. In TADS 2004, in which a total of four arms were included,

the psychotherapy was not blinded (one arm received cognitive behavioural therapy (CBT) alone and one arm received CBT and fluoxetine), but the medication arm was blinded (one arm received fluoxetine alone and one arm received placebo alone). In Melvin 2006 there were only three arms in total: one CBT alone, one sertraline alone, and one a combination of these; there was no medication placebo arm or placebo psychotherapy arm.

Therefore, in these two studies, which also tested medication alone against combination therapy, the psychotherapy was not blind. In two further studies testing this combination (ADAPT 2007; Clarke 2005) the psychotherapy was not blinded.

For studies testing the efficacy of psychotherapy alone against combination therapy, in five studies a placebo pill was used and participants were blind to medication intervention (Bernstein 2000; Cornelius 2009; Deas 2000; Mandoki 1997; Riggs 2007). In two studies testing this combination a placebo pill was not used in the psychotherapy condition (Melvin 2006; TADS 2004).

In one study, after an initial period of randomisation, participants selected the treatment arm they preferred (TASA 2009).

Melvin 2006 was the only study in which outcome assessment was not clearly blinded.

Incomplete outcome data

Nine of ten trials addressed incomplete data including description of ITT analyses and recording and explanation of participant dropouts adequately (ADAPT 2007; Bernstein 2000; Clarke 2005; Cornelius 2009; Deas 2000; Melvin 2006; Riggs 2007; TADS 2004; TASA 2009) while this was not adequately addressed in one trial (Mandoki 1997).

There was unbalanced drop out in two trials (Melvin 2006; TADS 2004) and reasons for dropout were not reported in three trials (Clarke 2005; Cornelius 2009; Deas 2000).

Selective reporting

Four trials were judged to have been free of selective reporting (ADAPT 2007; Cornelius 2009; Deas 2000; TADS 2004). We were unclear whether there was selective reporting in three trials (Bernstein 2000; Clarke 2005; Melvin 2006), as some trial outcomes were only reported at particular time points, or were difficult to interpret. Clarke 2005 reported using an ITT analysis, however when we did manual calculations for remission rates we found that remission was analysed for observed cases only. Mandoki 1997 was judged to have selective reporting, as the results contained no numerical data and all outcomes were presented in graph format. TASA 2009 also reported only selected data, providing results for the combination treatment group and overall results, but not for other comparison arms.

Other potential sources of bias

Five trials were determined to be free of additional sources of bias (ADAPT 2007; Cornelius 2009; Mandoki 1997; Melvin 2006; Riggs 2007). Clarke 2005 reported that telephone administration of self report measures may have created bias.

Effects of interventions

We report on results by objectives (one to three) with each relevant comparison for each objective listed. We do not report on heterogeneity for non-significant results.

Are psychological therapies or antidepressant medication more effective?

Data relevant to this research question are contained within the analyses undertaken in comparison 1.

Comparison 1: Psychological therapy versus antidepressant medications

Two studies (n = 220) compared psychological therapies versus antidepressant medication (Melvin 2006; TADS 2004) and contained data suitable for this comparison.

1.1 to 1.4: Remission from depressive disorder by clinical interview

Both studies (Melvin 2006; TADS 2004) reported remission rates based on observed case data. We undertook analysis based on numbers randomised in the first instance .

- At post-intervention the effect of antidepressants on the rate of remission was unclear (OR 0.62, 95% CI 0.28 to 1.35) Analysis 1.1. When observed case data was evidence of a small effect in favour of antidepressants (OR 0.52, 95% CI 0.27 to 0.98) Analysis 1.2. There was a large dropout from the CBT group in the TADS 2004 trial (28%), compared to the Melvin 2006 trial (5%); whereas at 6-9 months follow-up the dropout from the medication group in the TADS 2004 trial was 20% compared with 19% in the Melvin 2006 trial.
- One trial (n = 20) reported data for six to nine months follow-up (Melvin 2006) Analysis 1.3. The effect of taking medication compared with psychological therapy was unclear (OR 0.83, 95% CI 0.27 to 2.60) and there was little difference in the outcome when OC data was used (OR 0.67, 95% CI 0.18 to 2.49) Analysis 1.4.
- No trial provided data on remission at 12 months follow-up.

1.5 and 1.6: Dropouts

Both studies (Melvin 2006; TADS 2004) reported the number of dropouts during the intervention.

- At post-intervention, the effect on dropout of receiving psychological therapy compared with receiving antidepressant medication was unclear (OR 0.61, 95% CI 0.11 to 3.28) Analysis 1.5.
- At six to nine months follow-up there continued to be an unclear effect on dropout rates across the two treatment conditions (OR 1.17, 95% CI 0.63 to 2.19) Analysis 1.6.
- No trial provided data on dropouts at 12 months follow-up.

Suicide-related SAEs

TADS 2004 also reported on 'spontaneously reported suicide-related events', measured using the Columbia Classification Algorithm of Suicide Assessment. At post-intervention, 10 out of 109 participants in the medication treatment arm had experienced a suicide-related event; this included two suicide attempts, and eight instances of suicidal ideation. Five out of 111 participants receiving psychological therapy reported a suicidal event, of which one was a suicide attempt, and four were suicidal ideation.
The TADS 2004 trial also reported on the total number of suicide-related events that occurred up to the 36-week follow-up point. Sixteen out of 109 participants who received medication experienced a suicide-related event during the entire trial, and seven out of 111 participants in the psychological therapy arm experienced a suicide-related event.

1.7 to 1.11 Suicide-related outcomes

TADS 2004 reported dichotomous data regarding suicidal ideation, as defined by a score of more than 31 on the SIQ-JR.

- At post-intervention (n = 188) there were significantly fewer participants experiencing suicidal ideation in the psychological therapy group than in the medication group (OR 0.26, 95% CI 0.09 to 0.72) Analysis 1.7.
- At six to nine months follow-up, this effect was still evident (OR 0.26, 95% CI 0.07 to 0.98) Analysis 1.8.
- There were no data available for 12 months follow-up.

Two trials (Melvin 2006; TADS 2004) reported continuous suicidal ideation data, and used the SIQ-JR.

- At post-intervention, there was a small effect favouring psychological therapy compared with medication (MD -3.12, 95% CI -5.91 to -0.33) Analysis 1.9.
- The effect remained at six to nine months follow-up (MD -2.89, 95% CI -5.49 to -0.28) Analysis 1.10.
- Only one trial (TADS 2004) provided data at 12 months follow-up. The reduction in suicidal ideation experienced by those receiving psychological therapy did not reach statistical significance (MD -2.50, 95% CI -5.09 to 0.09) Analysis 1.11.

1.12 to 1.14 Remission from depressive disorder by cut-off

One trial (TADS 2004) reported data regarding remission from depressive disorder by cut-off score, using an upper threshold of $\leq$ 28 on the CDRS-R scale.

- At post-intervention, the effect on remission rates of receiving medication or psychological therapy was unclear (OR 0.65, 95% CI 0.33 to 1.28) Analysis 1.12.
- The effect remained unclear at six to nine months follow-up (OR 1.50, 95% CI 0.88 to 2.58) Analysis 1.13.
- It was also unclear at 12 months follow-up (OR 0.84, 95% CI 0.49 to 1.47) Analysis 1.14.

1.15 to 1.17 Depressive symptoms: Clinician rated

Data on clinician rated depression symptoms were only available for the TADS 2004 trial (n = 220), and were measured using the CDRS-R.

- At post-intervention, there was evidence of a small effect on CDRS-R scores for those receiving medication, compared with those receiving psychological therapy (MD 5.76, 95% CI 3.46 to 8.06) Analysis 1.15.
- At six to nine months follow-up, the effect of receiving medication or psychological therapy was unclear (MD 0.05, 95% CI -2.11 to 2.21) Analysis 1.16.
- At 12 months follow-up, the effect remained unclear (MD 0.90, 95% CI -0.93 to 2.73) Analysis 1.17.

1.18 to 1.20 Depressive symptoms: Self rated

Two trials provided data for this outcome (Melvin 2006; TADS 2004), with a total of 144 participants.

- At post-intervention, the effect on self reported depressive symptoms of receiving medication or psychological therapy was unclear (SMD 0.16, 95% CI -0.69 to 1.01) Analysis 1.18. There was a difference in the direction of the effect of the interventions in the two trials included in the meta-analysis (and considerable heterogeneity between the trials (I^2 = 81%, P = 0.02)), with Melvin 2006 favouring psychological therapy, and TADS 2004 favouring medication.
- At six to nine months follow-up, the effect remained unclear (SMD -0.04, 95% CI -0.51 to 0.42) Analysis 1.19, and heterogeneity between them was non-significant (I^2 = 57%, P = 0.13).
- At 12 months follow-up, only TADS 2004 had suitable data for meta-analysis and the effect of medication or psychological therapy on levels of self reported depressive symptoms remained unclear (MD 0.50, 95% CI -2.74 to 3.74) Analysis 1.20.

1.21 and 1.22 Functioning

One trial assessed functioning in this comparison (Melvin 2006).

- At post-intervention (n = 42) the effect of medication compared with psychological therapy in improving functioning was unclear (MD 2.19, 95% CI -3.36 to 7.74) Analysis 1.21.
- The effect remained unclear at six to nine months follow-up (MD -0.39, 95% CI -6.66 to 5.88) Analysis 1.22.
- No data were available for 12 months follow-up.

Is combination therapy more effective than antidepressant medication?

Data relevant to this research question are contained within the analyses undertaken in comparison 2.

Comparison 2: Combination therapy versus antidepressant medication

Four studies (n = 618) provided useable data for this comparison (ADAPT 2007; Clarke 2005; Melvin 2006; TADS 2004).

2.1 to 2.5 Remission from depressive disorder by clinical interview

Three studies reported data on rates of remission by clinical interview (Clarke 2005; Melvin 2006; TADS 2004). The Melvin 2006 and TADS 2004 trials reported observed case data. We used numbers randomised in the analysis in the first instance.

- At post-intervention, based on data from three trials with 419 participants (Clarke 2005; Melvin 2006; TADS 2004), there was an effect on remission rates favouring combination therapy that did not reach significance compared with those who received medication alone (OR 1.50, 95% CI 0.99 to 2.27) Analysis 2.1. There was little difference in outcome when OC data were used (three trials; 378 participants; OR 1.56, 95% CI 0.98 to 2.47) Analysis 2.2.
- At six to nine months follow-up, data from two trials with 265 participants (Clarke 2005; Melvin 2006) again showed some effect of combination therapy that did not reach significance (OR 1.93, 95% CI 0.93 to 4.00) Analysis 2.3, with no real change in outcome when OC data were used (OR 1.94, 95% CI 0.88 to 4.27) Analysis 2.4.
- At 12 months, only one trial had data suitable for meta-analysis (Clarke 2005). The effect of the intervention was in the opposite direction, favouring medication alone, however this effect was small and did not reach significance (OR 0.49, 95% CI 0.14 to 1.69) Analysis 2.5.

2.6 to 2.8 Dropouts

Four studies provided data concerning dropouts at post-intervention and three to six months follow-up (ADAPT 2007; Clarke 2005; Melvin 2006; TADS 2004).

- At post-intervention (n = 627) the effect of combination therapy compared with medication alone was unclear (OR 0.89, 95% CI 0.49 to 1.63) Analysis 2.6.
- At three to six months (n = 420) there appeared to be no difference between the two treatment approaches (OR 0.94, 95% CI 0.54 to 1.64) Analysis 2.7.
- At 12 months only one study provided data (Clarke 2005), with significantly fewer participants dropping out from medication alone, compared with combination therapy (OR 2.42, 95% CI 1.05 to 5.59) Analysis 2.8.

Suicide-related SAEs

At post-intervention, TADS 2004 reported that six out of 107 participants in the combination therapy group experienced a suicide-related event; two were suicide attempts, one act was of unknown intent, and three participants reported suicidal ideation. For participants in the medication alone group, 10 out of 109 experienced an event, with two being an attempt and eight being episodes of suicidal ideation.

In total, nine out of 107 participants in the combination therapy group experienced a suicidal event at any point during the study. For participants in the medication alone group, 16 out of 109 experienced a suicidal event.

ADAPT 2007 measured suicidal acts using the K-SADS-PL depression section. At 12 weeks, 8% of participants in the medication alone group reported attempting suicide, compared with 6.9% of the combination therapy group. At 28-week follow-up 6.4% of the medication alone group and 7.1% of the combination therapy group had reported attempting suicide.

Melvin 2006 report that one participant in the combination therapy group and four in the medication alone group attended treatment sessions with 'high levels of suicidality' (pg. 1159), however no one had to discontinue treatment due to these symptoms, and no suicidal behaviours were reported as part of the adverse events.

2.9 to 2.14 Suicidal-related behaviours

Dichotomous data from the ADAPT 2007 and TADS 2004 trials were included in this analysis. ADAPT 2007 data is based on the ideation outcome of the K-SADS-PL, and TADS 2004 is based on a cut-off score of the SIQ-JR.

- At post-intervention, the effect of combination therapy compared with medication alone is unclear (OR 0.75, 95% CI 0.26 to 2.16) Analysis 2.9. There was significant heterogeneity (I^2 = 68%, P = 0.08).
- At six to nine months follow-up, the effect of the two intervention approaches remains unclear (OR 0.53, 95% CI

0.06 to 4.58) Analysis 2.10. There was significant heterogeneity (I^2 = 83%; P = 0.08).

- Data at 12 months follow-up was only available from the TADS 2004 trial, and this favoured combination therapy, with fewer individuals reporting suicidal ideation, compared with those treated with medication alone; however this did not reach significance Analysis 2.11.

Two trials (Melvin 2006; TADS 2004) provided continuous suicidal ideation data.

- There were no differences in treatment approaches post-intervention (MD -2.57, 95% CI -5.53 to 0.40) Analysis 2.12, at six to nine months (MD -1.89, 95% CI -4.50 to 0.72) Analysis 2.13; or at 12 months follow-up (only TADS 2004 provided data for this time point) (MD -1.60, 95% CI -4.18 to 0.98) Analysis 2.14.

2.15 to 2.17 Remission from depressive disorder by cut-off

Data from one study (TADS 2004) containing 216 participants was suitable for the post-intervention and six to nine months time points, and is based on a CDRS-R score of less than 28. At 12 months follow-up, data from two studies was combined in a meta-analysis (Clarke 2005; TADS 2004).

- At post-intervention, significantly more participants receiving combination therapy were in remission compared with those who received medication alone (OR 2.01, 95% CI 1.11 to 3.63) Analysis 2.15.
- At six to nine months follow-up, the effect of the two treatment approaches is unclear (OR 0.90, 95% CI 0.53 to 1.53) Analysis 2.16.
- The effect remains unclear at 12 months follow-up (OR 1.45, 95% CI 0.60 to 3.52) Analysis 2.17.

2.18 to 2.20 Depressive symptoms: Clinician rated

Two trials (ADAPT 2007; TADS 2004, 415 participants) provided data at post-intervention and six to nine months follow-up on clinician rated depressive symptom scales.

- At post-intervention, the effect of combination therapy compared to medication alone on clinician rated depressive symptoms was unclear (MD -0.27, 95% CI -4.95 to 4.41) Analysis 2.18. The direction of effect of the two trials included in the meta-analysis was opposite (and there was significant heterogeneity between the trials (I^2 = 74%, P = 0.05)), with TADS 2004 favouring combination therapy, and ADAPT 2007 favouring medication alone.
- At six to nine months follow-up, the effect of the two interventions remained unclear (MD-0.27, 95% CI -2.26 to 1.72) Analysis 2.19.
- At 12 months follow-up data were only available from the TADS 2004 trial, and the effect of the two treatment approaches was unclear (MD -0.70, 95% CI -2.46 to 1.06) Analysis 2.20.

2.21 to 2.23 Depression symptoms: Self rated

Four trials were included in this analysis (ADAPT 2007; Clarke 2005; Melvin 2006; TADS 2004, 593 participants).

- At post-intervention, the effect of the two intervention approaches on self reported depressive symptoms was unclear (SMD -0.07, 95% CI -0.25 to 0.12) Analysis 2.21.
- The effect remained unclear at six to nine months follow-up (SMD -0.06, 95% CI -0.28 to 0.17) Analysis 2.22.
- At 12 months, two trials with 368 participants provided data for meta-analysis, and there was evidence of a small effect favouring the use of combination therapy over medication alone in producing lower levels of self reported depressive symptoms (SMD -0.26, 95% CI -0.46 to -0.05) Analysis 2.23.

2.24 to 2.26 Functioning

Data regarding level of functioning was provided by three trials (ADAPT 2007; Clarke 2005; Melvin 2006) at post-intervention and six to nine months follow-up.

- At post-intervention (n = 396), the effect of receiving combination therapy compared with medication alone was unclear (SMD 0.09, 95% CI -0.11 to 0.28) Analysis 2.24.
- At six to nine months follow-up the effect remained unclear (SMD 0.08, 95% CI -0.12 to 0.28) Analysis 2.25.
- Only data from the Clarke 2005 trial were available at 12 months follow-up; this showed a small effect favouring combination therapy compared with medication alone (MD 3.00, 95% CI 0.40 to 5.60) Analysis 2.26.

Is combination therapy more effective than psychological therapies

Data relevant to this clinical question are contained within the analyses undertaken as part of comparisons 3 and 4. The most appropriate trial design to answer this research question is the comparison between combination therapy and psychological therapies plus placebo, contained in comparison 4.

Comparison 3: Combination therapy versus psychological therapy

We included two trials for this comparison (Melvin 2006; TADS 2004).

3.1 and 3.4 Remission from depressive disorder by clinical interview

Both trials (Melvin 2006; TADS 2004) contained data on remission by clinical interview based on observed case data. We used numbers randomised in the analysis.

- At post-intervention (n = 265), the effect of combination therapy, compared with those who received psychological therapy alone was unclear (OR 1.61, 95% CI 0.38 to 6.90) Analysis 3.1 with no real change in outcome when OC data were used (N = 222) (OR 1.82, 95% CI 0.38 to 8.68) Analysis 3.2. The direction of effect of the two trials included in the meta-analysis was opposite (there was significant heterogeneity between the trials (I^2 = 72%, P = 0.05)), with Melvin 2006 favouring psychological therapy alone and TADS 2004 favouring combination treatment.
- At six to nine months follow-up, data from one study was available for meta-analysis (Melvin 2006, 47 participants). The effect favoured combination therapy but did not reach significance (OR 2.55, 95% CI 0.78 to 8.36) Analysis 3.3 with wider CIs when OC data used (OR 3.40, 95% CI 0.81 to 14.24) Analysis 3.4.
- No study reported data at 12 months follow-up.

3.5 to 3.6 Dropouts

Two studies contained data suitable for this comparison (Melvin 2006; TADS 2004).

- At post-intervention, the effect of receiving combination therapy compared with receiving psychological therapy alone was unclear (OR 1.23, 95% CI 0.12 to 12.71) Analysis 3.5. The direction of effect of the two trials included in the meta-analysis was opposite (there was statistical heterogeneity between the trials (I^2 = 77%, P = 0.04)), with Melvin 2006 favouring psychological therapy alone and TADS 2004 favouring combination treatment.
- At six to nine months follow-up there appears to be no difference in the rate of dropout between the two intervention types (OR 0.75, 95% CI 0.40 to 1.42) Analysis 3.6.
- No data was available for meta-analysis at 12 months follow up.

Suicide-related SAEs

In the TADS 2004 study, at post-intervention, 5.6% of participants in the combination group and 4.5% of participants in the psychological therapy only group reported a suicide-related event. During the 36-week study period, 8.4% of combination treatment participants and 6.3% of psychological therapy only participants had experienced a suicidal event.

3.7 to 3.11 Suicidal-related behaviours

Only TADS 2004 provided dichotomous suicidal ideation data, at post-intervention, and six to nine months follow-up. Suicidal ideation events were based on a cut-off score on the SIQ-JR.

- At post-intervention, there is little evidence of any difference between treatment approaches (OR 1.68, 95% CI 0.53 to 5.34) Analysis 3.7.
- The effect is unclear at six to nine months follow-up (OR 0.63, 95% CI 0.10 to 3.89) Analysis 3.8.

Continous suicidal ideation data from Melvin 2006 and TADS 2004 were available for post-intervention and six to nine months follow-up. Both used the SIQ-JR scale. At 12 months follow-up only the TADS 2004 study was available.

- There appears to be little effect of either intervention in level of suicidal ideation at post-intervention (MD 0.60, 95% CI -2.25 to 3.45) Analysis 3.9, six to nine months follow-up (MD 1.78, 95% CI -2.29 to 5.85) Analysis 3.10or 12 months follow-up (MD 0.90, 95% CI -1.37 to 3.17) Analysis 3.11.

3.12 to 3.14 Remission from depressive disorder by cut-off

One trial (TADS 2004) reported data for remission from depressive disorder utilising a CDRS-R cut-off of less than 28.

- At post-intervention, results indicated an effect in favour of combination treatment, compared with psychological therapy alone (OR 3.08, 95% CI 1.63 to 5.84) Analysis 3.12.
- At six to nine months follow-up, the effect is unclear (OR 0.60; 95% CI 0.35 to 1.02) Analysis 3.13.
- At 12 months, the effect remains unclear (OR 1.15; 95% CI 0.66 to 2.00) Analysis 3.14.

3.15 to 3.17 Depressive symptoms: Clinician rated

The TADS 2004 trial (n = 218) was the only study to provide data for this outcome.

- At post-intervention, there was evidence of an effect favouring combination treatment in producing lower levels of clinician rated depressive symptoms compared with psychological therapy alone (MD -8.27, 95% CI -10.58 to -5.96) Analysis 3.15.
- At six to nine months follow-up, the effect is in the same direction, favouring combination treatment, however the effect no longer reaches significance (MD -0.87, 95% CI -3.10 to 1.36) Analysis 3.16.
- At 12 months there remains a small effect favouring combination treatment that does not reach significance (MD -1.60, 95% CI -3.49 to 0.29) Analysis 3.17.

3.18 to 3.20 Depression symptoms: Self rated

Self rated depression symptom scores were obtained for two trials (Melvin 2006; TADS 2004) in this comparison (n = 265).

- At post-intervention, the effect of the two treatment approaches on self rated depression scores is unclear (SMD -0.28, 95% CI -1.41 to 0.84) Analysis 3.18. The direction of the effect of the two trials included in the meta-analysis is opposite (there was significant heterogeneity between the trials (I^2 = 92%, P = 0.0004)), with TADS 2004 favouring combination therapy and Melvin 2006 favouring psychological therapy alone.
- At six to nine months follow-up, the effect remains unclear with the direction of effect the opposite for each trial included in the meta-analysis (SMD -0.16, 95% CI -0.63 to 0.31) Analysis 3.19.
- At 12 months follow-up only data from TADS 2004 was available and the effect is unclear (MD -3.10, 95% CI -6.38 to 0.18) Analysis 3.20.

3.21 to 3.22 Functioning

Functioning data was only obtained from Melvin 2006.

- At post-intervention, the effect of psychological therapy alone compared with combination therapy is unclear (MD -2.38, 95% CI -8.65 to 3.89) Analysis 3.21.
- At six to nine months, the effect of each intervention approach is unclear (MD 0.43, 95% CI -7.04 to 7.90) Analysis 3.22.
- No data was available for 12 months follow-up.

Comparison 4: Combination therapy versus psychological therapy plus placebo

All of the trials in this comparison were unique to those described in the above comparisons in that they targeted comorbid diagnoses, rather than depression in isolation. Additionally the Bernstein 2000 trial contained participants with a diagnosis of school refusal syndrome in addition to a comorbid diagnosis of depression and anxiety.

We included four studies (n = 249) for this comparison (Bernstein 2000; Cornelius 2009; Deas 2000; Riggs 2007).

Remission from depressive disorder by clinical interview

No data were reported for this outcome measure.

4.1 Dropouts

All four studies provided data for dropouts at post-intervention.

- At post-intervention (n = 249) the effect on the dropout rate for participants receiving a combination treatment compared with a psychological therapy plus placebo treatment was unclear (OR 0.98, 95% CI 0.42 to 2.28) Analysis 4.1.
- No data were available for comparisons at six to nine months or 12 months follow-up.

Suicide-related SAEs

Riggs 2007 reports that there were no serious suicide attempts or completed suicides during the trial; however, five participants were seen in the emergency room for 'worsening suicidality'; four participants were in the medication group and one was in the placebo group.

4.2 Suicide-related behaviours

One trial (Riggs 2007) containing 126 participants reported data based on question 13 of the CDRS-R about suicidal ideation.

- At post-intervention, the effect of combination treatment compared with psychological therapy plus placebo was unclear (MD -0.06, 95% CI -0.36 to 0.24) Analysis 4.2.

4.3 and 4.4 Remission from depressive disorder by cut-off

Two studies (Bernstein 2000; Riggs 2007) containing 173 participants provided data for this outcome.

- At post-intervention, there was evidence of an effect favouring combination treatment compared with psychological therapy plus placebo (OR 2.15, 95% CI 1.15 to 4.02) Analysis 4.3.
- No data were reported for the six to nine months follow-up.
- At 12 months follow-up, data from Riggs 2007 were available. The effect of the two treatment approaches was unclear (OR 1.20, 95% CI 0.29 to 5.02) Analysis 4.4.

4.5 Depressive symptoms: Clinician rated

Data concerning clinician rated depressive symptoms were available from three studies (Bernstein 2000; Cornelius 2009; Riggs 2007) containing a total of 239 participants.

- At post-intervention, there was evidence that combination therapy, resulted in significantly lower levels of clinician rated depressive symptoms compared with psychological therapy plus placebo (SMD -0.52, 95% CI -0.78 to -0.26) Analysis 4.5.
- No data were available for six to nine months or 12 months follow-up.

4.6 Depressive symptoms: Self rated

Three studies (Bernstein 2000; Cornelius 2009; Deas 2000) containing a total of 123 participants provided data for self reported depressive symptoms.

- At post-intervention, although self reported depressive symptoms were lower in the combination condition, this did not reach significance (SMD -0.34, 95% CI -0.70 to 0.02) Analysis 4.6.
- There were no data available for six to nine months or 12 months follow-up.

Functioning

There were no suitable data for this outcome.

While included as objectives, we did not have the data and so we were unable to explore subgroup analyses of the potential modifying effects of age and severity of depression on the results reported above.

DISCUSSION

Summary of main results

We have compared psychological therapy alone, antidepressant medication alone, and a combination of the two, for the treatment of depression in children and adolescents. We included 10 studies in our review, with participants aged 8 to 19 years.

We could not draw clear conclusions from our analysis; we could pool few data for meta-analysis because of the variety of interventions, there were small numbers of studies in each comparison, and data were conflicting at times.

Psychological therapy versus antidepressant medication

The effect of antidepressants on remission rates (as defined by clinical interview) was unclear compared with psychological intervention. This is based on two studies using ITT data, and assumes that those who dropped out during treatment did not achieve remission (Melvin 2006; TADS 2004). Using OC data, there was a small effect in favour of antidepressants because dropouts (who are assumed not to have achieved remission in the medication group) are not counted in the analysis. It cannot be assumed, however that those who dropped out did not achieve remission, making the results unclear. It should also be noted that this effect was driven by the positive findings in the TADS 2004 study, but these were not replicated by Melvin 2006. Nor is this finding supported by the analysis using a cut-off on continuous measures to define remission. There was also no evidence of superiority of medication over psychological therapy in the longer-term (Melvin 2006; TADS 2004). Significantly fewer instances of suicidal ideation were reported in participants receiving psychological therapy compared with medication post-intervention, and at three to six months follow-up. Psychological therapy may be associated with less suicidal ideation, however additional data are needed to substantiate this claim.

The differences in short-term findings between the two studies may be related to the use of different antidepressant medications (Melvin 2006 used sertraline and TADS 2004 used fluoxetine). Meta-analyses (Whittington 2004) have asserted fluoxetine as the more effective SSRI for reducing depressive symptoms in children and adolescents. From the TADS 2004 study, it appears that fluoxetine may lead to a faster reduction in symptoms; however, it appears no more beneficial than psychological therapy over time. Sertraline was no more effective than psychological therapy. Acceptability of treatment, measured by dropout rate, did not differ between medication, and psychological therapy approaches. Again, the finding that medication may lead to faster reduction in symptoms should be interpreted with caution, given the inconsistent results between TADS 2004 and Melvin 2006, and the diversity in the direction of results across various outcome measures.

Combination therapy versus either psychologival therapy or antidepressant medication alone

Given the above findings, a combination of treatment approaches could be expected to provide both a faster treatment response and potential protection against suicidality, and thus be superior to medication or psychological intervention alone. We did not find compelling data to support this view. The results differed by outcome measure.

Combination therapy versus antidepressant medication

- The TADS 2004 study did show that combination therapy was superior to medication alone, immediately after intervention, but this was only a significant effect for remission using a cut-off score on a rating scale, and did not persist at follow-up.

- When a clinical interview was used to define remission, while the effects favoured combination therapy up to six to nine months follow-up, the effect did not reach significance (Clarke 2005; Melvin 2006; TADS 2004), and there were differences in the direction of effect for each of the studies included (possibly due to the different medications used in each trial), making the effects of different intervention strategies on remission unclear. Again, it should be noted that two of these trials reported this outcome using observed case data (Melvin 2006; TADS 2004).

- In contrast, the ADAPT 2007 study favoured medication alone. The collaborative context in which medication was

delivered in the ADAPT 2007 study may have influenced this result. Participants receiving medication in this study did so within a well co-ordinated case management approach.

- The effect of the different intervention approaches on clinician rated depression symptoms were unclear. There were some differences between groups on self rated depression, with large variability within the data; the ADAPT 2007 and Clarke 2005 trials favoured medication alone at post-treatment, whereas Melvin 2006 and TADS 2004 favoured combination therapy.

- At 12 months follow-up, meta-analysis based on two trials (Clarke 2005; TADS 2004) favoured combination therapy, resulting in significantly lower self reported depressive symptoms in the longer-term.

- In one study that measured this outcome (TADS 2004), rates of suicidal ideation at 12 months showed that combination therapy may provide some protective benefits against suicidal behaviour over time. Note that these differences were not apparent immediately after intervention. The effects of the treatment strategies were unclear on continuous measures of suicidal ideation.

Combination therapy versus psychological therapy

- Based on two trials (Melvin 2006; TADS 2004), the effect of the two intervention approaches to increase remission rates (by clinical interview), was unclear. It should be noted that the direction of effect in these trials differed and may be due to the use of different SSRI compounds (fluoxetine in TADS 2004 and sertraline in Melvin 2006), and again data were based on observed cases only.

- The TADS 2004 trial was the only study to provide data for remission based on a cut-off score, clinician rated depressive symptoms and self rated depressive symptoms. At post-intervention, there were significantly higher remission rates in those receiving combination therapy; however, this benefit appeared to be short-lived. .
- While not significant there was some evidence of a small effect of combination therapy on clinician rated depressive symptoms from TADS 2004.
- The effects on self reported depressive symptoms were unclear with the direction of the effect differing for trials.

- There was no difference in rates of suicidal behaviours or in suicidal ideation.

Combination therapy versus psychological therapy plus placebo

These trials all included participants with a comorbid diagnosis of either anxiety or addiction.

- Remission rates as defined by a cut-off score, were higher in those receiving combination therapy at post-intervention only.
- Clinician rated depressive symptoms were lower at post-intervention in those who received combination therapy compared with psychological therapy plus placebo, based on three trials (Bernstein 2000; Cornelius 2009; Riggs 2007).
- Although the effect was not as strong for self reported depressive symptoms, results from all three trials favoured combination therapy in general.

- There was no evidence of effect on suicide-related outcomes.

Overall, these trials suggest that medication is exerting a small effect on depression, over and above that of a placebo pill, in the short-term. This experimental design is interesting and methodologically robust.

As can be seen, there is limited evidence about the effects of different treatment approaches. In the acute phase of treatment, medication may ensure a faster treatment response; however, the benefit of medication over psychotherapy or a combination approach does not appear to be maintained over time. The limited evidence in this review suggests that psychological interventions may have the potential to provide some protection against suicidal ideation in the long-term, and may also result in effectiveness similar to other treatment approaches in the long-term. These tentative conclusions should be interpreted with caution given the considerable heterogeneity between trials, the variety of ways in which remission is defined across studies, and the inconsistent results across other outcome measures.

Recent guidelines for the treatment of depression in adolescents and young adults in Australia recommend psychotherapy as a first line treatment in this population. Only when symptoms are severe, should pharmacological approaches be considered, and then only in combination with ongoing psychotherapy (McDermott 2010). These recommendations are consistent with a number of guidelines produced internationally. The results of this review, while not contradicting these recommendations, introduce some uncertainty and highlight the need for more evidence to inform the treatment of youth depression. In the absence of conclusive evidence, guideline developers have to take into account a number of factors, including the need to guide clinicians in their approach to treatment.

Overall completeness and applicability of evidence

With few trials available in each comparison and the availability of data limited, it is difficult to draw conclusions at present about the most effective course of treatment for young people with depression.

Many of the significant outcomes derived from the meta-analyses were driven by data from the TADS 2004 study. Although this

trial is large and the design robust, its generalisability is limited because a significant proportion of participants were recruited for the study through advertisements and may not reflect those young people seen in clinical practice.

Although all studies in the review contained participants with a formal diagnosis of depression on a standardised and validated scale according to DSM-III or DSM-IV criteria, there was considerable variability in the study populations. For example, anxiety disorders were comorbid in 50% of the studies (ADAPT 2007; Bernstein 2000; Melvin 2006; TADS 2004; TASA 2009) and alcohol/substance use comorbid in two trials (Deas 2000; Riggs 2007). Furthermore, in one trial all participants were formally diagnosed with an anxiety disorder and school refusal syndrome (Bernstein 2000). While inclusion of these trials widens the diversity of the sample in terms of clinical presentation, it should be noted that in clinical practice, clients who present to services may be even more complex in their presentation. Comorbid diagnoses are common within the adolescent population, and the severity of depression in participants is also varied. The ADAPT 2007 trial also required that a young person had failed to respond to a trial of psychosocial intervention in order to meet entry criteria. This subsample of participants has been described as having "persistent ....depression" (Harrington 2002), and thus in essence may respond better to a different class of treatment as a function of depression persistence. The difference in study population between ADAPT 2007 (conducted in a clinical population), and TADS 2004 (with high recruitment via advertising,) may limit the appropriateness of performing meta-analysis on these two populations together.

There was also considerable variation in the type of medication used in the trials. The majority used SSRIs, including fluoxetine, venlafaxine and sertraline, with a couple of trials using a variety of SSRIs and one trial using a TCA. Meta-analyses (Whittington 2004) found that fluoxetine was the only SSRI to demonstrate reliable efficacy in reducing depressive symptoms in children and adolescents, and TCAs have no evidence of efficacy (Hazell 2002). Combining studies with medications that have varying efficacy limits the conclusions that can be drawn from this data set.

Many of the trials reported on adverse effects, and suicide-related behaviours were also included within that battery of outcomes. However, there was considerable variability in the way in which these data were collected or reported, and it was challenging to extract appropriate and homogenous data suitable for meta-analysis. It is important to report data concerning suicidality across all treatment approaches in a consistent way so that meaningful comparisons can be made. Brent 2009 found rates of suicidal and non-suicidal self injury were higher in young people who were systematically monitored for such outcomes. This highlights the importance of collecting suicide-related measures systematically.

Although there were data on follow-up to 12 months the diversity in trial design meant that few data could be aggregated.

We were unable to explore the potential modifying effects of age and severity of depression on the results because this type of data was also unavailable.

A strength of our review is that we used remission from disorder, rather than response to treatment because it is a more stringent measure and one that is more closely related to the goals of most people seeking treatment.

Quality of the evidence

We included large scale RCTs such as TADS 2004 (n = 439) and ADAPT 2007 (n = 208) in this review.

In general, the reporting of the conduct of trials allowed adequate evaluation of the risk of bias. Around 50% of trials had adequate sequence generation and allocation concealment. In the majority of trials, outcome assessors were blind to intervention, reducing the chance of experimenter bias. However, as is the nature with administering psychological interventions, many participants in the research trials would have been aware that they were receiving a psychological intervention, which raises the potential for bias in itself. ITT analysis was routinely used in the trials to account for missing data and reported as such. However, for the primary outcome of 'remission by clinical interview' two trials, from which the majority of data were derived, report this on the basis of observed case data only. It is unclear what the impact of missing participants is on the outcome in this case.

There are also potential biases that arise from the design of studies. Clarke 2005 allowed uncontrolled medication (any SSRI of any dose) within the medication arm. A study of comparable design, ADAPT 2007, contained much stricter guidelines around medication management during the experimental period. Furthermore, participants in the medication only group were also administered medication within the context of ongoing clinical care, during which time there was some limited focus on recent family and peer conflicts that could constitute more intensive case management when compared with Clarke 2005.

Potential biases in the review process

The review authors wrote to trialists in order to obtain data relating to the outcomes specific to this review, and sought to locate all published and unpublished trials testing the effect of a psychological therapy or medication against a combination of the two. We obtained some data from some trialists, and we have noted this where applicable. However, not all authors were able to provide data for our outcomes of interest.

Agreements and disagreements with other studies or reviews

Two recent meta-analyses investigating the efficacy of combined treatment with cognitive behavioural therapy (CBT) in adolescent depression concluded that adding CBT to antidepressants re-

sulted in little additional benefit over and above medication alone (Dubrika 2010; Hetrick 2011). The reviews differed from ours in two ways, only trials which tested new generation SSRIs were included, and trials with 'treatment resistant' participants were included. Authors of these reviews cautioned against making firm conclusions given the limitations of the data. It should be noted that both reviews included the ADAPT 2007 trial. As highlighted above, the context within which participants received medication alone (compared to combination treatment) in this trial was collaborative, and co-ordinated in nature, meaning that any potential benefits of adjunctive CBT to medication could have been masked by this procedure.

A number of recent reviews have concluded that SSRIs are associated with an increase in suicidal behaviour in children and adolescents (Dubicka 2006; Hammad 2006; Hetrick 2007). There are limited data from this review that suggest that suicidal ideation is more common in participants treated with medication in isolation, compared with psychological therapy at post-intervention and three- to six-month follow-up, or a combination of the two at 36-week follow-up. The data also suggest that suicidal ideation decreased less with medication only. It is possible that psychological therapy may exert a protective effect against suicidal behaviours when combined with medication.

It was not possible in this review to draw robust conclusions, nor to establish which intervention strategy was most effective.

Implications for research

Further research is needed in which: i) remission is used as a main outcome measure, in order to assess the effectiveness of an intervention in treating depression in children and adolescents; ii) measures of suicidal-related behaviours are measured robustly and consistently; iii) combination interventions are evaluated in young people who have first failed to respond to a first line psychological therapy for depression such as CBT or IPT. Given the dominance of the combination approach to treatment, it is unlikely, although it may still be useful to investigate the efficacy of psychotherapies against medication. There is a need for studies in populations that are more representative of the clinical populations taking into account the severity of depression at presentation. One of the practical difficulties in clinical practice is accessing CBT or IPT. Techonology has enabled a variety of creative and innovative methods of delivering psychological interventions (e.g. telephone, Internet; Richardson 2010), and while this isn't yet reflected in the literature in terms of high quality RCTs, studies testing these innovations in delivery methods would be worthwhile.

AUTHORS' CONCLUSIONS

Implications for practice

There is little evidence about the benefits and risks of various approaches to treating child and adolescent depression, with differences in type of participants and the treatment regimens in studies published to date.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADAPT 2007

Methods	Duration: 12 weeks Follow-up assessment points: Post-intervention, 28 weeks Funded by: NHS Health Technology Assessment (HTA) Programme, Central Manchester and Manchester Children's University Hospitals
Participants	N = 208 Adolescents only (11 to 17 years) Depression diagnoses included: DSM-IV; criteria for major or probable major depression (four symptoms with psychosocial impairment). Participants also had to obtain a score of 7 or more on the Health of the Nation Outcome scales for children and adolescents (HoNOSCA; Gowers 1999) Baseline risk of suicide: Measured using the suicidality items from the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL; Kaufman 1997). Patients with active suicidal intent were included in the study

Baseline	**Fluoxetine + CBT n = 105 (%)**	**Fluoxetine n = 103 (%)**
Thoughts	50 (47.6)	48 (46.6)
Ideation	40 (38.1)	44 (42.7)
Acts	13 (12.4)	21 (20.4)
Medical lethality	3 (2.9)	4 (3.9)
Self harm	30 (28.6)	23 (22.3)

Baseline severity of depression: Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996). Mean t-score (SD): Fluoxetine + CBT = 75.1 (6.7) Fluoxetine = 75.3 (6.7)

Comorbidity included:

Comorbidity	**Fluoxetine + CBT (n = 105)**	**Fluoxetine (n = 103)**
Social Phobia	43	49
Obsessive compulsive disorder	42	37
Post-traumatic stress disorder	42	36
Agorophobia	36	29
Separation anxiety disorder	31	28
Specific phobia	25	22
Conduct disorder	18	17
Panic disorder	21	14
Oppositional defiance disorder	17	13
Generalised anxiety disorder	19	13
Panic disorder (with agoraphobia)	20	13
ADHD	5	6
Bulemia Nervosa	8	4
Alcohol abuse	1	4
Transient tic disorder	2	3
Tourettes syndrome	2	2
Alcohol dependence	1	2

	Encopresis	1	0
	Enuresis	1	0
	Dysthymia	1	0
	Age: Range = 11 to 17 years		
	Fluoxetine + CBT (median) = 14		
	Fluoxetine (median) = 14		
	Sex (M:F):		
	Total: 54:154		
	Fluoxetine + CBT = 26:79		
	Fluoxetine = 28:75		
	Setting: Outpatient setting		
	Excluded psychiatric diagnoses: Schizophrenia or bipolar disorder; global learning disability (formal testing not undertaken)		
	Country: UK		
Interventions	Combination (Fluoxetine+CBT) **N = 105** Name: CBT with core interventions including engagement and goal setting, emotional recognition, self monitoring, self reinforcement and activity scheduling, challenging negative thinking and cognitive restructuring, social problem-solving and communication skills # sessions/length: 19 sessions over 28 weeks. (1 session per week for 12 weeks, 1 session per fortnight for 12 weeks, 1 final session at 28 weeks) Manualised (Y/N): Yes Individual or group: Individual Parent involvement: Encouraged at the end of each session by therapist Fidelity check: Yes. Audiotapes of the session were rated with a modified version of the cognitive therapy scale (Vallis 1986) Inter-rater reliability k = 0.8 Delivered by: 4 Psychiatrists who either had previous CBT training or attended a 3-day training course on CBT for depression, and 10 CBT therapists (mostly Psychologists) Name (class & type): SSRI (Fluoxetine). However, 26 participants were taking a different SSRI when admitted to the trial; 3 switched to fluoxetine and 11 changed from fluoxetine to another SSRI Dose (mg/day)/length: 10 mg daily for 1 week, increasing to 20 mg for 5 weeks. If no response, increase considered to 40 mg on alternate days for one week followed by 5 weeks of 40 mg. Option to increase dose to 60 mg on alternate days for 1 week followed by 60 mg daily for 5 weeks if participant did not respond by 12 weeks. Overall, there was a mean dose of 30 mg for both groups, and 2 patients received 60 mg Delivered by: psychiatrists in the context of ongoing clinical care. The content of contact was an explanation of depression and attention to recent family or peer group conflicts. Liaison with schools and other agencies undertaken when appropriate. Participants offered 9 outpatient sessions of usual care over 28 weeks, with the option of more if needed Medication Only **N = 103** Medication details as above Y/N: Yes		
Outcomes	Clinician reported The Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) Children's Global Assessment Scale (C-GAS; Shaffer 1983) Suicidality items from the Kiddie Schedule for Affective Disorders and Schizophrenia		

	Present and Lifetime Version (K-SADS-PL; Kaufman 1997) Self reported The Mood and Feelings Questionnaire (MFQ; Wood 1995) Parent reported The Clinical Global Impression Improvement Scale (CGI-I; Guy 1976) Additional Measures The Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA; Gowers 1999) The Clinical Global Impression Improvement Scale (CGI-I; Guy 1976)
Notes	Dropouts during treatment to any or at least 1 adverse reaction: 1 participant experienced a fit possibly related to SSRI and 1 had an allergic reaction (possibly secondary to medication) Suicide-related outcome as an adverse event of treatment: 4 required admission for suicidality or self harm and were withdrawn from the study Authors only report median age

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Participants were randomised to SSRI alone or SSRI plus CBT by an equal allocation ratio using stochastic minimisation balancing for severity (Childrens Global Assessment Scale <40), centre, sex, concurrent comorbidity disorder, and age" pg. 2/8 (Under heading Assignment)
Allocation concealment (selection bias)	Low risk	"Research staff from the clinical sites enrolled patients, and an independent telephone randomisation centre allocated treatment" pg. 2 /8 (Under heading Assignment)
Blinding (performance bias and detection bias) Assessors	Low risk	"...research assistants blind to treatment assignment assessed outcome" pg. 4/8 (Under heading Outcomes)
Blinding (performance bias and detection bias) Participants	High risk	No placebo or control psychotherapy was used. As such, participants would be aware that the medication was active and the therapy was CBT
Incomplete outcome data (attrition bias)	Low risk	ITT analysis: "Analysis was by intention to treat subject to the availability of the data" pg. 4/8 (Under heading Statistical Analysis) Number randomised: Fluoxetine + CBT: 105 Fluoxetine:

		103 Total: 208 Number of dropouts during intervention: Fluoxetine + CBT: 11 Fluoxetine:6 Total: 17 Number dropouts in follow-up: Fluoxetine + CBT: 7 Fluoxetine: 7 Total: 14 Number analysed post-intervention: Fluoxetine + CBT: 105 Fluoxetine: 103 Total: 208 Number analysed follow-up 1: Fluoxetine + CBT: 105 Fluoxetine: 103 Total: 208 Reasons for dropout in each group: 12 patients were formally withdrawn from the study for the following reasons: 4 required admission to hospital for suicidality or self harm, 5 failed to improve, 1 had a fit, 1 had an allergic reaction, 1 was prescribed paroxetine by a GP 18 families withdrew participants from the study: 6 were improving and did not want further treatment, 5 did not want more treatment, 2 wanted CBT, 2 did not want CBT, 1 wanted a female therapist, 1 was getting worse, 1 moved
Selective reporting (reporting bias)	Unclear risk	Authors reported data for all outcomes specified in their methods. Do not have access to trial protocol
Other bias	Low risk	

Bernstein 2000

Methods	Duration: 8 weeks Follow-up assessment points: Post-intervention, 12 months Funded by: National Institute of Mental Health (NIMH)
Participants	N = 63 Adolescent only (12 to 18 years) Depression diagnoses included: DSM-III-R Major Depressive Disorder (MDD). Participants also had to obtain a score of 35 or more on the CDRS-R (Poznanski 1996) Baseline risk of suicide: Not measured Baseline severity of depression: Chidren's Depression Rating Scale (CDRS-R; Poznanski 1985). Mean score (SD): Imipramine + CBT = 46.8 (9.5) Placebo + CBT = 52.5 (10.8) Comorbidity included: All 63 subjects met criteria for at least 1 anxiety disorder based

	on either adolescent or parental interviews Age mean (SD): Total = 13.9 (3.6) Sex (M:F): 25:38 Setting: Unclear. Likely an outpatient setting based on information regarding medication monitoring throughout the trial Excluded psychiatric diagnoses: ADHD, conduct disorder, bipolar disorder, eating disorder, alcohol or drug abuse on the Diagnostic Interview for Children and Adolescents-Revised-Adolescent Version (DICA-R-A) or Parent Version (DICA-R-P; Reich 1990), or both, mental retardation by history, bipolar affective disorder in first degree relative Country: USA
Interventions	Combination (Imipramine + CBT) **N = 31** Name: CBT. Based on school refusal treatment by Last 1998. Included the identification of negative thoughts surrounding school attendance and teaching adaptive coping strategies # sessions/length: 8 (45 to 60 minutes) sessions over 8 weeks Manualised (Y/N): Yes Individual or group: Individual Parent involvement: Yes. Parents joined each session for 10 to 15 minutes at the end Fidelity check: No formal check. Weekly discussions with all therapists and principal investigators, and a fortnightly telephone consultation with an expert on CBT for school refusal Delivered by: 3 therapists (1 behaviorally trained Clinical Psychologist, 1 Doctoral level therapist and 1 Masters level therapist) Name (class & type): TCA (Imipramine) Dose (mg/day)/length: Dose based on body weight. A gradual increase every 3 to 5 days to 3 mg/kg per day by the end of week 2 Mean dose at week 3 was 184.6mg ± 33.3 Delivered how: Weekly appointments monitoring side effects, and compliance were undertaken with a psychiatrist. Blood imipramine levels were monitored at 3 and 8 weeks Combination (Placebo medication + CBT) **N = 32** Details as above (Y/N): Yes
Outcomes	Clinician reported Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1985) with a score of ≤ 35 Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1985) Self reported The Beck Depression Inventory (BDI; Beck 1979) Additional Measures Anxiety Rating for Children-Revised (ARC-R; Bernstein 1996) The Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds 1978) Weekly school attendance rates
Notes	Dropouts during treatment to any or at least 1 adverse reaction: 1 participant developed manic symptoms and 1 developed psychiatric symptoms and required hospitalisation Suicide-related outcome as an adverse event of treatment: No

	Denominator and numerator for remission rates calculated from percentages reported in the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Random assignment to treatment was blocked on gender and whether subjects had a school vacation that lasted 5 or more days during the 8 week treatment period". (Under heading Procedure)
Allocation concealment (selection bias)	Unclear risk	No information contained in paper to make a judgement
Blinding (performance bias and detection bias) Assessors	Low risk	"All project personnel...were blind to medication assignment". (Under heading Procedure)
Blinding (performance bias and detection bias) Participants	Low risk	"...imipramine pills and matching placebo" "To preserve the blind, increases and decreases were also suggested for randomly selected patients on placebo". (Under heading Medication Management)
Incomplete outcome data (attrition bias)	Low risk	ITT analysis: "All randomized subjects were included in analyses based on intent to treat". (Under heading Statistical Analyses) Number randomised: Imipramine + CBT: 31 Placebo + CBT: 32 Total: 63 Number of dropouts during intervention Imipramine + CBT: 7 Placebo + CBT: 9 Total: 16 Number analysed post-intervention: Imipramine + CBT: 31 Placebo + CBT: 32 Total: 63 Reasons for dropout in each group: 1 missed 22 does of medication, 1 missed 2 therapy appointments, 1 developed manic symptoms on study medication, 1 required hospitalisation for psychiatric symptoms, and 12 declined further participation
Selective reporting (reporting bias)	Unclear risk	Authors report data for all outcomes post-intervention. Do not have access to trial protocol

Bernstein 2000 (*Continued*)

Other bias	High risk	Authors note that placebo group significantly more symptomatic at baseline compared with imipramine group despite randomisation

Clarke 2005

Methods	Duration: 6 weeks Follow-up assessment points: Post-intervention, 12, 26 and 52 weeks Funded by: The Agency for Healthcare Research and Quality and the Garfield Memorial Fund
Participants	N = 152 Adolescent only (12 to 18 years) Depression diagnoses included: DSM-IV episode of major depression Baseline risk of suicide: 73.7% (112/152) of participants reported significant levels of suicidal behaviour; assessment tool not explicitly referenced Baseline severity of depression: Centre for Epidemiological Studies - Depression Scale (CES-D; Radloff 1977): TAU + CBT = 35.4 (11.8) TAU = 33.7 (9.3) Comorbidity included: Not reported Age mean (SD): Total = 15.30 (1.61) TAU + CBT = 15.29 (1.62) TAU = 15.32 (1.60) Sex (M:F): 34:118 TAU + CBT = 17:60 TAU = 17:58 Setting: Primary care health maintenance organization (HMO) Excluded psychiatric diagnoses: Schizophrenia or a significant developmental/intellectual disability Country: USA
Interventions	TAU (SSRI) + CBT **N = 77** Name: CBT employing cognitive restructuring, or behavioural training, or both. Participants able to choose which type to try first. After completion of first module (2 to 5 sessions), therapist and youth reviewed recovery and decided whether to proceed with the second module (sessions 6 to 9), focusing on skills training # sessions/length: Between 0 and 9, mean 5.3 sessions. Each session 1 hour. Weekly in frequency Manualised (Y/N): No information Individual or group: Individual Parent involvement: Clinicians organised separate parent meetings, however "parents' attendance was "sparse" Fidelity check: Yes. All sessions audio taped. 57 sessions selected at random and rated by a senior supervisor. 87.2% adherence to protocol

	Delivered by: Masters level Psychologists Name (class & type): SSRI (varied). All trial participants were able to receive any medications provided by either the HMO or outside providers Dose (mg/day)/length: Varied Delivered by: No information TAU (SSRI) **N = 75** Details as above (Y/N): Yes
Outcomes	Clinician reported Mood disorders module of the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime version (K-SADS-PL; Kaufman 1997) and the Longitudinal Interview Follow-Up Evaluation (Keller 1982). This was used to define remission i.e. those who had did not have a continuing or new mood disorder since the last interview according to the K-SADS-PL). It was unclear if DSM-IV or ICD time criteria were employed Centre for Epidemiological Studies-Depression Scale (CES-D; Radloff 1977), cut-off of ≤ 15 Children's Global Adjustment Scale (C-GAS; Shaffer 1983) Self reported Centre for Epidemiological Studies-Depression Scale (CES-D; Radloff 1977) Parent reported The Child Behaviour Checklist (CBCL; Achenbach 1978) Additional Measures Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) Youth Self Report (YSR; Achenbach 1991) Internalising and Externalising subscales and an extracted depression subscale created to match DSM criteria for major depression (Clarke 1992) Social Adjustment Scale Self Report for Youth (Weissman 1980) Short Form-12 (Ware 1998)
Notes	Authors do not report reasons for dropout Dropouts during treatment to any or at least 1 adverse reaction: Not reported Suicide-related outcome as an adverse event of treatment: Not reported Numbers who reached remission by interview were calculated by review authors using percentages based on depressive episodes (Table 3). Data from Table 3 were based on observed cases not ITT following advice from statistician

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Youths were randomized using a blocked procedure to minimize study arm imbalance". pg. 889
Allocation concealment (selection bias)	Unclear risk	No information contained in paper to make a judgement

Blinding (performance bias and detection bias) Assessors	Low risk	"Blinded interviewers assessed each adolescent and a participating parent by telephone at baseline and at 6, 12, 26 and 52 weeks post-randomization". pg. 890
Blinding (performance bias and detection bias) Participants	High risk	No placebo or therapy control arm. As such, participants were aware if they were receiving CBT in the trial or not
Incomplete outcome data (attrition bias)	Unclear risk	ITT analysis: "...all subjects were considered part of the study from the point of randomisation (an intent-to-treat design)" pg.890 "We examined continuous depression and functioning outcome measures using random effect regression analysis". pg. 892 Number randomised: TAU + CBT: 77 TAU: 75 Total: 152 Number completing post-intervention: (dropouts) TAU + CBT: 67 (10) TAU: 65 (10) Total: 132 (20) Number completing follow-up 12 weeks: TAU + CBT: 61 (16) TAU: 61 (14) Total: 122 (30) Number completing follow-up 26 weeks: TAU + CBT: 65 (12) TAU: 62 (13) Total: 127 (25) Number completing follow-up 52 weeks: TAU + CBT: 56 (21) TAU: 58 (17) Total: 114 (38) *Data obtained from Fig 1. Summary of study procedures. Number analysed not clearly stated in paper Reasons for dropout in each group: Not reported
Selective reporting (reporting bias)	Unclear risk	Remission rates only reported at 52 weeks. Do not have access to trial protocol
Other bias	High risk	Authors note that telephone administration of self report measures may have created bias

Cornelius 2009

Methods	Duration: 12 weeks Follow-up assessment points: Post-intervention (12 weeks) Funded by: National Institute on Alcohol Abuse and Alcoholism
Participants	N = 50 Adolescent only (15 to 20 years) Depression diagnoses included: DSM-IV diagnosis of major depressive disorder (MDD) Baseline risk of suicide: Not measured and suicidality not stated as an exclusion criteria Baseline severity of depression: Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) Mean (SD): CBT + fluoxetine = 16.88 (7.09) CBT + placebo = 22.88 (8.79) Comorbidity included: All participants were required to have a DSM-IV diagnosis of an alcohol use disorder (AUD) confirmed using the Substance Use Disorders Section of the Structured Clinical Interview for the DSM (SCID) Age mean: Not reported Sex (M:F): Total = 28:22 CBT + fluoxetine = 12:12 CBT + placebo = 16:10 Setting: Outpatient? Psychiatric diagnoses excluded: DSM-IV diagnosis of bipolar disorder, schizoaffective disorder, or schizophrenia, persons with and substance abuse or dependence other than nicotine dependence or cannabis use and dependence, persons with a history of intravenous drug use, persons who had received antipsychotic or antidepressant medication within 1 month prior to baseline assessment also excluded Country: USA
Interventions	Combination: Psychotherapy + Medication **N = 24** Name (description): CBT for depressive disorder and the treatment of alcohol use disorder combined with Motivation Enhancement Therapy (MET) for the treatment of alcohol use disorder # sessions/length: 9 sessions over 12 weeks Manualised (Y/N): Yes Individual or group: Not reported Parent involvement: Not reported Fidelity check: No fidelity check reported Delivered by: Not reported Medication Name (class & type): SSRI; fluoxetine Dose (mg/day)/length: initiated at 10 mg, increased to 20 mg after week 2 until the end of the study, as 20 mg was target dose of the study Delivered how: Study physicians prescribed all medication Combination: Psychotherapy + Placebo **N = 26** Delivered how: Pill placebo delivered in the same context as above

Outcomes	Clinician reported Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) Self reported Beck Depression Inventory (BDI; Beck 1988) Additional Measures Drinking behaviour measured using the Timeline Follow-back Method (TLFB; Sobell 1988)
Notes	Dropouts during treatment to any or at least 1 adverse reaction: 0 Suicide-related outcome as an adverse event of treatment: 0 Suicidality was not measured with a formalised tool 3 dropouts during study from placebo group due to persistent depressive symptoms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patient randomisation was conducted by urn randomisation stratified by gender" pg. 906 (Treatment and assessment)
Allocation concealment (selection bias)	Low risk	"Active medication and matching placebo were prepared by the research pharmacy" pg. 906 (Treatment and assessment)
Blinding (performance bias and detection bias) Assessors	High risk	"The study was conducted in a double blind fashion, though one study physician remained non-blinded in order to handle any problems which may have arisen" pg. 906 (Assessment and treatment)
Blinding (performance bias and detection bias) Participants	Low risk	"...participants were randomly assigned to receive fluoxetine or placebo administered in identical-looking opaque capsules" pg. 906 (Assessment and treatment)
Incomplete outcome data (attrition bias)	Unclear risk	"Statistical analyses were completed on an intent-to-treat study group" pg. 907 (Statistical Analyses) Number randomised: CBT + fluoxetine: 24 CBT + placebo: 26 Number dropped out during intervention: CBT + fluoxetine: 0 CBT + placebo: 3 Number analysed post-intervention: CBT + fluoxetine: 24 CBT + placebo: 26
Selective reporting (reporting bias)	Unclear risk	Do not have access to trial protocol

Other bias	Low risk	Baseline imbalance of HAM-D and BDI scores with fluoxetine group have significantly lower baseline depression scores

Deas 2000

Methods	Duration:12 weeks Follow-up assessment points: Post-intervention Funded by: National Institute of Alcohol and Alcoholism (NIAAA)
Participants	N = 10 Adolescent only (15 to 18 years) Depression diagnoses included: Not clearly stated. The Child Schedule for Affective Disorders and Schizophrenia (K-SADS; Chambers 1985) was used to assess psychiatric disorders Baseline risk of suicide: Not measured Baseline severity of depression: measured using the Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) Sertraline + CBT = 20.40 (5.55) Placebo + CBT = 20.80 (5.45) Comorbidity included: All participants presented with an alcohol use disorder Age mean (SD): Total = 16.6 (0.52) Sertraline + CBT = 16.4 (0.55) Placebo + CBT = 16.8 (0.45) Sex (M:F): 8:2 Sertraline + CBT = 4:1 Placebo + CBT = 4:1 Setting: Outpatient Excluded psychiatric diagnoses: Not reported Country: USA
Interventions	Combination (Sertraline+CBT) **N = 5** Name (description): CBT focusing on relapse prevention, coping skills, anger management, modelling and role playing # sessions/length: 12, average attendance was 8.2 sessions and 10.6 sessions for the placebo and sertraline groups respectively Manualised (Y/N): No Individual or group: Group Parent involvement: Not reported Fidelity check: Not reported Delivered by: A psychiatrist, on a weekly basis Name (class & type): SSRI (Sertraline) Dose (mg/day)/length: 25 mg/day, increased to 25 mg weekly, to a maximum dose of 100 mg in about 4 weeks Delivered by: A psychiatrist monitored side effects, made medication adjustments, and supplied participants with additional medication on a weekly basis Combination (Placebo medication + CBT)

	N = 5 Details as above (Y/N): Yes
Outcomes	Self reported Outcome 4: Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) Additional Measures The Time Line Follow Back (TLFB; Sobell 1988) assessed alcohol use
Notes	Dropouts during treatment to any or at least 1 adverse reaction: No. Authors note that all the side effects of sertraline were transient and did not lead to any dropouts Suicide-related outcome as an adverse event of treatment: No

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Following the baseline assessments, subjects were randomized using a computer-generated randomisation table into sertraline or placebo groups" pg. 462
Allocation concealment (selection bias)	Low risk	All of the medication supplied by the study pharmacist were identical in appearance" pg. 462
Blinding (performance bias and detection bias) Assessors	Unclear risk	"This study was a 12 week double blind, placebo-controlled trial" pg. 462
Blinding (performance bias and detection bias) Participants	Low risk	Participants in both arms were blind to medication. Both received CBT "This study was a 12 week double blind, placebo-controlled trial" pg. 462
Incomplete outcome data (attrition bias)	Unclear risk	ITT analysis: All subjects randomised were included in the final analysis. No information is reported regarding imputation method for missing data Number randomised: SSRI + CBT: 5 Placebo + CBT: 5 Total: 10 Number of dropouts during intervention: * SSRI + CBT: 2 Placebo + CBT: 0 Total: 2 Number analysed post-intervention: SSRI + CBT: 5 Placebo + CBT:5 Total: 10 Treatment completion was defined a priori

Deas 2000 (*Continued*)

		as 8 sessions
Selective reporting (reporting bias)	Unclear risk	All outcome data specified in methods was reported. Do not have access to trial protocol
Other bias	High risk	Small study sample, and no follow-up

Mandoki 1997

Methods	Duration: 6 weeks Follow-up assessment points: Post-intervention Funded by: Not specified
Participants	N = 33 Child and adolescent (8 to 17 years) Depression diagnoses included: DSM-IV Major Depression Baseline risk of suicide: Participants who were acutely suicidal were excluded form the study. No other specific suicide measurements were administered Baseline severity of depression: Not reported Comorbidity included: Not reported Age mean (SD): Total based on completed participants: 12.7 (2.88) Sex (M:F): 25:8 Setting: Outpatient Excluded psychiatric diagnoses: Schizophrenia, mental retardation and Gilles de la Tourette's syndrome Country: USA
Interventions	Combination (SNRI + Psychotherapy) **N = 20** Name: Predominantly behavioural/cognitive in nature # sessions/length: One weekly session over 6 weeks Manualised (Y/N): Not reported Individual or group: Individual sessions of 60 minutes (45 minutes plus 15 minutes "collateral") Parent involvement: 15 minutes at the end of each session was "collateral" with parents and participants Fidelity check: Not reported Delivered by: Masters level therapists, trained in the procedural aspects of the study Name (class & type): SNRI (Venlafaxine) Dose (mg/day)/length: Children (8 to 12 yrs) began at 12.5 mg q.d for 3 days, increasing to 12.5 mg b.i.d for 3 days, and further increased to 12.5 mg t.i.d for the remainder of the study. Adolescents (13-17yrs) began at 25mg q.d. for 3 days, increased to 25mg b.i.d for 3 days and then 25mg t.i.d. for the remainder of the study Delivered how: Weekly clinic supplied medication/placebo and monitored vital signs and side effects Combination (Placebo+Psychotherapy)

	N = 20 Details as above (Y/N): Yes
Outcomes	Clinician reported The Child Depression Rating Scale (CDRS; Poznanski 1979) Self reported Children's Depression Inventory (CDI; Kovacs 1992) Parent reported The Child Behaviour Checklist (CBCL; Achenbach 1993) Additional Measures The Hamilton Rating Scale for Depression (Hamilton 1960)
Notes	Age and gender calculated manually from Figure 1 Dropouts during treatment to any or at least 1 adverse reaction: One participant developed a manic episode, was hospitalised and subsequently put on lithium. Authors note in discussion that "There are specific side effects associated with venlafaxine treatment.. ..However, these side effects were not severe enough to discontinue the medication" Suicide-related outcome as an adverse event of treatment: None reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information contained in paper to make a judgement
Allocation concealment (selection bias)	Unclear risk	As authors quote study as being 'double blind'
Blinding (performance bias and detection bias) Assessors	Low risk	"After the 6-week treatment, the study ended. The blind was broken...". pg. 151 Under heading Procedures, Measurements, and Medication Dose
Blinding (performance bias and detection bias) Participants	Low risk	"The patients were randomly assigned, in a double blind fashion, to either the venlafaxine and psychotherapy or the placebo and psychotherapy treatment group". pg. 151 Under heading Procedures, Measurements, and Medication Dose
Incomplete outcome data (attrition bias)	High risk	ITT analysis: No. "Figure 1 shows the age and sex composition of the final sample on which the statistical analysis was based". Manual calculation shows the analysis was conducted only on participants completing the trial. pg. 150 Under heading Subjects Number randomised: SNRI + Psychotherapy: 20 Placebo

		+ Psychotherapy: 20 Total: 40 Number of dropouts during intervention: SNRI + Psychotherapy: 4 Placebo + Psychotherapy: 3 Total: 7 Number analysed post-intervention: SNRI + Psychotherapy: 16 Placebo + Psychotherapy: 17 Total: 33 Reasons for dropouts: 6 did not continue coming to the clinic by week 2 for unknown reasons, and 1 patient (in the venlafaxine group) developed a manic episode and was hospitalised
Selective reporting (reporting bias)	High risk	No numerical outcome data was reported in the article, all data was presented in graphs only. Do not have access to trial protocol
Other bias	Low risk	

Melvin 2006

Methods	Duration: 12 weeks Follow-up assessment points: Post-intervention, 6 months. Funded by: Beyond Blue, Premiers Youth Suicide Taskforce, Department of Human Services Victoria and Australian Rotary Health Research Fund
Participants	N = 73 Adolescents only (12 to 18 years) Depression diagnoses included: DSM-IV major depressive disorder (MDD), dysthymic disorder (DD) and depressive disorder not otherwise specified (DDNOS) Baseline risk of suicide: Participants who were 'actively suicidal' were excluded from the study, however 'suicidally depressed teenagers (who did not require hospitalisation) were included. Measured using the Suicidal Ideation Questionnaire-Junior High School Version (SIQ-JR; Reynolds 1987) CBT = 26.05 (19.93) Sertraline = 29.42 (27.24) Sertraline + CBT = 30.64 (24.42) Participants exhibiting active suicidality that required acute hospital admission were excluded from the study Baseline severity of depression: CBT = 83.77 (13.8) Sertraline = 84.92 (11.20) Sertraline + CBT = 83.96 (15.01) Comorbidity included: 69% were diagnosed with at least 1 comorbid disorder, 22% were diagnosed with 2 or more

Comorbid disorder (n)	**CBT**	**Sertraline**	**Sertraline + CBT**
Anxiety disorders	8	9	10

	Dysthymic disorder	1	2	3
	Conduct Disorder/ODD	2	3	1
	Body dysmorphic disorder	1	0	0
	Adjustment disorder with anxiety	0	1	0
	Enuresis	1	0	0
	Reading Disorder	0	1	0
	Cannabis-related disorder NOS	0	1	0
	Parent-child relational problem	5	6	8
	Sibling relational problem	1	2	3
	Age mean (SD): 15.3 (1.5) CBT= 15.0 Sertraline = 15.5 CBT + Sertraline = 15.3 Sex (M:F): 25:48 CBT = 7:15 Sertraline = 7:19 CBT + Sertraline = 11:14 Setting: 3 clinics collocated with public child and adolescent mental health services Excluded psychiatric diagnoses: Bipolar disorder, psychotic disorder, primary diagnosis of substance abuse disorder, severe psychiatric disturbance that required acute hospital admission, and intellectual disability of sufficient severity to preclude participation in the study Country: Australia			
Interventions	Psychotherapy (CBT) **N = 22** Name: CBT course based in the Adolescent Coping with Depression Course (Clarke 1990). Modules included; goal setting, psycho education, affective education, self monitoring, relaxation training, social skills training, pleasant events scheduling, cognitive therapy and life goals planning # sessions/length: Twelve 50 minute sessions over 12 weeks. Three 'booster' sessions were also delivered over 3 months Manualised (Y/N): Yes Individual or group: Individual Parent involvement: Parents who chose to participate received concurrent CBT sessions, with 2 family sessions Fidelity check: No formal check. Clinicians received weekly to twice weekly supervision with an expert therapist. Peer supervision held weekly Delivered by: 7 registered psychologists, a supervised probationary psychologist, 2 general medical practitioners, and a social worker with experience in providing CBT for adolescent depression. Training provided by chief investigators Medication (Sertraline) **N = 26** Name (class & type): SSRI (Sertraline) Dose (mg/day)/length: 25 mg/day for 1 week, increased to 50 mg/day at week 2 depending on response and adverse events. Maximum dose of 100 mg/day administered depending on clinical response and tolerability Delivered how: Review sessions occurred every 2 to 3 weeks to monitor adverse effects, and included education about depression but no CBT strategies			

	Combination (Sertraline + CBT) **N = 25** Details as above (Y/N): Yes
Outcomes	Clinician reported The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Lifetime Version (KSADS-PL; Kaufman 1997) was used to assess for disorder or remission, which was based on DSM-IV criteria for full remission (i.e. 8 weeks asymptomatic) The Global Assessment of Functioning Scale (GAF; APA 1994) Dropouts: Post-intervention: CBT: 21/22 completed (1 dropout) Sertraline: 21/26 completed treatment (5 dropouts) Sertraline + CBT: 20/25 completed treatment (5 dropouts) 6 month follow-up: CBT: 19/22 completed assessment (3 dropouts) Sertraline: 23/26 completed assessment (3 dropouts) Sertraline + CBT: 24/25 completed assessment (1 dropout) Self reported Reynolds Adolescent Depression Scale (RADS; Reynolds 1986) The Suicidal Ideation Questionnaire-Junior High School Version (SIQ-JR; Reynolds 1987) Parent reported The Child Behaviour Checklist (CBCL; Achenbach 1991) Additional Measures The Global Assessment of Relational Functioning Scale (APA 1994) Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds 1978) The Self Efficacy Questionnaire for Depressed Adolescents (SEQ-DA; Tonge 2005) Family Assessment Device General Functioning Scale (Epstein 1983)
Notes	Dropouts during treatment to any or at least 1 adverse reaction: 6% discontinued medication due to adverse affects. These effects included slurred speech and dizziness, feeling agitated and restless, and diarrhoea Suicide-related outcome as an adverse event of treatment: 11.1% (n = 45) of participants taking sertraline either alone or with CBT reported suicidal ideation. 1 participant in the sertraline + CBT received an inpatient admission for several hours, however treatment according to protocol was subsequently continued

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...subjects were randomly allocated by an independent statistician using a computer generated assignment to CBT, MED or COMB". pg. 1154

Allocation concealment (selection bias)	Low risk	"...allocated by an independent statistician. ..Allocation for those eligible for the trial was concealed to all until after pre-treatment assessment". pg. 1154
Blinding (performance bias and detection bias) Assessors	High risk	"Independent raters blind to treatment allocation were not used because of resource limitations but may have reduced the risk of experimenter bias in assessments". pg. 1160
Blinding (performance bias and detection bias) Participants	High risk	Psychotherapy administered in both groups and no placebo control used for medication
Incomplete outcome data (attrition bias)	Unclear risk	ITT analysis: "data were analysed using an intent-to-treat strategy to counter any possible overestimation of treatment outcomes, using the last observation carried forward method (Nelson 1996)". pg. 1155 Number randomised: CBT: 22 Sertraline: 26 CBT + Sertraline: 25 Total: 73 Number of dropouts during intervention CBT: 1 Sertraline: 5 CBT + Sertraline: 5 Total: 11 Number dropouts in follow-up: CBT: 3 Sertraline: 3 CBT + Sertraline: 1 Total:7 Number analysed post-intervention: CBT: 22 Sertraline: 26 CBT + Sertraline: 25 Total: 73 Number analysed follow-up 1: CBT: 22 Sertraline: 26 CBT + Sertraline: 25 Total: 73 Reasons for dropouts: CBT: At post-intervention, 1 participant reported symptoms had improved. At 6-month follow-up, 2 refused to attend and 1 was unable to be located Sertraline: At post-intervention, 2 participants reported symptoms had improved, 1 reported side effects, 1 dissatisfied with programme and 1 did not pursue treatment. At 6-month follow-up, 1 participant refused to attend, 1 was unable to be located and 1 'trial closure' CBT + sertraline: At post-intervention:

Melvin 2006 (*Continued*)

		2 reported side effects, 1 symptoms improved, 1 dissatisfied with programme, and 1 did not respond. At 6-month follow-up, 1 refused to attend
Selective reporting (reporting bias)	Unclear risk	Remission data not reported by group and functioning data not reported in a useable format. All other outcomes were reported. Do not have access to trial protocol
Other bias	Low risk	

Riggs 2007

Methods	Duration:16 weeks Follow-up assessment points: Post-intervention Funded by: National Institute on Drug Abuse, National Institutes of Health
Participants	N = 126 Adolescent only (13 to 19 years) Depression diagnoses included: DSM-IV current MDD episode Baseline risk of suicide:Primary measure of suicidality was question 13 on the Childhood Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) Baseline suicidality data: Fluoxetine + CBT = 25/63 (39.7%) CBT + placebo = 24/63 (38.1%). N = 13 displayed severe suicidal ideation (≥ 5 on CDRS-R Q13) "Adolescents with past, current or intermittent suicidal ideation (39% at baseline) were not excluded from study participation unless suicidal ideation were severe or they were otherwise considered by the study physician and according to baseline CDRS-R ratings (question 13) to be at high risk for a suicide attempt during the trial" Baseline severity of depression: Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) mean t-score (SD): Fluoxetine + CBT: 73.74 (8.51) Placebo + CBT: 73.03 (7.70) Comorbidity included: All participants had at least 1 non-tobacco Substance Use Disorder (SUD), and lifetime Conduct Disorder (CD) Age mean (SD): Total = 17.16 (1.66) Sex (M:F): Total = 85:41 Setting: Outpatient Excluded psychiatric disorders: Current or past diagnosis of a psychotic disorder or of bipolar disorder (type I or II) Country: USA
Interventions	Combination (Fluoxetine + CBT) **N = 63** Name: CBT approach using behavioural, cognitive behavioural and motivational enhancement techniques to help adolescents reduce their drug use. The programme contains 1 session specifically on depression, helping adolescents to identify, manage and regulate mood states that often trigger substance use # sessions/length: 1 hour, 16 weekly sessions

Riggs 2007 (*Continued*)

	Manualised (Y/N): Yes Individual or group: Individual Parent involvement: Not specifically but could include up to 2 parent sessions Fidelity check: Yes. All sessions videotaped and self rated by therapists. 32 videotapes randomly selected and independently rated for adherence and fidelity. "...neither therapist fell below present fidelity/adherence standards during any point of the study" Delivered by: Study therapists (MD) who were trained and certified by one of the manuals developers. The developer provided ongoing supervision and quality monitoring Name (class and type): SSRI (Fluoxetine) Dose (mg/day)/length: 20 mg fixed daily dose Delivered how: Monitoring of adverse effects and medication adherence was undertaken by research nurses, and occurred either immediately before or after the weekly CBT session Combination (Placebo + CBT) Details as above (Y/N): Yes
Outcomes	Clinician reported Remission of depression defined as as post-intervention Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) score of $\leq$ 28 Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) The Clinical Global Impression Improvement rating (CGI-I; Guy 1976) Self reported Question 13 on the Children's Depression Rating Scale (CDRS-R; Poznanski 1996) Additional Measures Self reported number of non-tobacco drugs used in the past 30 days Urine samples for substance use Conduct Disorder: Number of self reported DSM-IV symptoms in the past 30 days
Notes	Group means for age and gender not reported Dropouts during treatment to any or at least 1 adverse reaction: Authors list 6 as 'lost to follow-up' and 2 to 'withdrew consent' but do not disclose if this was due to an adverse reaction Suicide-related outcome as an adverse event of treatment: 5 participants (4 in the fluoxetine + CBT group and 1 in the Placebo + CBT group were evaluated in an emergency department or hospitalised for concerns of worsening suicidality during the study Standard error and sample size was used to calculate standard deviations for group means

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"A non-blinded research pharmacist assigned eligible participants to receive 20 mg of fluoxetine hydrochloride or matching placebo using a small block (6) randomisation scheme of 20 blocks to achieve balance in the treatment assignment". pg. 1027

Riggs 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Active medication and matching placebo were prepared by the research pharmacy at the University of Colorado at Denver and Health Sciences Centre and then provided to clinical research staff in pre-randomized and pre-blinded medication bottles". pg. 1027
Blinding (performance bias and detection bias) Assessors	Low risk	"Research staff....remained blinded to medication status throughout the trial". pg. 1027
Blinding (performance bias and detection bias) Participants	Low risk	: ".....participants remained blinded to medication status throughout the trial". pg. 1027
Incomplete outcome data (attrition bias)	Low risk	ITT analysis: "All analyses were intent-to-treat (including all randomized study participants)". pg. 1028 Impulation method used: "Analyses of dichotomous and continuous primary outcome measures over time used generalized estimating equation (GEE) and likelihood based methods, respectively. Both allow for estimates of changes in repeated measures in the presence of missing data, assuming those data were missing at random". pg. 1028 Number randomised: Combination (Fluoxetine + CBT): 63 Combination (Placebo + CBT): 63 Total: 126 Number of dropouts during intervention: Combination (Fluoxetine+CBT): 11 Combination (Placebo + CBT):9 Total:20 Number analysed post-intervention: Combination (Fluoxetine + CBT): 63 Combination (Placebo + CBT): 63 Total:126 Reasons for dropouts: Fluoxetine + CBT: 4 participants went to jail/detention, 3 went to residential treatment at facility and were unable to continue the study, 3 were lost to follow-up and 1 moved out of area Placebo + CBT: 1 participant went to jail/detention, 3 were lost to follow-up, 3 moved out of area and 2 withdrew consent

Riggs 2007 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No group data on suicide outcomes reported. All other outcomes specified in methods reported. Do not have access to trial protocol
Other bias	Low risk	

TADS 2004

Methods	Duration: 12 weeks acute treatment, 6 weeks continuation treatment and 18 weeks maintenance treatment Follow-up assessment points: Post-intervention (12 weeks), 18 weeks (after continuation) , 36 weeks (after maintenance) Funded by: National Institution of Mental Health to Duke University Medical Centre
Participants	N = 439 Adolescent only (12 to 17 years) Depression diagnoses included: DSM-IV Major Depressive Disorder (MDD) and a score of 45 or more on the CDRS-R (Poznanski 1996) Baseline risk of suicide: *data obtained from Table 2, 2004 paper Measured using the Suicidal ideation Questionnaire-Junior High School Version (SIQ-JR; Reynolds 1987) Adjusted mean (SD): CBT: 21.91 (16.28) Fluoxetine: 21.81 (15.68) Fluoxetine + CBT: 27.33 (18.51) Placebo: 24.20 (16.46) Analysed according to a cut-off score of ≤ 31 CBT: 27/107 (25.2%) Fluoxetine: 28/107 (26.2%) Fluoxetine + CBT: 42/106 (39.6%) Participants excluded if deemed 'high risk' because of a suicide attempt requiring medical attention within 6 months. Also excluded on the basis of having a clear intent or active plan to attempt suicide, or suicidal ideation accompanied by a disorganised family unable to guarantee adequate safety monitoring Baseline severity of depression: *data obtained from Table 1, 2004 paper, t-scores presented Children's Depression Rating Score (CDRS-R; Poznanski 1996): CBT: 75.37 (6.32) Fluoxetine: 74.73 (6.74) Fluoxetine + CBT: 75.67 (6.53) Placebo: 76.14 (6.11) Comorbidity included: **Comorbidity (%) CBT Fluoxetine Fluoxetine+CBT Placebo** Any psychiatric comorbidity 58.18 43.12 55.66 51.

	35 Dysthymia 15.45 5.5 10.28 10.71 Anxiety 32.43 23.85 28.4 25.23 Disruptive behaviour 24.32 22.94 21.50 25. 00 Obsessive compulsive/tic 1.80 1.83 3.74 3.57 Substance use 0.90 2.75 2.80 0 Attention-deficit/hyperactivity 12.61 11.93 13.08 16. 96 Taking medications 3.60 2.75 3.74 8.93 Age mean (SD): Total = 14.6 (1.54) CBT = 14.62 (1.50) Fluoxetine = 14.50 (1.57) CBT + Fluoxetine = 14.6 (1.48) Placebo = 14.51 (1.62) Sex (M:F): 200:239 CBT= 50:61 Fluoxetine = 50:59 CBT + Fluoxetine = 47:60 Placebo = 53:59 Setting: Outpatient Excluded psychiatric disorders: Current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence, pervasive developmental disorder (s), thought disorder or psychiatric disorders requiring out of protocol treatments Country: USA
Interventions	Psychotherapy (CBT) **N = 111** Name: CBT modules included psycho education about depression and it's causes, goal-setting, mood monitoring, increasing pleasant activities, social problem-solving, and cognitive restructuring # sessions/length: Fifteen 1 hour sessions during stage 1, 6 additional sessions for partial responders and bi-weekly sessions for full responders in stage 2, and 3 sessions (1 every 6 weeks) in stage 3 Manualised (Y/N): Yes Individual or group: Individual Parent involvement: 1 to 3 conjoint parent and adolescent sessions took place Fidelity check: Not reported Delivered by: Not reported Medication (Fluoxetine) **N = 109** Name (class and type): Fluoxetine (SSRI) Dose (mg/day)/length: 10 mg/day and increased up to 40 mg/day by week 8. At week 12, dose raised to 50 to 60mg/day for 'partial responders' and 'full responders' remained on same fluoxetine dose Delivered how: Monitoring and status and medication effects occurred during 20 to 30 minute visits. Clinician also offered general encouragement about the effectiveness of

	pharmacotherapy for MDD Combination (Fluoxetine+CBT) **N = 107** Details as above (Y/N): Yes Placebo **N = 112**
Outcomes	Clinician reported Schedule for Affective Disorder and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-P-L; Kaufman 1997) This was used to define remission i.e. those who had did not have a continuing or new mood disorder since the last interview according to the K-SADS-PL).It was unclear if DSM-IV or ICD time criteria were employed Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) Self reported Reynolds Adolescent Depression Scale (RADS; Reynolds 1986). Suicidal ideation Questionnaire-Junior High School Version (SIQ-JR; Reynolds 1987) Additional Measures Clinical Global Impression Improvement (CGI-I; Guy 1976) Child and Adolescent Impact Assessment (Angold 1998) Columbia University classification scheme of the US Food and Drug Administration analyses of antidepressant-associated suicidal events
Notes	Dropouts during treatment to any or at least 1 adverse reaction: Suicide-related outcome as an adverse event of treatment: 24 (5.5%) of participants experienced a suicide-related adverse event Total number (%): *data obtained from 2006 paper CBT: 5 (4.5) Fluoxetine: 10 (9.2) CBT + Fluoxetine: 5 (4.7) Placebo: 3 (2.7)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomly assigned...using a computerized stratified randomisation, a 1:1:1:1 treatment allocation ratio, permuted blocking (first block size = 4, with subsequent random block sizes of 4 and 8) within each striatum, and site and sex stratification variables". pg. 808
Allocation concealment (selection bias)	Low risk	"Participants were randomly assigned...at the coordinating centre". pg. 449

Blinding (performance bias and detection bias) Assessors	Low risk	"TADS used 2 primary measures of depression status assessed...by an independent evaluator blind to condition". pg. 448
Blinding (performance bias and detection bias) Participants	High risk	"Participants and all study staff remained masked in the 'pills only' condition (fluoxetine therapy and placebo) until the end of stage 1 (week 12). Patients and treatment providers in the combination and CBT conditions were aware of treatment assignment". pg. 1133
Incomplete outcome data (attrition bias)	Unclear risk	"The primary analyses of remission rates. ..were conducted using an "intention to treat" (ITT) approach in which the analysis included all participants randomized to treatment regardless of protocol adherence and/or treatment completion". pg. Under heading Data Analysis, 2009 Imputation method: LOCF Number randomised: CBT: 111 Fluoxetine: 109 Fluoxetine + CBT: 107 Placebo: 112 Total: 439 Number of dropouts during intervention CBT: 41 Fluoxetine: 38 Fluoxetine + CBT: 23 Placebo: 14 Total: 116 Number of dropouts in follow-up (18 weeks): CBT: 21 Fluoxetine: 37 Fluoxetine + CBT: 15 Placebo: 8 Total: 81 Number of dropouts in follow-up (36 weeks): CBT: 25 Fluoxetine: 21 Fluoxetine+CBT:23 Placebo: 15 Total: 84 Number analysed post-intervention: CBT: 111 Fluoxetine: 109 Fluoxetine + CBT:107 Placebo: 112 Total: 439 Number analysed follow-up 1 (18 weeks): CBT: 111 Fluoxetine: 109 Fluoxetine + CBT:107 Total: 327 Number analysed follow-up 2 (36 weeks): CBT: 111 Fluoxetine: 109 Fluoxetine + CBT: 107 Total: 327 For active treatment arms: 84/327 exited the study because of loss of follow-up or withdrawal of consent (n = 21 for CBT + fluoxetine, n = 32 for fluoxetine, n = 31 for

TADS 2004 (*Continued*)

		CBT). 96/327 discontinued treatment before week 36 due to premature termination or non-response at the end of stage 1 (n = 25 for CBT + fluoxetine, n = 39 for fluoxetine, n = 32 for CBT), and this discontinuation was decided by the study physician For placebo: 13/112 participants were terminated prematurely from the study by week 12 due to clinical worsening
Selective reporting (reporting bias)	Unclear risk	Trial protocol located
Other bias	High risk	Combination therapy group had an excess of suicidal ideation at baseline relative to fluoxetine or CBT

TASA 2009

Methods	Duration: 6 months Follow-up assessment points: Post-intervention (24 weeks) Funded by: National Institute of Mental Health (NIMH)
Participants	N = 124 Adolescent only (12 to 18 years) Depression diagnoses included: DSM-IV Major Depressive Disorder (MDD), Dysthymic Disorder (DD) or Depressive Disorder not otherwise specified (DD-NOS). Participants also had to obtain a score of 36 or more on the CDRS-R (Poznanski 1996) Baseline risk of suicide: Participants were only eligible for participation if they had made a suicide attempt in the last 90 days. Beck Scale for Suicidal Ideation (SSI; Beck et al 1979). Mean (SD): Total = 6.3 (7.7) CBT-SP = 5.0 (6.0) SSRI = 3.9 (6.0) SSRI+CBT-SP = 6.9 (8.2) Baseline severity of depression: 96% met criteria for MDD and 10.5% had DD and DD. Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996). Mean (SD): Total = 50.4 (12.6) CBT-SP = 46.9 (14.7) SSRI = 43.4 (11.1) SSRI+CBT-SP= 52.1 (12.0) Comorbidity included: **Comorbidity (%)** **CBT-SP** **SSRI** **SSRI+CBT-SP** Anxiety 23.5 28.6 63.4 ADHD 11.8 14.3 23.7 ODD/CD 0.0 35.7 15.1 Age mean (SD): Total = 15.7 (1.5) CBT-SP = 15.7 (1.5)

TASA 2009 (*Continued*)

	SSRI = 15.6 (1.4) SSRI + CBT-SP = 15.7 (1.6) Sex (M:F): 28:96 CBT-SP = 1:16 SSRI = 1:13 SSRI + CBT-SP = 26:67 Setting: Academic sites Excluded psychiatric diagnoses: Substance dependence, bipolar disorder, psychosis and pervasive developmental disorders (PDD) Country: USA
Interventions	Psychotherapy (CBT-SP) **N = 17** Name: CBT + Suicide prevention (CBT-SP). Modules included; chain analysis of the suicide attempt, safety planning, formulation of the participants cognitive, behavioural, affective and contextual problems, behavioural activation, cognitive restructuring, problem-solving, and relapse prevention # sessions/length: Up to 22 sessions, length not specified Manualised (Y/N): Yes Individual or group: Individual Parent involvement: Parent-youth sessions were included Fidelity check: No formal check. Weekly telephone conferences were held to review cases Delivered by: Trained psychotherapists under the supervision of senior experts Medication (SSRI) **N = 14** Name (class and type): SSRI. Step 1: Monotherapy with an SSRI. Step 2: In the case of non-response changed to a different SSRI. Stage 3: Medication changed to an alternative class (venlafaxine, duloxetine, mirtazapine, or bupropion) with option of augmenting with lithium or another SSRI Dose (mg/day)/length: Not specified Delivered how: By psychopharmacologists Combination (SSRI + CBT-SP) **N = 93** Details as above (Y/N): Yes
Outcomes	Clinician reported Children's Depression Rating Scale-Revised (CDRS-R; Poznanski 1996) Children's Global Assessment Scale (C-GAS; Shaffer 1983) Self reported Beck Depression Inventory (BDI; Beck 1988) Beck Scale for Suicidal Ideation (SSI; Beck 1979a) Recurrence of a suicidal event Additional Measures The Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery 1979) The Multidimensional Anxiety Scale for Children (MASC; March 1997) The Clinical Global Impressions-Severity (CGI-S) and Improvement scales (CGI-I; Guy 1976)

Notes	Dropouts during treatment to any or at least 1 adverse reaction: Suicide-related outcome as an adverse event of treatment: 19.5% of participants experienced a suicide event and 12% made a suicide attempt. 1 participant died of suicide 20 days after completing the 24 week SSRI + CBT - SP treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"The study started as a randomized controlled trial; however; after approximately 9 months of low enrolment despite intensive recruitment efforts, the design was changed so that patients and their families could accept randomisation or choose which treatment to receive". pg. 998
Allocation concealment (selection bias)	High risk	As participants chose their treatment condition, allocation concealment is not applicable
Blinding (performance bias and detection bias) Assessors	Low risk	"Independent evaluators were trained to ensure interrater reliability and remained blind to patient treatment assignment". pg. 999
Blinding (performance bias and detection bias) Participants	High risk	"Most (n = 104) chose their treatment rather than being randomized". pg. 1000
Incomplete outcome data (attrition bias)	Unclear risk	"The data were analysed with an intent-to-treat approach". pg. 999 Imputation method: LOCF Number enrolled (included non-randomised participants): CBT-SI: 17 SSRI: 14 SSRI + CBT-SP: 93 Total: 124 Number of dropouts during intervention CBT-SI: 6 SSRI: 6 SSRI + CBT-SP: 26 Total: 36 Number analysed post-intervention: CBT-SI: 17 SSRI: 14 SSRI+ CBT-SP: 93 Total: 124 Reasons for dropout: 2 participants reported suicidal intent with inability to commit to safety plan, 5 showed lack of adherence to treatment, 9 had a need for different treatments and services and 23 with-

		drew consent or failed to return for visits for unspecified reasons
Selective reporting (reporting bias)	High risk	Only total and combination treatment outcomes reported. Do not have access to trial protocol
Other bias	High risk	The SSRI + CBT - SP group had higher levels of depression severity at baseline compared with the SSRI or CBT alone group. The SSRI + CBT - SP group also had a higher prevalence of comorbid anxiety and more functional impairment than the other 2 groups Only 20/124 participants were randomised, the remaining 104/124 chose their treatment option

ADHD: Attention Deficit Hyperactvity Disorder; b.i.d: twice daily; CDI: Children's Depression Inventory; CDRS-R; Childrens Depression Rating Scale-Revised; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HMO: Health Maintenance Organisation; ICD: Internation Classification of Diseases; ITT: Intention to Treat; NHS: National Health Service; NOS: Not Otherwise Specified; ODD; Oppositional Definant Disorder; q.i.d: four times daily; SD: Standard Deviation; SSRI: Selective Serotonin REuptake Inhibitor; TAU: Treatment As Usual; t.i.d: three times daily.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cheung 2008	Antidepressant versus placebo only, no psychological intervention
Dujovne 1994	Randomised cross-over trial, which is an exclusion criteria
Emslie 2002 (Eli 2002)	Trial did not include a suitable comparison condition
Emslie 2004	Medical algorithm
Findling 2008	Trial did not include a suitable comparison condition
Fristad 2009	Trial did not include a suitable comparison condition.
King 2009	Trial did not include a suitable comparison condition
Tang 2009	Trial did not include a suitable comparison condition

(*Continued*)

TORDIA 2008	Treatment of resistant depression
Wagner 2003	Antidepressant versus placebo only, no psychological intervention

DATA AND ANALYSES

Comparison 1. Psychological therapy versus antidepressant medication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission by clinical interview (post-intervention) ITT	2	268	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.28, 1.35]
2 Remission by clinical interview (post-intervention) OC	2	220	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.98]
3 Remission by clinical interview (six to nine months follow-up) ITT	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4 Remission by clinical interview (six to nine months follow-up) OC	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5 Dropouts (post-intervention)	2	271	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.11, 3.28]
6 Dropouts (six to nine months follow-up)	2	223	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.63, 2.19]
7 Suicidal ideation (post-intervention)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
8 Suicidal ideation (six to nine months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
9 Suicidal ideation (post-intervention)	2	268	Mean Difference (IV, Random, 95% CI)	-3.12 [-5.91, -0.33]
10 Suicidal ideation (six to nine months follow-up)	2	268	Mean Difference (IV, Random, 95% CI)	-2.89 [-5.49, -0.28]
11 Suicidal ideation (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Remission by cut-off (post-intervention)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
13 Remission by cut-off (six to nine months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
14 Remission by cut-off (12 months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
15 Depression symptoms clinician rated (CDRS-R) (post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
18 Depression symptoms self rated (post-intervention)	2	255	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.69, 1.01]
19 Depression symptoms self rated (six to nine months follow-up)	2	268	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.51, 0.42]

20 Depression symptoms self rated (12 months follow-up)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Functioning (post-intervention)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
22 Functioning (six to nine months follow-up)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 2. Combination therapy versus antidepressant medication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission by clinical interview (post-intervention) ITT	3	419	Odds Ratio (M-H, Random, 95% CI)	1.50 [0.99, 2.27]
2 Remission by clinical interview (post-intervention) OC	3	378	Odds Ratio (M-H, Random, 95% CI)	1.56 [0.98, 2.47]
3 Remission by clinical interview (six to nine months follow-up) ITT	2	203	Odds Ratio (M-H, Random, 95% CI)	1.93 [0.93, 4.00]
4 Remission by clinical interview (six to nine months follow-up) OC	2	193	Odds Ratio (M-H, Random, 95% CI)	1.94 [0.88, 4.27]
5 Remission by clinical interview (12 months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6 Dropouts (post-intervention)	4	627	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.49, 1.63]
7 Dropouts (six to nine months follow-up)	3	420	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.54, 1.64]
8 Dropouts (12 months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
9 Suicidal ideation (post-intervention)	2	388	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.26, 2.16]
10 Suicidal ideation (six to nine months follow-up)	2	344	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.06, 4.58]
11 Suicidal ideation (12 months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
12 Suicidal ideation (post-intervention)	2	267	Mean Difference (IV, Random, 95% CI)	-2.57 [-5.53, 0.40]
13 Suicidal ideation (six to nine months follow-up)	2	267	Mean Difference (IV, Random, 95% CI)	-1.89 [-4.50, 0.72]
14 Suicidal ideation (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Remission by cut-off (post-intervention)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
16 Remission by cut-off (six to nine months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
17 Remission by cut-off (12 months follow-up)	2	319	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.60, 3.52]
18 Depression symptoms clinician rated (CDRS-R) (post-intervention)	2	415	Mean Difference (IV, Random, 95% CI)	-0.27 [-4.95, 4.41]

19 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)	2	408	Mean Difference (IV, Random, 95% CI)	-0.27 [-2.26, 1.72]
20 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Depression symptoms self rated (post-intervention)	4	618	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.25, 0.12]
22 Depression symptoms self rated (six to nine months follow-up)	4	610	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.28, 0.17]
23 Depression symptoms self rated (12 months follow-up)	2	368	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.46, -0.05]
24 Functioning (post-intervention)	3	396	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.11, 0.28]
25 Functioning (six to nine months follow-up)	3	385	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]
26 Functioning (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 3. Combination therapy versus psychological therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission by clinical interview (post-intervention) ITT	2	265	Odds Ratio (M-H, Random, 95% CI)	1.61 [0.38, 6.90]
2 Remission by clinical interview (post-intervention) OC	2	222	Odds Ratio (M-H, Random, 95% CI)	1.82 [0.38, 8.68]
3 Remission by clinical interview (six to nine months follow-up) ITT	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4 Remission by clinical interview (six to nine months follow-up) OC	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5 Dropouts (post-intervention)	2	265	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.12, 12.71]
6 Dropouts (six to nine months follow-up)	2	231	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.40, 1.42]
7 Suicidal ideation (post-intervention)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
8 Suicidal ideation (six to nine months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
9 Suicidal ideation (post-intervention)	2	265	Mean Difference (IV, Random, 95% CI)	0.60 [-2.25, 3.45]
10 Suicidal ideation (six to nine months follow-up)	2	265	Mean Difference (IV, Random, 95% CI)	1.78 [-2.29, 5.85]
11 Suicidal ideation (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Remission by cut-off (post-intervention)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

13 Remission by cut-off (six to nine months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
14 Remission by cut-off (12 months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
15 Depression symptoms clinician rated (CDRS-R) (post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
18 Depression symptoms self rated (post-intervention)	2	265	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-1.41, 0.84]
19 Depression symptoms self rated (six to nine months follow-up)	2	265	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.63, 0.31]
20 Depression symptoms self rated (12 months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Functioning (post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
22 Functioning (six to nine months follow-up)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 4. Combination therapy versus psychological therapy plus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts (post-intervention)	4	249	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.42, 2.28]
2 Suicidal ideation (post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Remission by cut-off (post-intervention)	2	173	Odds Ratio (M-H, Random, 95% CI)	2.15 [1.15, 4.02]
4 Remission by cut-off (12 months follow-up)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5 Depression symptoms clinician rated (CDRS-R) (post-intervention)	3	239	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.78, -0.26]
6 Depression symptoms self rated (post-intervention)	3	123	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.70, 0.02]

Analysis 1.1. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 1 Remission by clinical interview (post-intervention) ITT.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 1 Remission by clinical interview (post-intervention) ITT

Study or subgroup	Psychological therapy n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Melvin 2006	5/22	5/26		25.0 %	1.24 [0.31, 4.98]
TADS 2004	53/111	71/109		75.0 %	0.49 [0.28, 0.84]
Total (95% CI)	**133**	**135**		**100.0 %**	**0.62 [0.28, 1.35]**

Total events: 58 (Psychological therapy), 76 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 1.47$, df = 1 (P = 0.22); $I^2 = 32\%$

Test for overall effect: Z = 1.21 (P = 0.23)

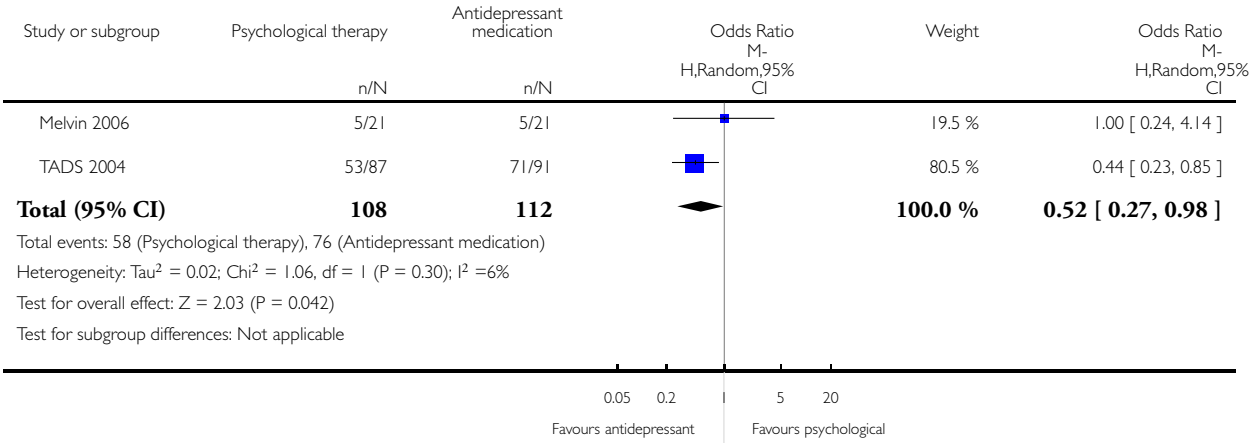
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 2 Remission by clinical interview (post-intervention) OC.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 2 Remission by clinical interview (post-intervention) OC

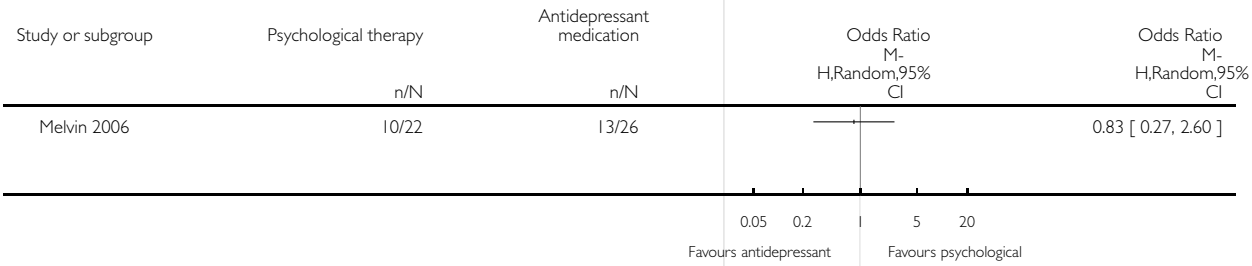


Analysis 1.3. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 3 Remission by clinical interview (six to nine months follow-up) ITT.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 3 Remission by clinical interview (six to nine months follow-up) ITT

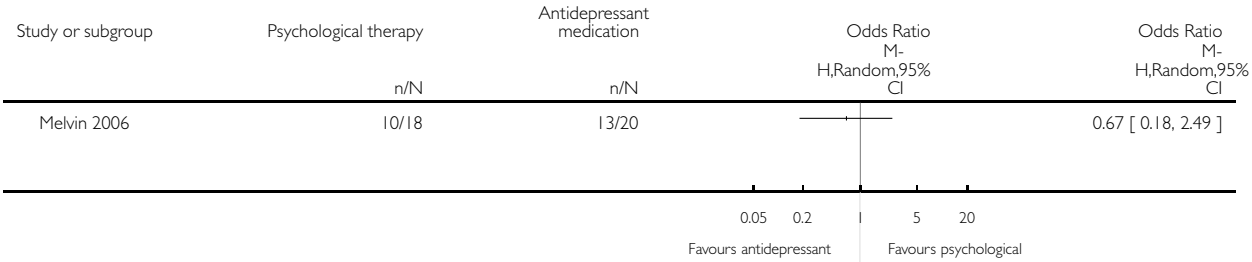


Analysis 1.4. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 4 Remission by clinical interview (six to nine months follow-up) OC.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 4 Remission by clinical interview (six to nine months follow-up) OC

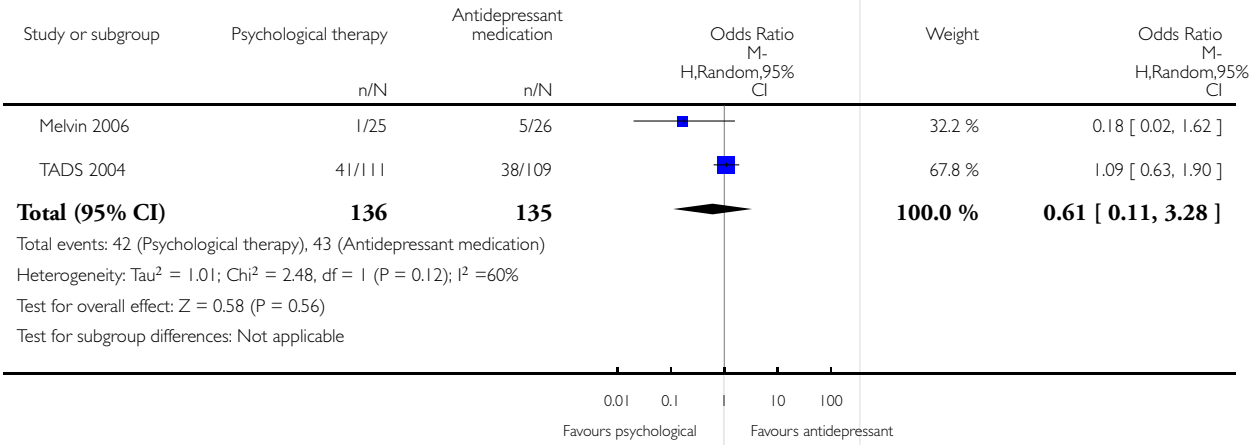


Analysis 1.5. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 5 Dropouts (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 5 Dropouts (post-intervention)



Analysis 1.6. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 6 Dropouts (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 6 Dropouts (six to nine months follow-up)

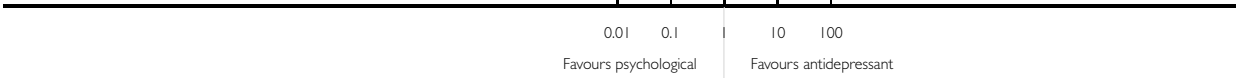
Study or subgroup	Psychological therapy n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Melvin 2006	3/24	3/21		13.3 %	0.86 [0.15, 4.79]
TADS 2004	25/90	21/88		86.7 %	1.23 [0.63, 2.41]
Total (95% CI)	**114**	**109**		**100.0 %**	**1.17 [0.63, 2.19]**

Total events: 28 (Psychological therapy), 24 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.49 (P = 0.62)

Test for subgroup differences: Not applicable



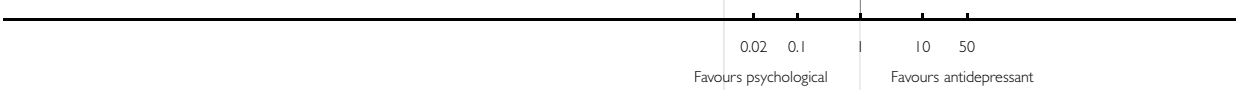
Analysis 1.7. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 7 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 7 Suicidal ideation (post-intervention)

Study or subgroup	Psychological therapy n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
TADS 2004	5/91	18/97		0.26 [0.09, 0.72]



Analysis 1.8. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 8 Suicidal ideation (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 8 Suicidal ideation (six to nine months follow-up)

Study or subgroup	Psychological therapy n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
TADS 2004	3/76	10/73		0.26 [0.07, 0.98]

Analysis 1.9. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 9 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

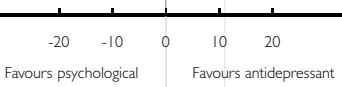
Outcome: 9 Suicidal ideation (post-intervention)

Study or subgroup	Psychological therapy N	Mean(SD)	Antidepressant medication N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Melvin 2006	22	19.41 (19.64)	26	24.23 (26.9)		4.5 %	-4.82 [-18.02, 8.38]
TADS 2004	111	11.4 (10.44)	109	14.44 (11.13)		95.5 %	-3.04 [-5.89, -0.19]
Total (95% CI)	**133**		**135**			**100.0 %**	**-3.12 [-5.91, -0.33]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 10 Suicidal ideation (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 10 Suicidal ideation (six to nine months follow-up)

Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Melvin 2006	22	13.5 (9.09)	26	20.96 (26.12)		5.9 %	-7.46 [-18.19, 3.27]
TADS 2004	111	9.5 (9.1)	109	12.1 (11.1)		94.1 %	-2.60 [-5.28, 0.08]
Total (95% CI)	**133**		**135**			**100.0 %**	**-2.89 [-5.49, -0.28]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.74$, df = 1 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 2.17 (P = 0.030)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 11 Suicidal ideation (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 11 Suicidal ideation (12 months follow-up)

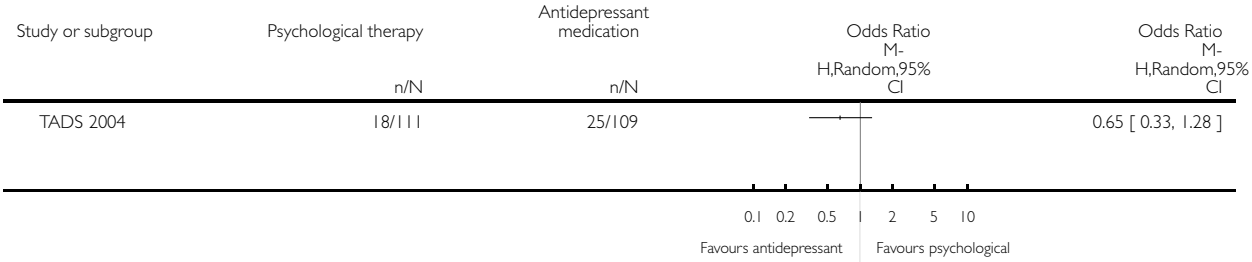
Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	111	9 (8.7)	109	11.5 (10.8)		-2.50 [-5.09, 0.09]

Analysis 1.12. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 12 Remission by cut-off (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 12 Remission by cut-off (post-intervention)

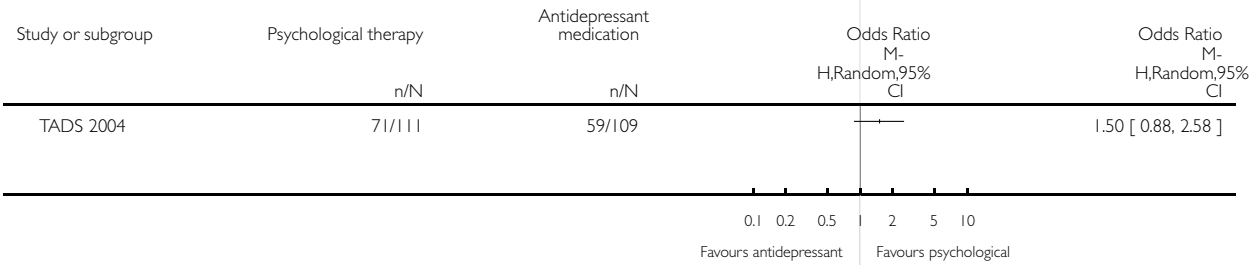


Analysis 1.13. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 13 Remission by cut-off (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 13 Remission by cut-off (six to nine months follow-up)

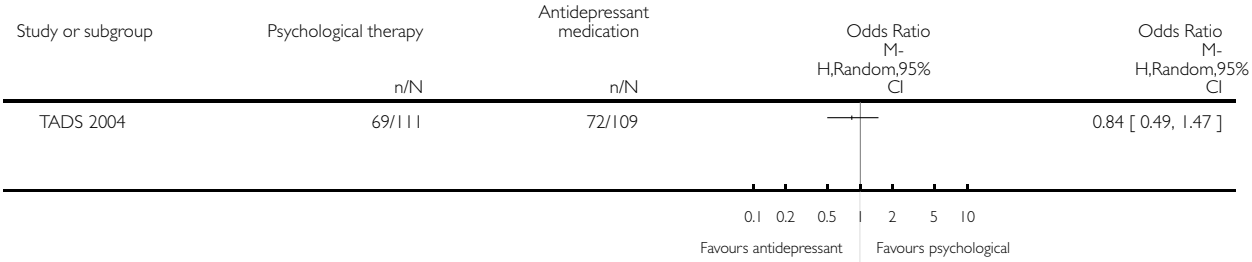


Analysis 1.14. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 14 Remission by cut-off (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 14 Remission by cut-off (12 months follow-up)

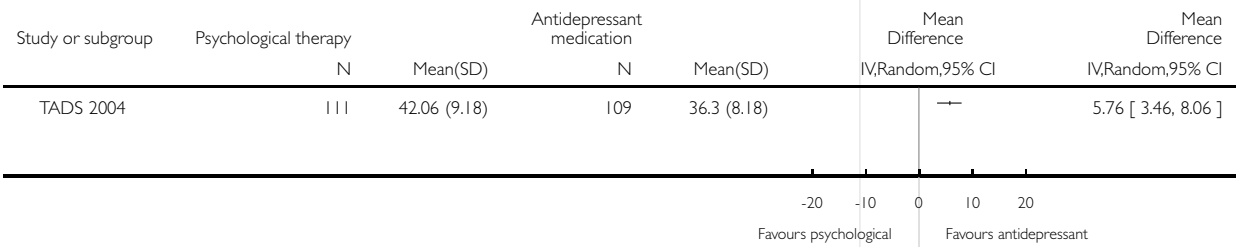


Analysis 1.15. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 15 Depression symptoms clinician rated (CDRS-R) (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 15 Depression symptoms clinician rated (CDRS-R) (post-intervention)



Analysis 1.16. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)

Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	111	28.49 (8.77)	109	28.44 (7.53)		0.05 [-2.11, 2.21]

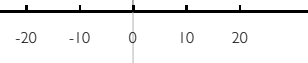
Analysis 1.17. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)

Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	111	29.9 (7.4)	109	29 (6.4)		0.90 [-0.93, 2.73]

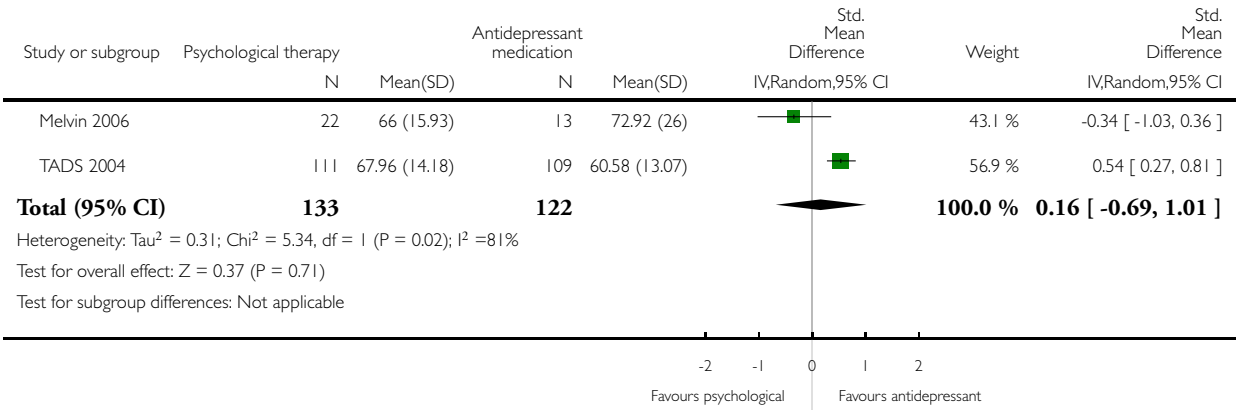


Analysis 1.18. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 18 Depression symptoms self rated (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 18 Depression symptoms self rated (post-intervention)

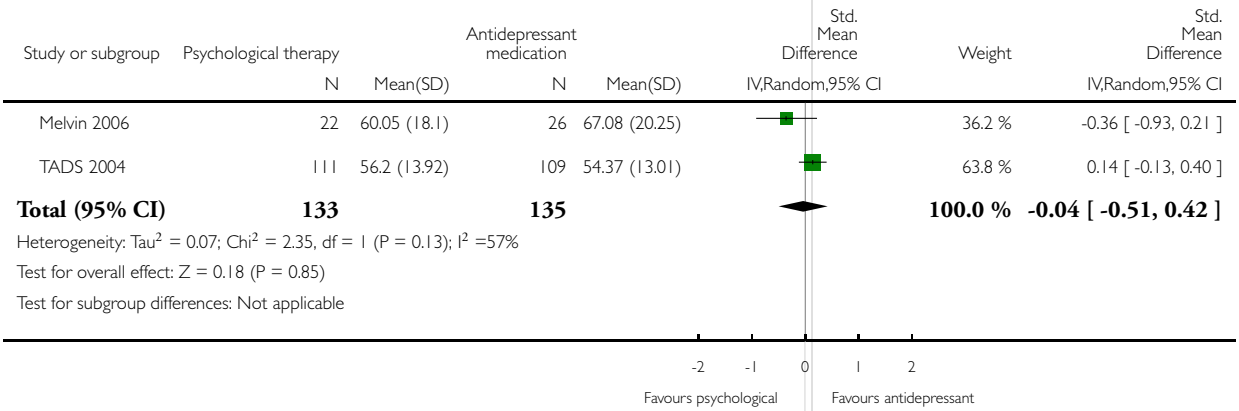


Analysis 1.19. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 19 Depression symptoms self rated (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 19 Depression symptoms self rated (six to nine months follow-up)



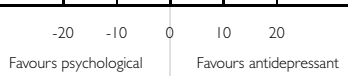
Analysis 1.20. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 20 Depression symptoms self rated (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 20 Depression symptoms self rated (12 months follow-up)

Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	111	56.2 (12.6)	109	55.7 (11.9)		0.50 [-2.74, 3.74]



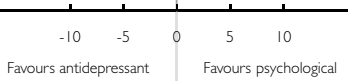
Analysis 1.21. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 21 Functioning (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 21 Functioning (post-intervention)

Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Melvin 2006	21	68.52 (8.13)	21	66.33 (10.11)		2.19 [-3.36, 7.74]



Analysis 1.22. Comparison 1 Psychological therapy versus antidepressant medication, Outcome 22 Functioning (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 1 Psychological therapy versus antidepressant medication

Outcome: 22 Functioning (six to nine months follow-up)

Study or subgroup	Psychological therapy		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Melvin 2006	17	67.76 (9.17)	20	68.15 (10.29)		-0.39 [-6.66, 5.88]

Analysis 2.1. Comparison 2 Combination therapy versus antidepressant medication, Outcome 1 Remission by clinical interview (post-intervention) ITT.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 1 Remission by clinical interview (post-intervention) ITT

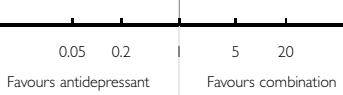
Study or subgroup	Combination	Antidepressant medication	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
	n/N	n/N			
Clarke 2005	44/77	32/75		41.3 %	1.79 [0.94, 3.41]
Melvin 2006	4/25	5/26		8.1 %	0.80 [0.19, 3.40]
TADS 2004	78/107	71/109		50.6 %	1.44 [0.81, 2.57]
Total (95% CI)	**209**	**210**		**100.0 %**	**1.50 [0.99, 2.27]**

Total events: 126 (Combination), 108 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.04$, df = 2 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 1.93 (P = 0.053)

Test for subgroup differences: Not applicable

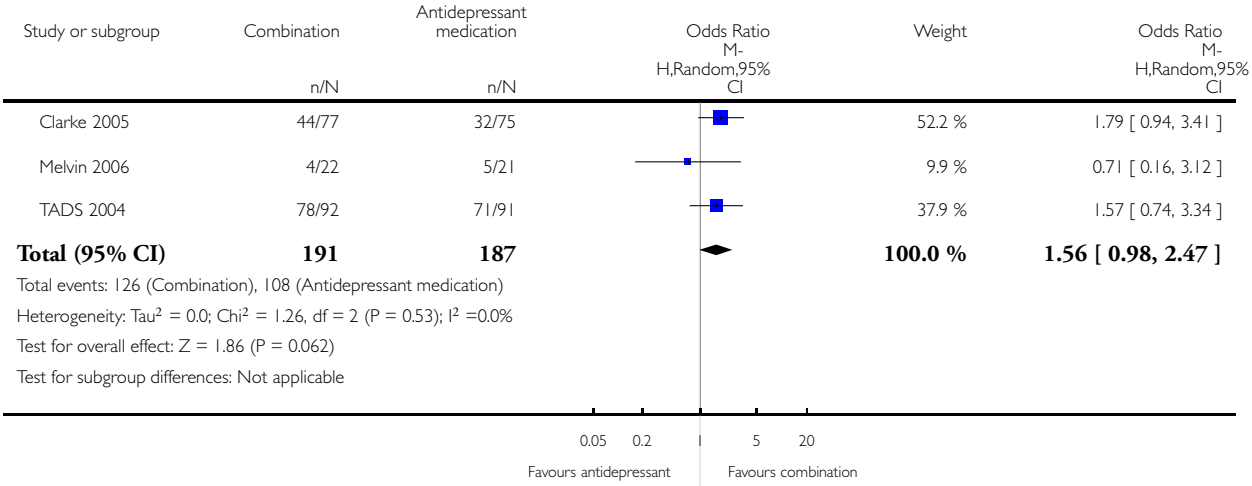


Analysis 2.2. Comparison 2 Combination therapy versus antidepressant medication, Outcome 2 Remission by clinical interview (post-intervention) OC.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 2 Remission by clinical interview (post-intervention) OC

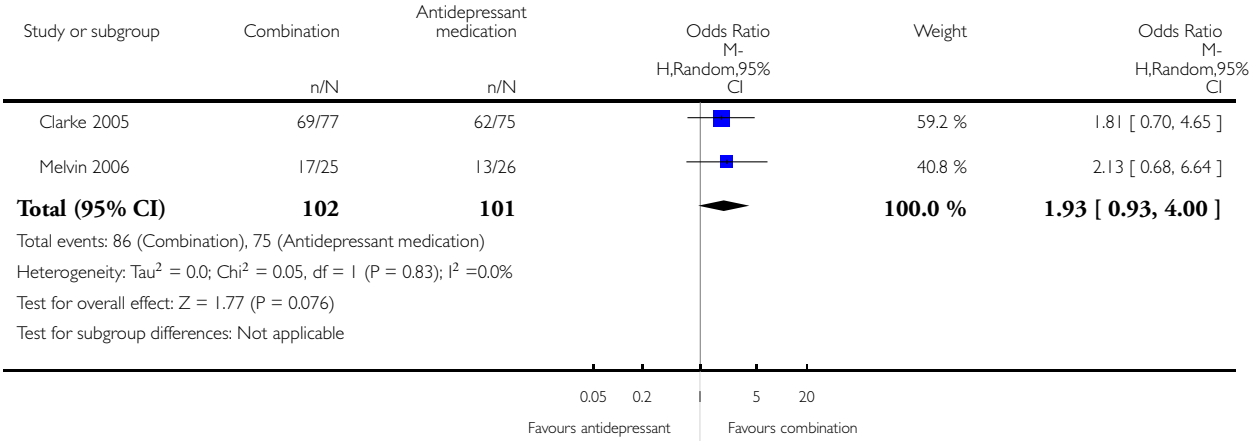


Analysis 2.3. Comparison 2 Combination therapy versus antidepressant medication, Outcome 3 Remission by clinical interview (six to nine months follow-up) ITT.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 3 Remission by clinical interview (six to nine months follow-up) ITT



Analysis 2.4. Comparison 2 Combination therapy versus antidepressant medication, Outcome 4 Remission by clinical interview (six to nine months follow-up) OC.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 4 Remission by clinical interview (six to nine months follow-up) OC

Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Clarke 2005	69/77	62/75		69.4 %	1.81 [0.70, 4.65]
Melvin 2006	17/21	13/20		30.6 %	2.29 [0.55, 9.52]
Total (95% CI)	**98**	**95**		**100.0 %**	**1.94 [0.88, 4.27]**

Total events: 86 (Combination), 75 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 1.65 (P = 0.098)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Combination therapy versus antidepressant medication, Outcome 5 Remission by clinical interview (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 5 Remission by clinical interview (12 months follow-up)

Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Clarke 2005	69/77	71/75		0.49 [0.14, 1.69]

Analysis 2.6. Comparison 2 Combination therapy versus antidepressant medication, Outcome 6 Dropouts (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 6 Dropouts (post-intervention)

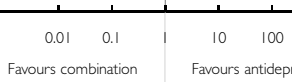
Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
ADAPT 2007	11/105	6/103		22.1 %	1.89 [0.67, 5.32]
Clarke 2005	10/77	10/75		24.9 %	0.97 [0.38, 2.49]
Melvin 2006	5/25	5/26		14.7 %	1.05 [0.26, 4.18]
TADS 2004	23/107	38/109		38.3 %	0.51 [0.28, 0.94]
Total (95% CI)	**314**	**313**		**100.0 %**	**0.89 [0.49, 1.63]**

Total events: 49 (Combination), 59 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 5.06$, df = 3 (P = 0.17); $I^2 = 41\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Combination therapy versus antidepressant medication, Outcome 7 Dropouts (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 7 Dropouts (six to nine months follow-up)

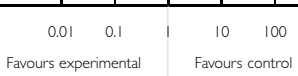
Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
ADAPT 2007	7/94	7/97		26.4 %	1.03 [0.35, 3.07]
Melvin 2006	1/24	3/21		5.7 %	0.26 [0.02, 2.72]
TADS 2004	23/96	21/88		67.9 %	1.01 [0.51, 1.98]
Total (95% CI)	**214**	**206**		**100.0 %**	**0.94 [0.54, 1.64]**

Total events: 31 (Combination), 31 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.22$, df = 2 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 0.22 (P = 0.82)

Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2 Combination therapy versus antidepressant medication, Outcome 8 Dropouts (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 8 Dropouts (12 months follow-up)

Study or subgroup	Combination n/N	Antidepressant medicaiton n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Clarke 2005	40/53	28/50		2.42 [1.05, 5.59]

Analysis 2.9. Comparison 2 Combination therapy versus antidepressant medication, Outcome 9 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 9 Suicidal ideation (post-intervention)

Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
ADAPT 2007	16/101	13/100		51.8 %	1.26 [0.57, 2.78]
TADS 2004	8/90	18/97		48.2 %	0.43 [0.18, 1.04]
Total (95% CI)	**191**	**197**		**100.0 %**	**0.75 [0.26, 2.16]**

Total events: 24 (Combination), 31 (Antidepressant medication)

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 3.17$, df = 1 (P = 0.08); $I^2 = 68\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 2.10. Comparison 2 Combination therapy versus antidepressant medication, Outcome 10 Suicidal ideation (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 10 Suicidal ideation (six to nine months follow-up)

Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
ADAPT 2007	13/98	9/94		54.3 %	1.44 [0.59, 3.56]
TADS 2004	2/79	10/73		45.7 %	0.16 [0.03, 0.77]
Total (95% CI)	**177**	**167**		**100.0 %**	**0.53 [0.06, 4.58]**

Total events: 15 (Combination), 19 (Antidepressant medication)

Heterogeneity: $Tau^2 = 2.00$; $Chi^2 = 5.76$, df = 1 (P = 0.02); $I^2 = 83\%$

Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable

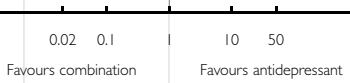
Analysis 2.11. Comparison 2 Combination therapy versus antidepressant medication, Outcome 11 Suicidal ideation (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 11 Suicidal ideation (12 months follow-up)

Study or subgroup	Combination n/N	Antidepressant medication n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
TADS 2004	2/79	10/73		0.16 [0.03, 0.77]



Analysis 2.12. Comparison 2 Combination therapy versus antidepressant medication, Outcome 12 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

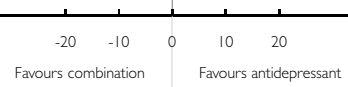
Outcome: 12 Suicidal ideation (post-intervention)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Melvin 2006	25	23.2 (20.24)	26	24.23 (26.9)		5.2 %	-1.03 [-14.06, 12.00]
TADS 2004	107	11.79 (11.69)	109	14.44 (11.13)		94.8 %	-2.65 [-5.69, 0.39]
Total (95% CI)	**132**		**135**			**100.0 %**	**-2.57 [-5.53, 0.40]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 1.70 (P = 0.090)

Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2 Combination therapy versus antidepressant medication, Outcome 13 Suicidal ideation (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

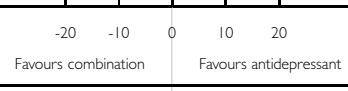
Outcome: 13 Suicidal ideation (six to nine months follow-up)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Melvin 2006	25	19.28 (17.72)	26	20.96 (26.12)		4.6 %	-1.68 [-13.89, 10.53]
TADS 2004	107	10.2 (8.8)	109	12.1 (11.1)		95.4 %	-1.90 [-4.57, 0.77]
Total (95% CI)	**132**		**135**			**100.0 %**	**-1.89 [-4.50, 0.72]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 2.14. Comparison 2 Combination therapy versus antidepressant medication, Outcome 14 Suicidal ideation (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 14 Suicidal ideation (12 months follow-up)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	107	9.9 (8.4)	109	11.5 (10.8)		-1.60 [-4.18, 0.98]

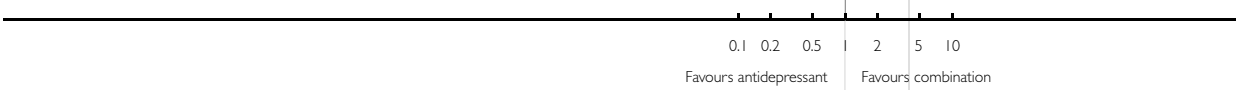
Analysis 2.15. Comparison 2 Combination therapy versus antidepressant medication, Outcome 15 Remission by cut-off (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 15 Remission by cut-off (post-intervention)

Study or subgroup	Combination	Antidepressant medication	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
	n/N	n/N		
TADS 2004	40/107	25/109		2.01 [1.11, 3.63]

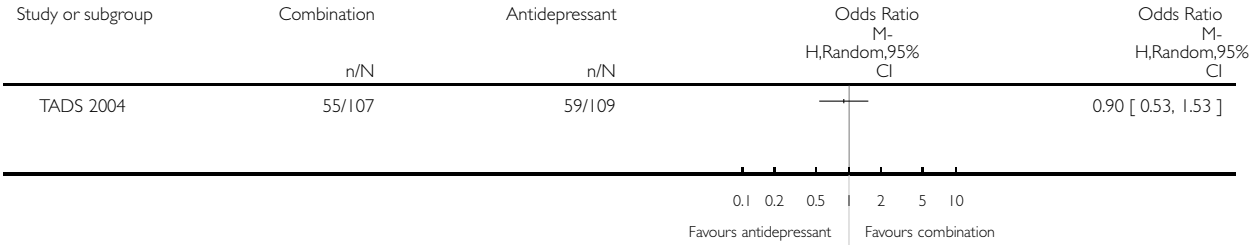


Analysis 2.16. Comparison 2 Combination therapy versus antidepressant medication, Outcome 16 Remission by cut-off (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 16 Remission by cut-off (six to nine months follow-up)

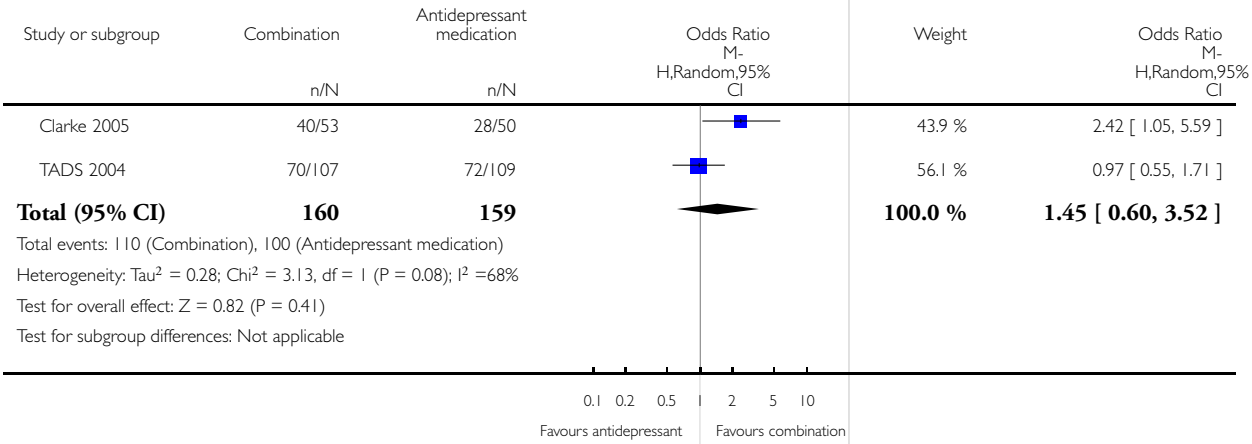


Analysis 2.17. Comparison 2 Combination therapy versus antidepressant medication, Outcome 17 Remission by cut-off (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 17 Remission by cut-off (12 months follow-up)



Analysis 2.18. Comparison 2 Combination therapy versus antidepressant medication, Outcome 18 Depression symptoms clinician rated (CDRS-R) (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 18 Depression symptoms clinician rated (CDRS-R) (post-intervention)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
ADAPT 2007	100	42.5 (16.8)	99	40 (13.9)		42.6 %	2.50 [-1.78, 6.78]
TADS 2004	107	33.65 (8.62)	109	35.98 (8.15)		57.4 %	-2.33 [-4.57, -0.09]
Total (95% CI)	**207**		**208**			**100.0 %**	**-0.27 [-4.95, 4.41]**

Heterogeneity: Tau² = 8.63; Chi² = 3.84, df = 1 (P = 0.05); I² =74%

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable

Analysis 2.19. Comparison 2 Combination therapy versus antidepressant medication, Outcome 19 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

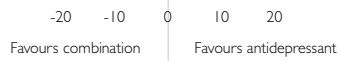
Outcome: 19 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
ADAPT 2007	98	36.4 (15.3)	94	34.8 (13.4)		22.8 %	1.60 [-2.46, 5.66]
TADS 2004	107	27.62 (8)	109	28.44 (7.53)		77.2 %	-0.82 [-2.89, 1.25]
Total (95% CI)	**205**		**203**			**100.0 %**	**-0.27 [-2.26, 1.72]**

Heterogeneity: Tau² = 0.22; Chi² = 1.08, df = 1 (P = 0.30); I² =7%

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: Not applicable



Analysis 2.20. Comparison 2 Combination therapy versus antidepressant medication, Outcome 20 Depression symptoms clinician rated (CDRS-R) (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 20 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	107	28.3 (6.8)	109	29 (6.4)		-0.70 [-2.46, 1.06]

Analysis 2.21. Comparison 2 Combination therapy versus antidepressant medication, Outcome 21 Depression symptoms self rated (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 21 Depression symptoms self rated (post-intervention)

Study or subgroup	Combination		Antidepressant medication		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
ADAPT 2007	100	22.7 (15.4)	99	21.6 (14.8)		31.2 %	0.07 [-0.21, 0.35]
Clarke 2005	77	20.1 (11.6)	75	19.6 (10.2)		25.7 %	0.05 [-0.27, 0.36]
Melvin 2006	25	71.64 (18.28)	26	72.92 (16.84)		10.4 %	-0.07 [-0.62, 0.48]
TADS 2004	107	56.95 (12.24)	109	60.58 (13.07)		32.7 %	-0.29 [-0.55, -0.02]
Total (95% CI)	**309**		**309**			**100.0 %**	**-0.07 [-0.25, 0.12]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.00$, df = 3 (P = 0.26); $I^2 = 25\%$

Test for overall effect: Z = 0.70 (P = 0.49)

Test for subgroup differences: Not applicable

Analysis 2.22. Comparison 2 Combination therapy versus antidepressant medication, Outcome 22 Depression symptoms self rated (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 22 Depression symptoms self rated (six to nine months follow-up)

Study or subgroup	Combination		Antidepressant medication		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
ADAPT 2007	98	18.9 (15.5)	93	15.5 (15)		29.6 %	0.22 [-0.06, 0.51]
Clarke 2005	77	13.7 (11.5)	75	15 (11.4)		26.4 %	-0.11 [-0.43, 0.21]
Melvin 2006	25	63.32 (17.88)	26	67.08 (20.25)		12.7 %	-0.19 [-0.74, 0.36]
TADS 2004	107	51.51 (13.38)	109	54.37 (13.01)		31.4 %	-0.22 [-0.48, 0.05]
Total (95% CI)	**307**		**303**			**100.0 %**	**-0.06 [-0.28, 0.17]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.40$, df = 3 (P = 0.14); $I^2 = 44\%$

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

Analysis 2.23. Comparison 2 Combination therapy versus antidepressant medication, Outcome 23 Depression symptoms self rated (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

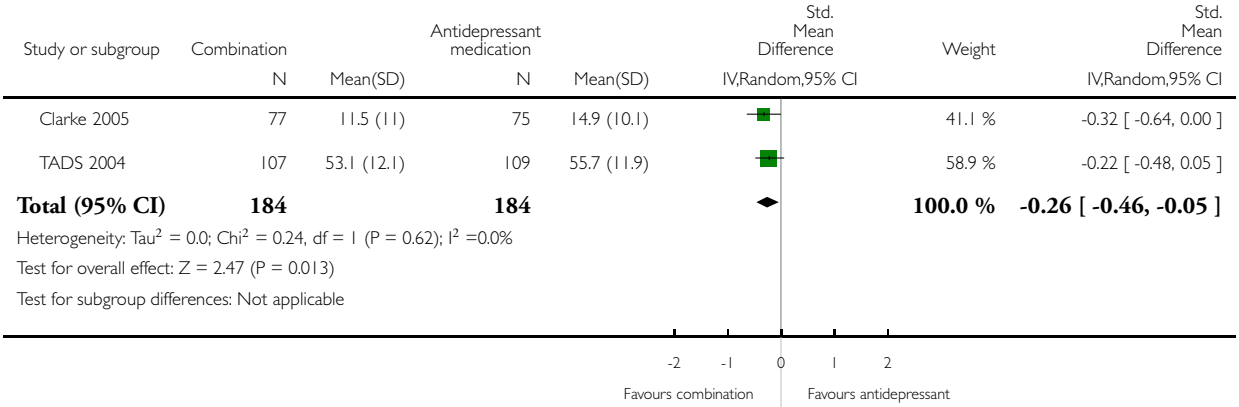
Outcome: 23 Depression symptoms self rated (12 months follow-up)

Study or subgroup	Combination		Antidepressant medication		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Clarke 2005	77	11.5 (11)	75	14.9 (10.1)		41.1 %	-0.32 [-0.64, 0.00]
TADS 2004	107	53.1 (12.1)	109	55.7 (11.9)		58.9 %	-0.22 [-0.48, 0.05]
Total (95% CI)	**184**		**184**			**100.0 %**	**-0.26 [-0.46, -0.05]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.24$, df = 1 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 2.47 (P = 0.013)

Test for subgroup differences: Not applicable



Analysis 2.24. Comparison 2 Combination therapy versus antidepressant medication, Outcome 24 Functioning (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 24 Functioning (post-intervention)

Study or subgroup	Combination		Antidepressant medication		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
ADAPT 2007	101	52.1 (14.3)	100	50.7 (12.1)		50.7 %	0.11 [-0.17, 0.38]
Clarke 2005	77	60.4 (10.1)	75	59.5 (9.5)		38.4 %	0.09 [-0.23, 0.41]
Melvin 2006	22	66.14 (12.5)	21	66.33 (10.11)		10.9 %	-0.02 [-0.61, 0.58]
Total (95% CI)	**200**		**196**			**100.0 %**	**0.09 [-0.11, 0.28]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 2 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable

Analysis 2.25. Comparison 2 Combination therapy versus antidepressant medication, Outcome 25 Functioning (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 25 Functioning (six to nine months follow-up)

Study or subgroup	Combination		Antidepressant medication		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
ADAPT 2007	98	57.2 (16.4)	94	57.8 (14.5)		50.0 %	-0.04 [-0.32, 0.24]
Clarke 2005	77	68.8 (8.4)	75	66.6 (8.7)		39.3 %	0.26 [-0.06, 0.58]
Melvin 2006	21	68.19 (14.19)	20	68.15 (10.29)		10.7 %	0.00 [-0.61, 0.62]
Total (95% CI)	**196**		**189**			**100.0 %**	**0.08 [-0.12, 0.28]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 2 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Not applicable

Analysis 2.26. Comparison 2 Combination therapy versus antidepressant medication, Outcome 26 Functioning (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 2 Combination therapy versus antidepressant medication

Outcome: 26 Functioning (12 months follow-up)

Study or subgroup	Combination		Antidepressant medication		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Clarke 2005	77	71.4 (8.7)	75	68.4 (7.6)		3.00 [0.40, 5.60]

Analysis 3.1. Comparison 3 Combination therapy versus psychological therapy, Outcome 1 Remission by clinical interview (post-intervention) ITT.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 1 Remission by clinical interview (post-intervention) ITT

Study or subgroup	Combination n/N	Psychological n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Melvin 2006	4/25	5/22		39.7 %	0.65 [0.15, 2.79]
TADS 2004	78/107	53/111		60.3 %	2.94 [1.67, 5.18]
Total (95% CI)	**132**	**133**		**100.0 %**	**1.61 [0.38, 6.90]**
Total events: 82 (Combination), 58 (Psychological)					
Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 3.58$, df = 1 (P = 0.06); $I^2 = 72\%$					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: Not applicable					

Analysis 3.2. Comparison 3 Combination therapy versus psychological therapy, Outcome 2 Remission by clinical interview (post-intervention) OC.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 2 Remission by clinical interview (post-intervention) OC

Study or subgroup	Combination n/N	Psychological n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Melvin 2006	4/22	5/21		41.6 %	0.71 [0.16, 3.12]
TADS 2004	78/92	53/87		58.4 %	3.57 [1.75, 7.30]
Total (95% CI)	**114**	**108**		**100.0 %**	**1.82 [0.38, 8.68]**

Total events: 82 (Combination), 58 (Psychological)

Heterogeneity: $Tau^2 = 0.95$; $Chi^2 = 3.72$, df = 1 (P = 0.05); $I^2 = 73\%$

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Combination therapy versus psychological therapy, Outcome 3 Remission by clinical interview (six to nine months follow-up) ITT.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 3 Remission by clinical interview (six to nine months follow-up) ITT

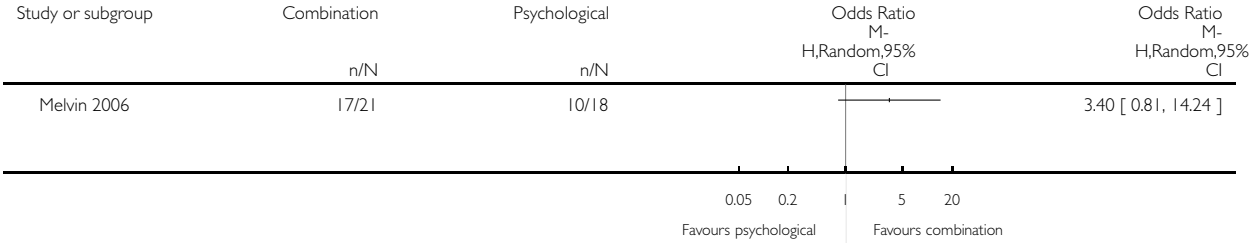
Study or subgroup	Combination n/N	Psychological n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Melvin 2006	17/25	10/22		2.55 [0.78, 8.36]

Analysis 3.4. Comparison 3 Combination therapy versus psychological therapy, Outcome 4 Remission by clinical interview (six to nine months follow-up) OC.

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 4 Remission by clinical interview (six to nine months follow-up) OC

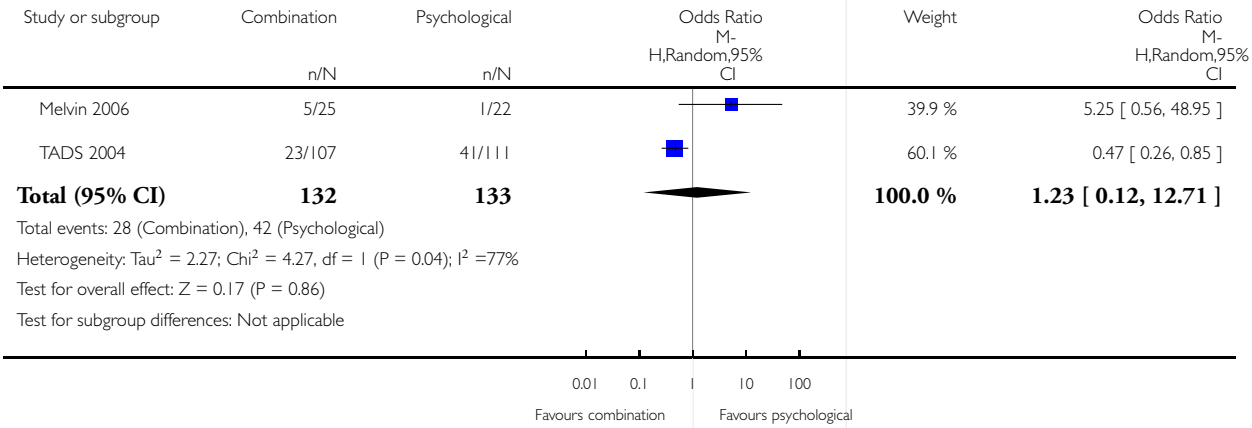


Analysis 3.5. Comparison 3 Combination therapy versus psychological therapy, Outcome 5 Dropouts (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 5 Dropouts (post-intervention)

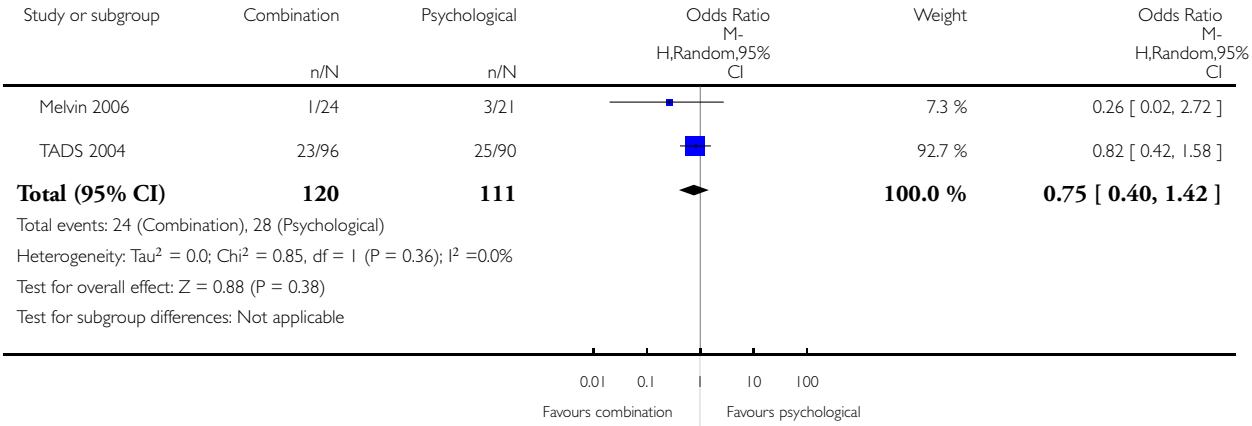


Analysis 3.6. Comparison 3 Combination therapy versus psychological therapy, Outcome 6 Dropouts (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 6 Dropouts (six to nine months follow-up)

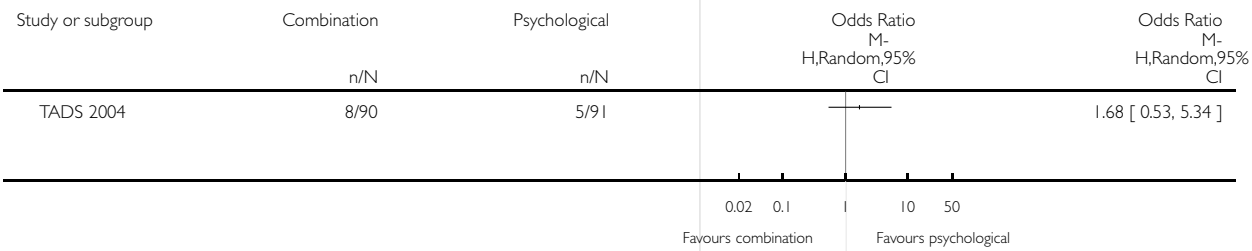


Analysis 3.7. Comparison 3 Combination therapy versus psychological therapy, Outcome 7 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 7 Suicidal ideation (post-intervention)



Analysis 3.8. Comparison 3 Combination therapy versus psychological therapy, Outcome 8 Suicidal ideation (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 8 Suicidal ideation (six to nine months follow-up)

Study or subgroup	Combination n/N	Psychological n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
TADS 2004	2/79	3/76		0.63 [0.10, 3.89]

Analysis 3.9. Comparison 3 Combination therapy versus psychological therapy, Outcome 9 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 9 Suicidal ideation (post-intervention)

Study or subgroup	Combination N	Mean(SD)	Psychological N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Melvin 2006	25	23.2 (20.24)	22	19.41 (19.64)		6.2 %	3.79 [-7.62, 15.20]
TADS 2004	107	11.79 (11.69)	111	11.4 (10.44)		93.8 %	0.39 [-2.56, 3.34]
Total (95% CI)	**132**		**133**			**100.0 %**	**0.60 [-2.25, 3.45]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 3.10. Comparison 3 Combination therapy versus psychological therapy, Outcome 10 Suicidal ideation (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

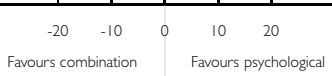
Outcome: 10 Suicidal ideation (six to nine months follow-up)

Study or subgroup	Combination		Psychological		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Melvin 2006	25	19.28 (17.72)	22	13.5 (9.09)		21.2 %	5.78 [-2.14, 13.70]
TADS 2004	107	10.2 (8.8)	111	9.5 (9.1)		78.8 %	0.70 [-1.68, 3.08]
Total (95% CI)	**132**		**133**			**100.0 %**	**1.78 [-2.29, 5.85]**

Heterogeneity: Tau² = 4.01; Chi² = 1.45, df = 1 (P = 0.23); I² =31%

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable



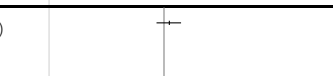
Analysis 3.11. Comparison 3 Combination therapy versus psychological therapy, Outcome 11 Suicidal ideation (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 11 Suicidal ideation (12 months follow-up)

Study or subgroup	Combination		Psychological		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	107	9.9 (8.4)	111	9 (8.7)		0.90 [-1.37, 3.17]

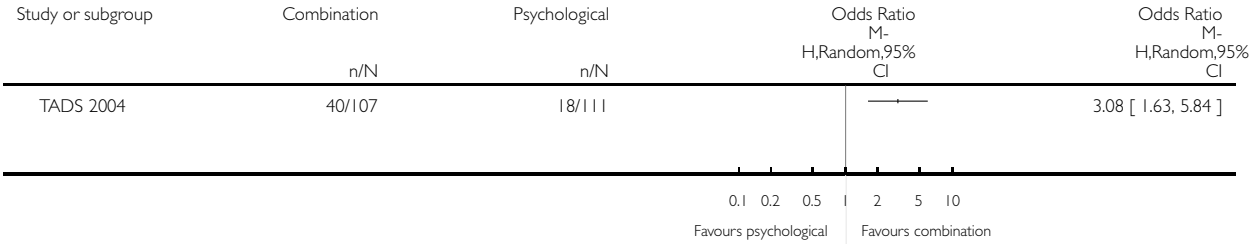


Analysis 3.12. Comparison 3 Combination therapy versus psychological therapy, Outcome 12 Remission by cut-off (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 12 Remission by cut-off (post-intervention)

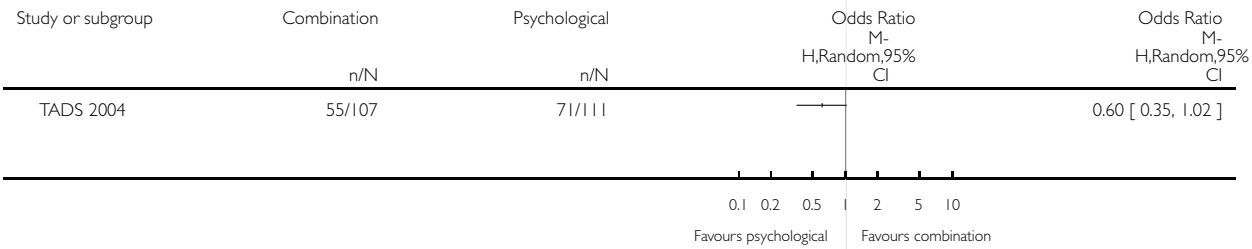


Analysis 3.13. Comparison 3 Combination therapy versus psychological therapy, Outcome 13 Remission by cut-off (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 13 Remission by cut-off (six to nine months follow-up)



Analysis 3.14. Comparison 3 Combination therapy versus psychological therapy, Outcome 14 Remission by cut-off (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 14 Remission by cut-off (12 months follow-up)

Study or subgroup	Combination n/N	Psychological n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
TADS 2004	70/107	69/111		1.15 [0.66, 2.00]

Analysis 3.15. Comparison 3 Combination therapy versus psychological therapy, Outcome 15 Depression symptoms clinician rated (CDRS-R) (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 15 Depression symptoms clinician rated (CDRS-R) (post-intervention)

Study or subgroup	Combination N	Mean(SD)	Psychological N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
TADS 2004	107	33.79 (8.24)	111	42.06 (9.18)		-8.27 [-10.58, -5.96]

Analysis 3.16. Comparison 3 Combination therapy versus psychological therapy, Outcome 16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)

Study or subgroup	Combination		Psychological		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	107	27.62 (8)	111	28.49 (8.77)		-0.87 [-3.10, 1.36]

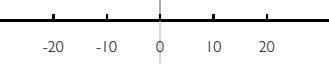
Analysis 3.17. Comparison 3 Combination therapy versus psychological therapy, Outcome 17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)

Study or subgroup	Combination		Psychological		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
TADS 2004	107	28.3 (6.8)	111	29.9 (7.4)		-1.60 [-3.49, 0.29]



Analysis 3.18. Comparison 3 Combination therapy versus psychological therapy, Outcome 18 Depression symptoms self rated (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 18 Depression symptoms self rated (post-intervention)

Study or subgroup	Combination		Psychological		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Melvin 2006	25	71.64 (18.28)	22	66 (15.93)		47.5 %	0.32 [-0.25, 0.90]
TADS 2004	107	56.95 (12.24)	111	67.96 (14.18)		52.5 %	-0.83 [-1.10, -0.55]
Total (95% CI)	**132**		**133**			**100.0 %**	**-0.28 [-1.41, 0.84]**

Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 12.39$, df = 1 (P = 0.00043); $I^2 = 92\%$

Test for overall effect: Z = 0.49 (P = 0.62)

Test for subgroup differences: Not applicable

Analysis 3.19. Comparison 3 Combination therapy versus psychological therapy, Outcome 19 Depression symptoms self rated (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

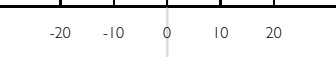
Outcome: 19 Depression symptoms self rated (six to nine months follow-up)

Study or subgroup	Combination		Psychological		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Melvin 2006	25	63.32 (17.88)	22	60.5 (18.1)		36.4 %	0.15 [-0.42, 0.73]
TADS 2004	107	51.51 (13.38)	111	56.2 (13.92)		63.6 %	-0.34 [-0.61, -0.07]
Total (95% CI)	**132**		**133**			**100.0 %**	**-0.16 [-0.63, 0.31]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 2.36$, df = 1 (P = 0.12); $I^2 = 58\%$

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable



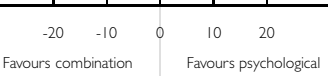
Analysis 3.20. Comparison 3 Combination therapy versus psychological therapy, Outcome 20 Depression symptoms self rated (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 20 Depression symptoms self rated (12 months follow-up)

Study or subgroup	Combination N	Mean(SD)	Psychological N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
TADS 2004	107	53.1 (12.1)	111	56.2 (12.6)		-3.10 [-6.38, 0.18]



Analysis 3.21. Comparison 3 Combination therapy versus psychological therapy, Outcome 21 Functioning (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 21 Functioning (post-intervention)

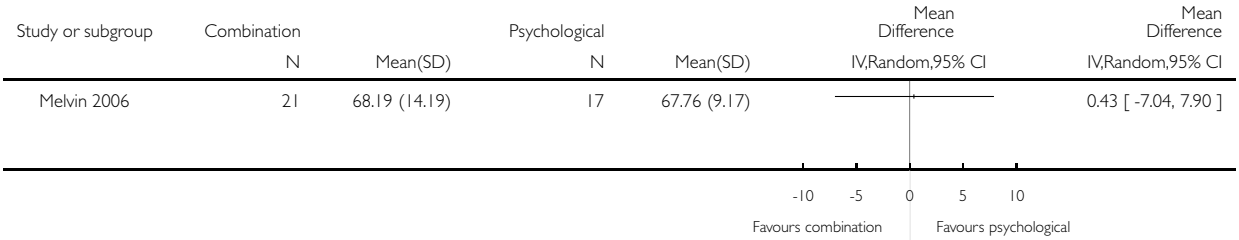
Study or subgroup	Combination N	Mean(SD)	Psychological N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Melvin 2006	22	66.14 (12.5)	21	68.52 (8.13)		-2.38 [-8.65, 3.89]

Analysis 3.22. Comparison 3 Combination therapy versus psychological therapy, Outcome 22 Functioning (six to nine months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 3 Combination therapy versus psychological therapy

Outcome: 22 Functioning (six to nine months follow-up)

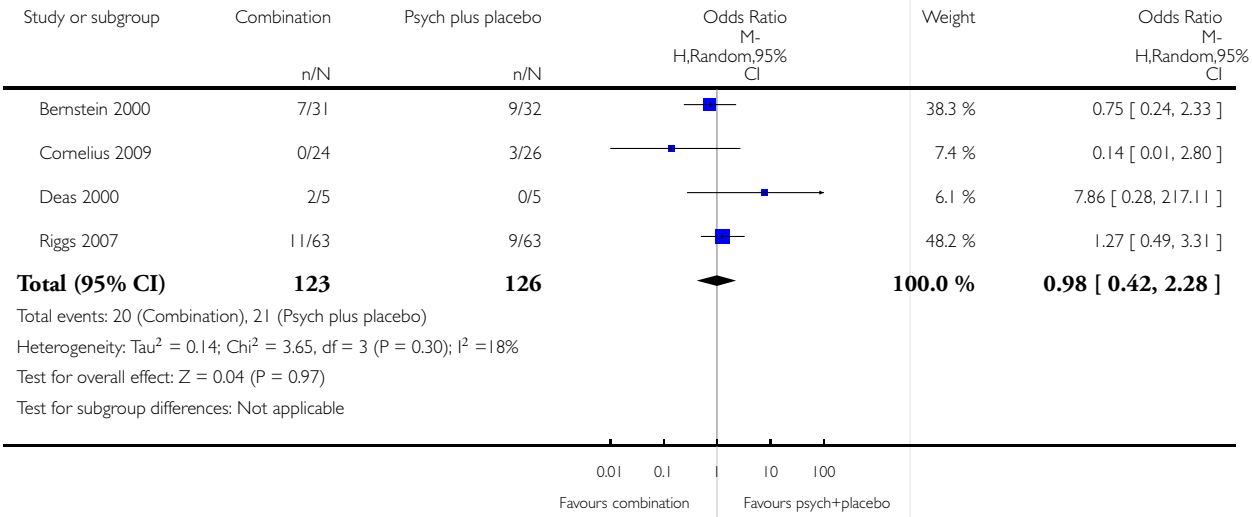


Analysis 4.1. Comparison 4 Combination therapy versus psychological therapy plus placebo, Outcome 1 Dropouts (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 4 Combination therapy versus psychological therapy plus placebo

Outcome: 1 Dropouts (post-intervention)



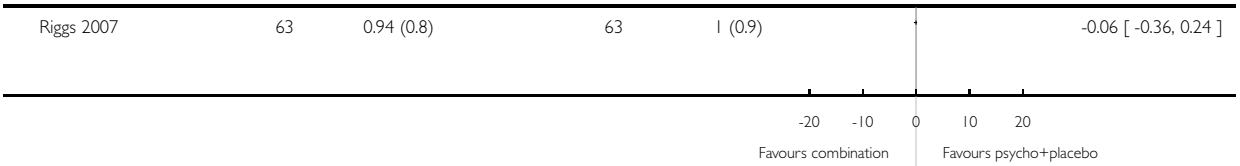
Analysis 4.2. Comparison 4 Combination therapy versus psychological therapy plus placebo, Outcome 2 Suicidal ideation (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 4 Combination therapy versus psychological therapy plus placebo

Outcome: 2 Suicidal ideation (post-intervention)

Study or subgroup	Combination		Psych plus placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Riggs 2007	63	0.94 (0.8)	63	1 (0.9)		-0.06 [-0.36, 0.24]

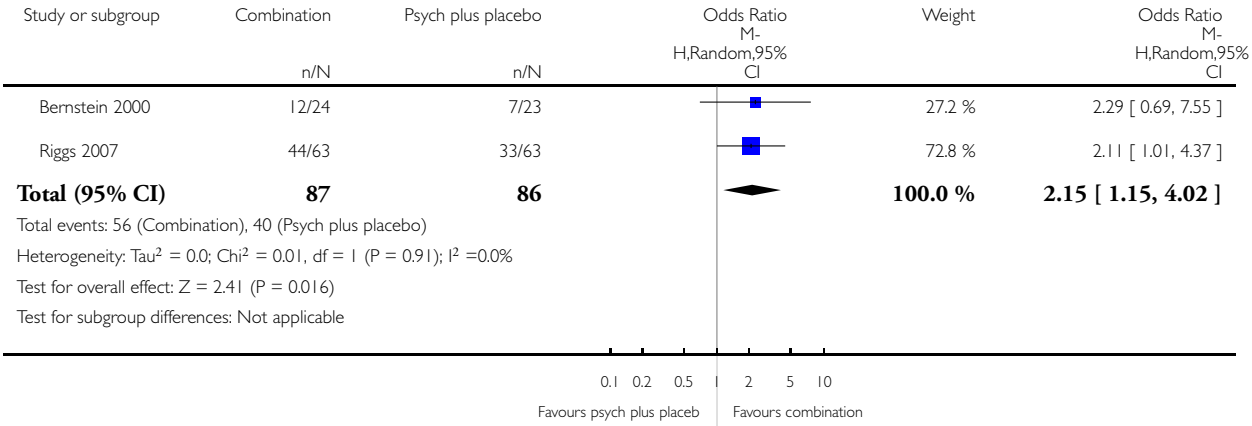


Analysis 4.3. Comparison 4 Combination therapy versus psychological therapy plus placebo, Outcome 3 Remission by cut-off (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 4 Combination therapy versus psychological therapy plus placebo

Outcome: 3 Remission by cut-off (post-intervention)

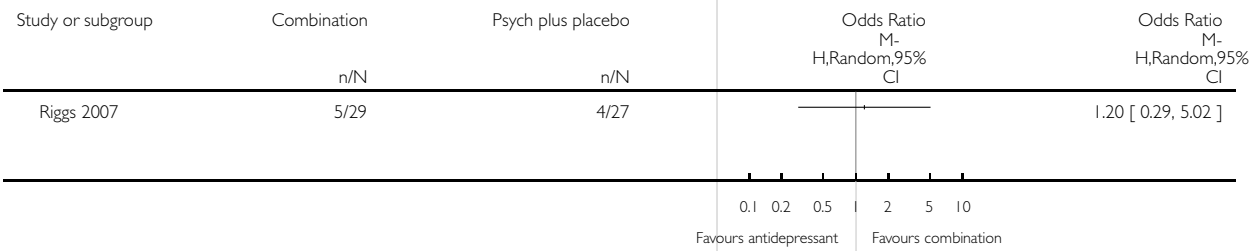


Analysis 4.4. Comparison 4 Combination therapy versus psychological therapy plus placebo, Outcome 4 Remission by cut-off (12 months follow-up).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 4 Combination therapy versus psychological therapy plus placebo

Outcome: 4 Remission by cut-off (12 months follow-up)



Analysis 4.5. Comparison 4 Combination therapy versus psychological therapy plus placebo, Outcome 5 Depression symptoms clinician rated (CDRS-R) (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 4 Combination therapy versus psychological therapy plus placebo

Outcome: 5 Depression symptoms clinician rated (CDRS-R) (post-intervention)

Study or subgroup	Combination		Psych plus placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Bernstein 2000	31	34.6 (8.9)	32	45.7 (16.5)		25.1 %	-0.82 [-1.34, -0.31]
Cornelius 2009	24	4.45 (7.06)	26	8.31 (8.97)		21.1 %	-0.47 [-1.03, 0.09]
Riggs 2007	63	25.99 (11.6)	63	30.55 (11.5)		53.8 %	-0.39 [-0.75, -0.04]
Total (95% CI)	**118**		**121**			**100.0 %**	**-0.52 [-0.78, -0.26]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.86$, df = 2 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 3.92 (P = 0.000090)

Test for subgroup differences: Not applicable

Analysis 4.6. Comparison 4 Combination therapy versus psychological therapy plus placebo, Outcome 6 Depression symptoms self rated (post-intervention).

Review: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents

Comparison: 4 Combination therapy versus psychological therapy plus placebo

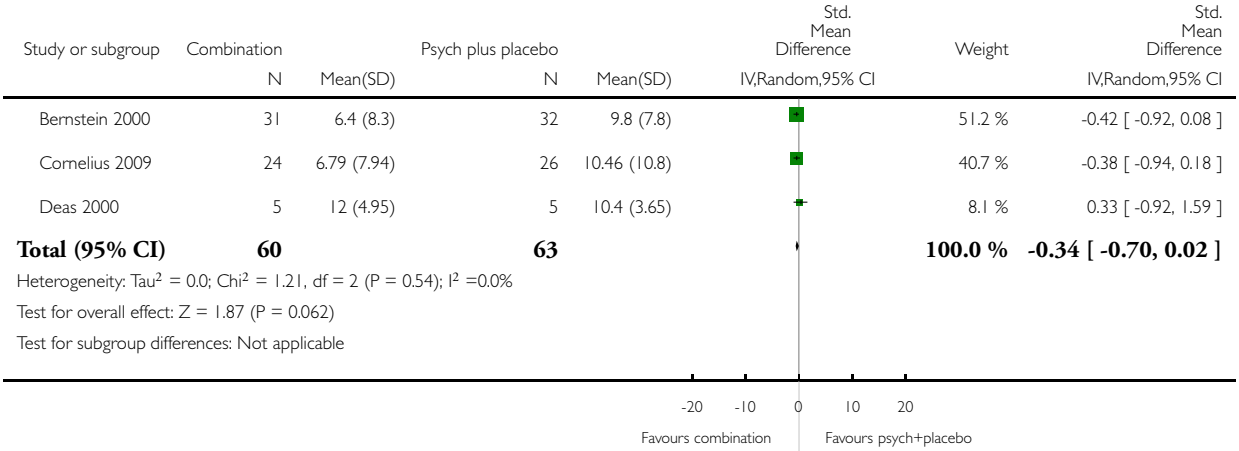
Outcome: 6 Depression symptoms self rated (post-intervention)

Study or subgroup	Combination N	Mean(SD)	Psych plus placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bernstein 2000	31	6.4 (8.3)	32	9.8 (7.8)		51.2 %	-0.42 [-0.92, 0.08]
Cornelius 2009	24	6.79 (7.94)	26	10.46 (10.8)		40.7 %	-0.38 [-0.94, 0.18]
Deas 2000	5	12 (4.95)	5	10.4 (3.65)		8.1 %	0.33 [-0.92, 1.59]
Total (95% CI)	**60**		**63**			**100.0 %**	**-0.34 [-0.70, 0.02]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.21$, df = 2 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 1.87 (P = 0.062)

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Additional search strategies

PsycINFO	MEDLINE	EMBASE
1. exp Major Depression/	1. exp Depressive Disorder/	1. exp Depression/
2. "Depression (Emotion)"/	2. Depression/	2. (depress$ or dysthymi$).tw.
3. (depress$ or dysthymi$).tw.	3. (depress$ or dysthymi$).tw.	3. 1 or 2
4. or/1-3	4. or/1-3	4. exp Psychotherapy/
5. exp Psychotherapy/	5. exp Psychotherapy/	5. behavio?r therap$.tw.
6. behavio?r therap$.tw.	6. exp Antidepressive Agents/	6. family therap$.tw.
7. family therap$.tw.	7. exp Serotonin Uptake Inhibitors/	7. cognitive therap$.tw.
8. cognitive therap$.tw.	8. 6 or 7	8. interpersonal.tw.
9. interpersonal.tw.	9. 4 and 5 and 8	9. psychotherap$.tw.
10. psychotherap$.tw.	10. Adult Children/	10. relaxation$.tw.
11. relaxation$.tw.	11. Minors/	11. problem solving.tw.
12. problem solving.tw.	12. Homeless Youth/	

(*Continued*)

13. bibliotherap$.tw.
14. play therap$.tw.
15. plaything$.tw.
16. physical reinforcement$.tw.
17. operant$.tw.
18. consultation$.tw.
19. reinforcement$.tw.
20. biofeedback$.tw.
21. social skill$.tw.
22. cognitive?behavio?ral.tw.
23. parent training$.tw.
24. behavio$.tw.
25. discussion group$.tw.
26. insight oriented.tw.
27. (client centered or client centred).tw.
28. counsel$.tw.
29. exercise.tw.
30. supportive.tw.
31. massag$.tw.
32. contract$.tw.
33. insight$.tw.
34. paradox$.tw.
35. psychoanalys$.tw.
36. psychodrama.tw.
37. roleplay$.tw.
38. transactional.tw.
39. primary control.tw.
40. secondary control.tw.
41. non-pharmacological.tw.
42. or/5-41
43. exp Antidepressant Drugs/
44. (benactyzine$ or clorgyline$ or deanol$ or iproniazid$ or isocarboxazid$ or lithium carbonate$ or moclobemide$ or nialamide$ or phenelzine$ or pizotyline$ or rolipram$ or sertraline$ or tranylcypromine$).tw
45. (5-hydroxytryptophan$ or amoxapine$ or bupropion$ or citalopram$ or fluoxetine$ or fluvoxamine$ or maprotiline$ or mianserin$ or paroxetine$ or quipazine$ or ritanserin$ or sulpiride$ or trazodone$ or tryptophan$ or viloxazine$).tw
46. (amitriptyline$ or clomipramine$ or desipramine$ or dothiepin$ or doxepin$ or imipramine$ or iprindole$ or lofepramine$ or nortriptyline$ or opipramol$ or protriptyline$ or trimipramine$).tw

13. (juvenile$ or underage$ or teen$ or youth$ or pubescen$ or adolescen$).tw
14. (young adult$ or young men or young women or young people or young person$).tw
15. (undergraduate$ or college student$ or high-school student$).tw
16. Adolescent/
17. exp Child/
18. child$.tw.
19. or/10-18
20. 9 and 19
21. clinical trial.pt.
22. clinical trial$.mp.
23. random$.mp.
24. placebo.ti,ab.
25. groups.ti,ab.
26. or/21-25
27. meta-analysis.pt.
28. meta-analysis/
29. (meta-anal$ or metaanal$ or meta analy$).tw.
30. review.pt.
31. systematic review$.tw.
32. or/27-31
33. 20 and 26
34. 20 and 32
35. 33 or 34

12. bibliotherap$.tw.
13. play therap$.tw.
14. plaything$.tw.
15. physical reinforcement$.tw.
16. operant$.tw.
17. consultation$.tw.
18. reinforcement$.tw.
19. biofeedback$.tw.
20. social skill$.tw.
21. cognitive?behavio?ral.tw.
22. parent training$.tw.
23. behavio$.tw.
24. discussion group$.tw.
25. insight oriented.tw.
26. (client centered or client centred).tw.
27. counsel$.tw.
28. exercise.tw.
29. supportive.tw.
30. massag$.tw.
31. contract$.tw.
32. insight$.tw.
33. paradox$.tw.
34. psychoanalys$.tw.
35. psychodrama.tw.
36. roleplay$.tw.
37. transactional.tw.
38. primary control.tw.
39. secondary control.tw.
40. non-pharmacological.tw.
41. or/4-40
42. exp Antidepressant Agent/
43. exp Monoamine Oxidase Inhibitor/
44. exp Noradrenalin Uptake Inhibitor/
45. exp Serotonin Uptake Inhibitor/
46. exp Tetracyclic Antidepressant Agent/
47. exp Tricyclic Antidepressant Agent/
48. or/42-47
49. 3 and 41 and 48
50. Adult Children/
51. Minors/
52. Homeless Youth/
53. (juvenile$ or underage$ or teen$ or youth$ or pubescen$ or adolescen$).tw
54. (young adult$ or young men or young women or young people or young person$).tw
55. (undergraduate$ or college student$ or high-school student$).tw

(*Continued*)

47. exp Tricyclic Antidepressant Drugs/ 48. exp Monoamine Oxidase Inhibitors/ 49. exp Adrenergic Blocking Drugs/ 50. exp Serotonin Reuptake Inhibitors/ or exp Serotonin Antagonists/ 51. (serotonin adj (uptake or reuptake or re-uptake)).tw. 52. ssri$.tw. 53. (amoxapine$ or citalopram$ or clomipramine$ or fenfluramine$ or fluoxetine$ or fluvoxamine$ or norfenfluramine$ or paroxetine$ or sertraline$ or trazodone$ or zimeldine$).tw 54. or/43-53 55. 4 and 42 and 54 56. (juvenile$ or underage$ or teen$ or youth$ or pubescen$ or adolescen$).tw 57. (young adult$ or young men or young women or young people or young person$).tw 58. (undergraduate$ or college student$ or high-school student$).tw 59. child$.tw. 60. or/56-59 61. 55 and 60 62. limit 55 to (180 school age or 200 adolescence) 63. limit 55 to 320 young adulthood 64. or/61-63 65. Clinical Trials/ 66. controlled trial$.tw. 67. (controlled studies or controlled study).tw. 68. random$.tw. 69. Random Sampling/ 70. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or dummy or mask$)).tw 71. placebo$.mp. 72. MetaAnalysis/ 73. (meta-analy$ or metaanaly$ or meta analy$).tw. 74. systematic review$.tw. 75. exp Treatment Effectiveness Evaluation/ 76. exp Mental Health Program Evaluation/ 77. or/65-76 78. 64 and 77		56. Adolescent/ 57. exp Child/ 58. child$.tw. 59. or/50-58 60. 49 and 59 61. exp Controlled Study/ 62. (controlled trial$ or controlled study or controlled studies).tw 63. exp Clinical Trial/ 64. (clinical trial$ or clinical study or clinical studies).tw 65. random$.tw. 66. Single Blind Procedure/ 67. Double Blind Procedure/ 68. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$ or dummy)).tw 69. placebo$.mp. 70. or/61-69 71. 60 and 70

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS

Sarah Hetrick (SH) conceived the review and co-ordinated the development of the original protocol. She assisted with selection of articles for inclusion, data extraction and guided the data analysis. She had oversight of the write-up of the review.

Georgina Cox (GC) assisted in selecting articles from the updated search, extracted descriptive and numerical data for all included studies, inputted data into meta-analyses and was heavily involved in writing the Methods, Description of studies, Results and Discussion sections of the review.

Patrick Callahan (PC) assisted in the development of the original protocol for this review, executed the search of electronic databases, screened and selected articles for inclusion, extracted descriptive and numerical data for all included studies, and was involved in inputting data into meta-analyses.

Rachel Churchill (RC) assisted in the development of the original protocol and provided input to the data analysis and write-up of the review.

Vivien Hunot (VH) assisted in the development of the original protocol and provided input to the data analysis and write-up of the review.

Alex Parker (AP) assisted in the development of the original protocol and had input into the write-up of the review.

Sally Merry (SM) assisted in the development of the original protocol and had input, particularly from a clinical point of view, into the write-up of the review.

DECLARATIONS OF INTEREST

There are no known conflicts of interest in this working group.

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

One additional objective was added to the review following the publication of the protocol. Given the concern that antidepressant medication may increase suicide related behaviours in children and adolescents, we felt it was important to assess the degree of suicide related behaviours related to antidepressant medication. Therefore a final objective was:

6. To determine whether there is an increased risk of suicide related outcomes in children and adolescents treated with antidepressant medication alone, compared with psychological therapy alone, or a combination of treatments.