ClinicalEvidence

Depression in children and adolescents

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ABSTRACT

INTRODUCTION: Depression may affect 2–8% of children and adolescents, with a peak incidence around puberty. It may be self-limiting, but about 40% of affected children experience a recurrent attack, a third of affected children will make a suicide attempt, and 3–4% will die from suicide. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of pharmacological, psychological, combination, and complementary treatments for depression in children and adolescents? What are the effects of treatments for refractory depression in children and adolescents? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2008 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 18 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: citalopram, cognitive behavioural therapy (CBT) (individual or group, to prevent relapse), escitalopram, electroconvulsive therapy, family therapy, fluoxetine (alone or with cognitive therapy or CBT), fluvoxamine, group therapeutic support (other than CBT), guided self-help, individual psychodynamic psychotherapy, interpersonal therapy, lithium, mirtazapine, monoamine oxidase inhibitors (MAOIs), omega-3 polyunsaturated fatty acids, paroxetine, sertraline (alone or with CBT), St John's Wort (Hypericum perforatum), tricyclic antidepressants, and venlafaxine.

QUESTIONS

What are the effects of pharmacological treatments for depression in children and adolescents? . . . 3

What are the effects of psychological treatments for depression in children and adolescents? . . . 11

What are the effects of combination treatments for depression in children and adolescents? . . . 19

What are the effects of complementary treatments for depression in children and adolescents? . . . 22

What are the effects of treatments for refractory depression in children and adolescents? . . . 22

INTERVENTIONS

PHARMACOLOGICAL TREATMENTS FOR DEPRESSION

Beneficial

Fluoxetine (improves remission rates and prevents relapse) in children and adolescents . . . 3

Unknown effectiveness

Citalopram/escitalopram in children and adolescents . . . 6

Fluvoxamine in children and adolescents . . . 6

MAOIs in children and adolescents . . . 7

Mirtazapine in children and adolescents . . . 7

Unlikely to be beneficial

Paroxetine in children and adolescents . . . 8

Sertraline in children and adolescents . . . 9

Likely to be ineffective or harmful

Tricyclic antidepressants (oral) in children and adolescents . . . 10

Venlafaxine in children and adolescents . . . 11

PSYCHOLOGICAL TREATMENTS FOR DEPRESSION

Likely to be beneficial

CBT (group) in children and adolescents with mild to moderate depression . . . 12

Interpersonal therapy in adolescents with mild to moderate depression . . . 11

Unknown effectiveness

CBT (individual) in children and adolescents with mild to moderate depression . . . 13

Family therapy in children and adolescents . . . 17

Group therapeutic support (other than CBT) in children and adolescents . . . 15

Guided self-help in children and adolescents . . . 16

Individual psychodynamic psychotherapy in children and adolescents . . . 16

Interpersonal therapy in children . . . 15

Unlikely to be beneficial

CBT (for relapse prevention) in children and adolescents . . . 16

COMBINATION TREATMENTS FOR DEPRESSION

Beneficial

Fluoxetine plus CBT in adolescents . . . 19

Unknown effectiveness

Fluoxetine plus CBT in children . . . 21

Sertraline plus CBT in adolescents New . . . 21

COMPLEMENTARY TREATMENTS FOR DEPRESSION

Unknown effectiveness

Omega 3 polyunsaturated fatty acids New . . . 22

St John's Wort (*Hypericum perforatum*) in children and adolescents . . . 22

REFRACTORY DEPRESSION 22

Unknown effectiveness

Electroconvulsive therapy in children and adolescents

Lithium in children and adolescents 22

Key points

- Depression in children and adolescents may have a more insidious onset than in adults, with irritability a more prominent feature than sadness.

  Depression may affect 2% of children and 4–8% of adolescents, with a peak incidence around puberty.

  It may be self-limiting, but about 40% of affected children experience a recurrent attack, a third of affected children will make a suicide attempt, and 3–4% will die from suicide.

- Fluoxetine improves symptoms and may delay relapse over 7–12 weeks compared with placebo in children and adolescents.

  Fluoxetine may be more effective at improving symptoms compared with CBT. Combined fluoxetine plus CBT treatment may be more effective than CBT alone in adolescents.

  Fluvoxamine, citalopram, and escitalopram, have not been shown to be beneficial in adolescents and children with depression. Paroxetine and sertraline may be unlikely to be beneficial.

  We don't know whether sertraline is as effective as CBT in the treatment of adolescents. We don't know whether sertraline and CBT as monotherapies are as effective as the combination of sertraline plus CBT.

  Tricyclic antidepressants have not been shown to reduce symptoms of depression and can be toxic in overdose, so their use is not recommended.

  We do not know whether moclobemide, omega-3 polyunsaturated fatty acids, or St John's Wort are beneficial.

- CAUTION: SSRIs (other than fluoxetine) and venlafaxine have been associated with serious suicide-related events in people under 18 years of age.

- Group CBT in children and adolescents and interpersonal therapy in adolescents may improve symptoms in those with mild to moderate depression, but may not prevent relapse.

  We do not know whether other psychological treatments,individual CBT, group therapeutic support, interpersonal therapy in children, guided self-help, or individual psychodynamic psychotherapy improve symptoms.

- We do not know whether electroconvulsive therapy or lithium are beneficial in children or adolescents with refractory depression.

DEFINITION

Compared with adult depression (see reviews on depression in adults: drug and other physical treatments and depression in adults: psychological treatments and care pathways), depression in children (6–12 years) and adolescents (13–18 years) may have a more insidious onset, may be characterised more by irritability than sadness, and occurs more often in association with other conditions such as anxiety, conduct disorder, hyperkinesis, and learning problems. [1] [2] The term "major depression" is used to distinguish discrete episodes of depression from mild, chronic (1 year or longer) low mood, or irritability, which is known as "dysthymia". [1] [2] The severity of depression may be defined by the level of impairment and the presence or absence of psychomotor changes and somatic symptoms (see review on depression in adults). In some studies, severity of depression is defined according to cut-off scores on depression rating scales. Definitions of refractory depression (also known as treatment-resistant depression) vary, but in this review it refers to depression that has failed to respond, or has only partially responded, to an adequate trial of at least two recognised treatments. [3]

INCIDENCE/ PREVALENCE

The prevalence of major depression is estimated to be approximately 2% in children and 4–8% in adolescents. [2] Pre-adolescent boys and girls are affected equally by the condition, but in adolescents, depression is more common among girls than boys. [2]

AETIOLOGY/ RISK FACTORS

Depression in children usually arises from a combination of genetic vulnerability, suboptimal early developmental experiences, and exposure to stresses. However, depressive syndromes sometimes occur as sequelae to physical illness, such as viral infection, and may overlap with fatigue syndromes. [4] The heritability of depression may increase with age, [5] but the findings from genetics studies are inconsistent. Recurrent depression seems to have a stronger familial association compared with single-episode depression. [6] Depression-prone individuals have a cognitive style characterised by an overly pessimistic outlook on events. [7] This cognitive style precedes the onset of depression and seems independent of recent life events and ongoing stresses. [8] Stressful life events may trigger the first occurrence of depression, but are rarely sufficient on their own to cause depression. After a first incidence of depression, lower levels of stress are needed to provoke

subsequent episodes of illness. [1] Enduring problems in the relationship with the primary caregivers is an important risk factor for depression, but such difficulties also predispose to other psychiatric disorders. [1]

PROGNOSIS

In children and adolescents, the recurrence rate after a first depressive episode is 40%. [9] Young people experiencing a moderate to severe depressive episode may be more likely than adults to have a manic episode within the following few years. [2] [1] [10] Trials of treatments for child and adolescent depression have found high rates of response to placebo (as much as two thirds of people in some inpatient studies) suggesting that episodes of depression may be self-limiting in many cases. [11] A third of young people who experience a depressive episode will make a suicide attempt at some stage, and 3–4% of those who experience depression will die from suicide. [12]

AIMS OF INTERVENTION

To improve mood, social and occupational functioning, and quality of life; to reduce morbidity and mortality; to prevent recurrence of depressive disorder, with minimal adverse effects.

OUTCOMES

In children and adolescents, developmentally specific pseudo-continuous outcome measures such as the Children's Depression Rating Scale and the Children's Depression Inventory are available, although some studies of adolescents use scales developed for use in adults, such as the Hamilton Rating Scale for Depression. Pseudo-continuous outcome measures reported by parents, such as the Children's Depression Inventory for Parents, are also used. Categorical outcomes are sometimes expressed as people no longer meeting specified criteria for depression on a structured psychiatric interview, such as the Kiddie-Schedule for Affective Disorders and Schizophrenia (Kiddie-SADS), which combines data from children and their parents. Global improvement in symptoms, as judged by an investigator, is sometimes reported using the Clinical Global Impressions Scale or the Children's Global Assessment Scale (see table 1, p 26).

METHODS

Clinical Evidence search and appraisal April 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2008, Embase 1980 to April 2008, PsycInfo 1996 to April 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 1. Additional searches were carried out using the NHS Centre for Reviews and Dissemination (CRD) website — for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language. RCTs could be blinded or open, and had to contain 20 or more individuals of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. We also did a search for cohort studies, case-control studies, case-series and case-studies on the following specific adverse effects for antidepressants: activation syndrome or switching to mania, akathisia, increase in suicide-related behaviours. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review, see table, p 28 .

QUESTION

What are the effects of pharmacological treatments for depression in children and adolescents?

OPTION

FLUOXETINE IN CHILDREN AND ADOLESCENTS

Symptom improvement

Compared with placebo Fluoxetine may be more effective at improving remission/response, reducing depressive symptoms, and increasing the mean time to relapse in people aged 7–18 years (low-quality evidence).

Compared with other antidepressants Fluoxetine may be more effective than nortriptyline (a tricyclic antidepressant) at improving depression scores at 8 weeks in people aged 7–16 years, but we don't know whether it is more effective at increasing remission (very low-quality evidence).

Compared with CBT Fluoxetine seems more effective at improving depressive symptoms at 12 and 18 weeks in people aged 12–17 years with major depression, but not at 24, 30, or 36 weeks (moderate-quality evidence).

Compared with fluoxetine plus CBT (in adolescents) We don't know whether fluoxetine alone is more effective at improving depressive symptoms at 12 weeks in people aged 11–17 years with major depression (very low-quality evidence).

Functional status
Compared with placebo Fluoxetine seems no more effective at improving functional status at 7–8 weeks in people aged 7–18 years (moderate-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Fluoxetine versus placebo:
We found three systematic reviews (search date 2004; [13] search date 2005; [14] search date 2007 [15]) which all identified the same 4 RCTs and reported slightly different analysis of the included RCTs, and we found one additional RCT. [16] The first review found that fluoxetine significantly increased remission (defined as a score of less than 29 on the Children's Depression Rating Scale [CDRS]) compared with placebo after 7–8 weeks (2 RCTs, 315 people aged 7–18 years; RR of non-remission for fluoxetine *v* placebo: 0.78, 95% CI 0.67 to 0.90). [13] The first review also found that fluoxetine significantly improved depressive symptoms compared with placebo after 7–12 weeks (3 RCTs, 531 people aged 7–18 years; CDRS score: SMD –0.53, 95% CI –0.70 to –0.35). [13] The review found no evidence that fluoxetine improved functional status (change in Children's Global Assessment Scale or Global Assessment of Functioning score) compared with placebo after 7–8 weeks (2 RCTs, 286 people aged 7–18 years; SMD in functioning score: –0.14, 95% CI –0.38 to +0.09). [13] The second review found that fluoxetine significantly increased response (defined as the predefined primary outcome measure reported by the RCT) compared with placebo after 8–12 weeks (3 RCTs, 536 people aged 7–18 years; response for fluoxetine *v* placebo: OR 2.39, 95% CI 1.69 to 3.39; P less than 0.0001). [15] It found that fluoxetine significantly increased treatment response (measured by Clinical Global Impression Improvement score [CGI-I equal or less than 2]) compared with placebo (3 RCTs, 536 people aged 7–18 years; OR 2.38, 95% CI 1.68 to 3.37). [15] The third review included additional data from the authors of one included RCT, and found similar results to the first and second reviews. [14] It found that fluoxetine significantly increased the proportion of people who responded to treatment compared with placebo (3 RCTs, 527 young people, RR 1.86, 95% CI 1.49 to 2.32; P less than 0.0001). [14] It also found that fluoxetine significantly reduced depressive-symptom severity scores (measured using CDRS) compared with placebo at the end of treatment (mean difference –5.63, 95% CI –7.38 to –3.38; P less than 0.0001; absolute numbers not reported). The review reported that it was unclear whether this reduction (–5.63 on the CDRS scale [range 17–113]) was of clinical importance. [14] The additional RCT found that fluoxetine prevented relapse of depressive symptoms (CDRS greater than 40) compared with placebo after 32 weeks (40 people aged 8–17 years who had responded to fluoxetine during 9 weeks of treatment; mean time to relapse: 180.7 days with fluoxetine *v* 71.2 days with placebo; P less than 0.05). [16]

Fluoxetine versus other antidepressants:
We found one RCT (40 people aged 7–16 years) comparing fluoxetine versus nortriptyline. [17] The RCT found that 10/20 (50%) of people treated with fluoxetine achieved remission from depression (defined as no longer meeting DSM-IV criteria for major depression) at 8 weeks compared with 2/20 (10%) treated with nortriptyline (significance not assessed). The RCT also found that mean Children's Depression Inventory scores were significantly lower at 8 weeks in people treated with fluoxetine compared with nortriptyline (mean CDI score at 8 weeks [change from baseline]: 17.9 [–10.95] with fluoxetine *v* 25.8 [–2.6] with nortriptyline; P = 0.004). The method of randomisation was unclear. In addition, 6 people dropped out of the RCT (4 from the nortriptyline arm and 2 from the fluoxetine arm; reasons for withdrawal not clear) and were replaced by new people. These methodological problems diminish the quality of the study and affect the generalisability of the results. We found no RCTs comparing fluoxetine versus other antidepressants.

Fluoxetine versus CBT:
We found one systematic review (search date 2004 [13]) and one subsequent report of a the longer-term follow-up of the RCT included in the review. [18] The review found that fluoxetine significantly improved depressive symptoms compared with CBT after 12 weeks (1 RCT, 220 adolescents aged 12–17 years with major depression; SMD in CDRS score: –0.66, 95% CI –0.93 to –0.39). [13] In the follow-up report, out of 220 participants initially randomised, 157 (71%) remained in the study at 36 weeks and 110 (50%) remained in the treatment condition to which they had been initially randomised. [18] However, the RCT reported an intention-to-treat analysis, which we have reported here. It found that fluoxetine significantly improved the CDRS score compared with CBT at 18 weeks (P = 0.04), but found no significant difference between groups at 24 weeks (P = 0.22), 30 weeks (P = 0.63), or 36 weeks (P = 0.94). [18]

Fluoxetine versus fluoxetine plus CBT (in adolescents):
See benefits of fluoxetine plus CBT (in adolescents), p 19 .

Harms:

Fluoxetine versus placebo:
The first systematic review [13] found that, compared with placebo, fluoxetine was not associated with an increased rate of any harms-related event (RR 2.23, 95% CI 0.88 to 5.65) or serious adverse events (RR 0.25, 95% CI 0.03 to 2.22). [13] It found no significant increase in suicidal ideation alone or suicidal ideation combined with suicidal behaviour (suicidal ideation alone: SMD –0.05, 95% CI –0.31 to +0.21; suicidal ideation combined with suicidal behaviour: RR 1.31, 95% CI 0.66 to 2.60). [13] The second review did not pool data on adverse effects. [15] The third review, which included the same 4 RCTs as the first review, found a significant increase in adverse events with fluoxetine compared with placebo in 1 RCT (219 people; RR 1.19, 95% CI 1.03 to 1.36). [14] It also found no significant difference between groups in suicidal ideation combined with suicidal behaviour (3 RCTs, 536 children and adolescents; RR 1.61, 95% CI 0.8 to 3.24; P = 0.2).

Fluoxetine versus other antidepressants:
The RCT found no significant difference between fluoxetine and nortriptyline in the rates of adverse effects, which included diarrhoea, hypersomnia, and abdominal pain (absolute numbers not reported; reported as not significant; P values not reported). [17] The most common adverse effect in both treatment groups was drowsiness (3/20 [15%] with fluoxetine *v* 3/20 [15%] with nortriptyline; reported as not significant; P value not reported).

Fluoxetine versus CBT:
We found one systematic review (search date 2004). [13] The review found no significant difference in rate of any harms-related event between fluoxetine and CBT (RR 2.65, 95% CI 0.98 to 7.18). There was also no significant difference between treatments in number of suicide attempts and suicide-related events (suicide attempts: RR 2.04, 95% CI 0.19 to 22.14; suicide-related events: RR 1.24, 95% CI 0.39 to 3.96).

SSRIs in general:
We found eight meta-analyses of harms data published in nine reports, all of which analysed the same set or subset of clinical trials. [19] [20] [21] [22] [23] [24] [25] [26] [14] There was some variability in the approach to the analyses and the manner in which studies were aggregated. Here we report data from a study commissioned by the FDA as the benchmark because of its comprehensiveness and transparency. This meta-analysis found no evidence that SRIs as a class increased suicidal behaviour/ideation after 7–12 weeks (10 RCTs, 1798 people; RR 1.41, 95% CI 0.84 to 2.37). [19] [20] The review found evidence that SRIs increased agitation and hostility (9 RCTs; RR 2.34, 95% CI 1.24 to 4.41). Although 10 RCTs found no conclusive evidence that SRIs were more likely than placebo to induce suicidal behaviour/ideation in depression trials, when data from RCTs involving venlafaxine, mirtazapine, nefazadone, and bupropion were included, and when anxiety disorder and obsessive compulsive disorder were included as outcomes, there was evidence that antidepressant medications were more likely than placebo to induce serious suicide-related events (RR 1.74, 95% CI 1.14 to 2.77). [19] [20] Such events were rare (fewer than 25/100,000 trial participants). We found one analysis of nationwide data for the period 1996–1998 that examined the relationship between prescription rates of SRIs within counties of the USA and deaths from suicide among people aged 5–14 years (estimated population 38,812,743). [27] There was a negative association between prescription rates and suicide deaths (maximal marginal likelihood estimate –0.17; P less than 0.01; regression analysis). The association remained statistically significant after adjustment for sex, race, income, access to mental healthcare, and county-to-county variability in suicide rates. A discontinuation syndrome after abrupt stopping or reduction in the dose of SSRIs has been described in a series of six cases. [28] The most frequent symptoms included dizziness, light-headedness, drowsiness, poor concentration, nausea, headache, and fatigue. [28]

Fluoxetine versus fluoxetine plus CBT (in adolescents):
See harms of fluoxetine plus CBT (in adolescents), p 19 .

Comment:

The conclusions drawn here about treatment efficacy differ slightly from those in the referenced reviews. [13] [15] [14] The focus here has been on fewer key outcome measures. Effect size has been determined by relative risk and standardised mean difference, but not area under the curve analyses.

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of fluoxetine to children and adolescents. That said, of the SSRIs and other newer antidepressants, fluoxetine has the most favourable risk–benefit ratio, [13] although it remains uncertain whether this reflects a true property of the drug or superiority in the design and

size of fluoxetine trials compared with other agents. Fluoxetine has been recommended as the most appropriate first-line medication treatment for children and adolescents with depression. [13] [29] The current NICE guideline does not recommend antidepressant medication for mild depression in children and adolescents, and recommends that medication be used for moderate to severe depression only after a 3-month trial of a specific psychological therapy has proved unsuccessful. There will be situations, however, where a young person does not have access to, or is not accessible by, specific psychological therapy. In such cases, professional judgement needs to be applied as to the most appropriate course of action.

OPTION CITALOPRAM/ESCITALOPRAM IN CHILDREN AND ADOLESCENTS

Symptom improvement
Citalopram compared with placebo Citalopram seems no more effective at increasing treatment response at 8 weeks in children and adolescents aged 7–18 years (moderate-quality evidence).

Escitalopram compared with placebo Escitalopram seems no more effective at increasing treatment response at 8 weeks in children and adolescents aged 6–17 years (moderate-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Citalopram versus placebo:
We found one systematic review (search date 2007). [15] The review found no significant difference between citalopram and placebo in response (defined as the predefined primary outcome measure reported by the RCT) after 8 weeks (2 RCTs, children and adolescents aged 7–18 years; 106/217 [49%] with citalopram *v* 86/205 [42%] with placebo; OR 1.38, 95% CI 0.92 to 2.06; P = 0.12). [15] The review also found no significant difference between citalopram and placebo in treatment response measured by Clinical Global Impression Improvement score (CGI-I equal or less than 2) after 8 weeks (1 RCT, children and adolescents aged 7–17 years; 42/93 [45%] with citalopram *v* 35/85 [41%] with placebo; OR 1.18, 95% CI 0.65 to 2.13). [15]

Escitalopram versus placebo:
We found one systematic review (search date 2007). [15] The review found no significant difference between escitalopram and placebo in response (defined as the predefined primary outcome measure reported by the RCT) after 8 weeks (1 RCT, children and adolescents aged 6–17 years; 59/132 [45%] with escitalopram *v* 50/136 [37%] with placebo; OR 1.39, 95% CI 0.85 to 2.27). [15] It also found no significant difference between escitalopram and placebo in treatment response measured by Clinical Global Impression Improvement score (CGI-I equal or less than 2) after 8 weeks (1 RCT, children and adolescents aged 6–17 years; 81/132 [61%] with citalopram *v* 69/136 [51%] with placebo; OR 1.54, 95% CI 0.95 to 2.51). [15]

Harms:

Citalopram versus placebo:
We found three systematic reviews that identified the same RCTs but performed slightly different analyses. [13] [15] [14] The first systematic review did not pool data on adverse effects. [15] The second review (search date 2004) found limited evidence that citalopram increased adverse effects but did not increase suicidal behaviour/ideation during 8–14 weeks of treatment (2 RCTs, 407 people; RR of adverse effect 1.13, 95% CI 1.01 to 1.27). [13] The third review (search date 2005) found no significant difference between groups in the risk of suicide-related outcomes (3 RCTs, 682 people; RR of suicidal behaviour/ideation 1.46, 95% CI 0.72 to 2.95; analysis included 2 RCTs of citalopram and 1 RCT of escitalopram). [14]

Escitalopram versus placebo:
The systematic review did not report on harms. [15]

Comment:

Escitalopram is an isomer of citalopram.

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of citalopram to children and adolescents. Given the less favourable risk–benefit profile, citalopram and escitalopram would usually only be considered after an adequate trial of fluoxetine had proved unsuccessful, or if fluoxetine had been poorly tolerated. [13]

OPTION FLUVOXAMINE IN CHILDREN AND ADOLESCENTS

We found no direct information about fluvoxamine in the treatment of depression in children or adolescents.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: **Fluvoxamine versus placebo:**
We found no systematic reviews or RCTs examining the effectiveness of fluvoxamine in treating depression in children or adolescents.

Harms: **Fluvoxamine versus placebo:**
We found no systematic review or RCTs.

Comment: **Clinical guide:**
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of fluvoxamine to children and adolescents. Given its unknown risk–benefit profile, fluvoxamine would usually only be considered after an adequate trial of fluoxetine had proved unsuccessful, or if fluoxetine had been poorly tolerated.

OPTION MIRTAZAPINE IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with placebo Mirtazapine may be no more effective at improving depressive symptoms at 8 weeks in people aged 7–17 years (low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: **Mirtazapine versus placebo:**
We found one systematic review (search date 2004, 2 RCTs, 164 people aged 7–17 years) comparing mirtazapine versus placebo. [13] The review found no significant improvement in depressive symptoms measured by the Children's Depression Rating Scale at 8 weeks for mirtazapine compared with placebo (SMD –0.20, 95% CI –0.46 to +0.06). [13]

Harms: **Mirtazapine versus placebo:**
Both RCTs included in the systematic review found no significant difference in rates of suicidal ideation or behaviour for mirtazapine compared with placebo at 8 weeks (RR of harm 1.58, 95% CI 0.06 to 38.37). [13]

Comment: **Clinical guide:**
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of mirtazapine to children and adolescents. Given its less favourable risk–benefit profile, mirtazapine would usually only be considered after an adequate trial of fluoxetine had proved unsuccessful, or if fluoxetine had been poorly tolerated. [13]

OPTION MAOIS IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with placebo We don't know whether the reversible MAOI moclobemide is more effective at improving depression scores in children aged 9–15 years with major depression and a comorbid disorder (very low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: **Reversible MAOIs versus placebo:**
We found no systematic review but found one small RCT comparing moclobemide versus placebo for 5 weeks. [31] The RCT (20 children aged 9–15 years with major depression, including 13 children with a comorbid disorder) found that moclobemide improved clinician-rated scale scores on the Clinical Global Impressions Scale (investigator assessment of severity of depression, adverse effects, and global recovery) compared with placebo at a borderline level of significance (P = 0.50, data presented graphically) after 5 weeks. There were no significant differences in mean scores on the Children's Depression Inventory for Parents for the moclobemide and placebo treated groups after 5 weeks (13 with moclobemide *v* 13 with placebo; P = 0.88). There were no significant differences in mean scores on the self-reported Children's Depression Inventory for the moclobemide and placebo treated groups; P = 0.40). [31] The small sample size limits the conclusions that may be drawn from this RCT. [31]

Non-reversible MAOIs versus placebo:
We found no systematic review or RCTs.

Harms:

Reversible MAOIs versus placebo:
The RCT found no significant difference between moclobemide and placebo in adverse events assessed using the Clinical Global Impression scale or self-assessed adverse effects forms (CGI scale: P = 0.75, data presented graphically; self-assessed adverse effects forms: P = 0.68). [31]
We found no information on the safety of moclobemide usage in children younger than 9 years.

Non-reversible MAOIs versus placebo:
We found no RCTs.

Comment:

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of MAOIs to children and adolescents.

OPTION PAROXETINE IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with placebo Paroxetine may be no more effective at increasing response or improving depression symptom severity scores after 8–12 weeks in people aged 7–18 years (low-quality evidence).

Compared with tricyclic antidepressants We don't know whether paroxetine is more effective than imipramine at improving remission rates. We don't know whether paroxetine is more effective than clomipramine at increasing rates of clinical improvement (measured by Clinical Global Impressions scores) in people aged 12–20 years with major depression (low-quality evidence).

Adverse effects
Compared with placebo Paroxetine seems to be associated with more adverse effects (including serious adverse effects) in people aged 7–18 years (moderate-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Paroxetine versus placebo:
We found two systematic reviews comparing paroxetine versus placebo, which identified the same three RCTs but performed slightly different analyses. [15] [14] The first review (search date 2007) included published RCTs and found no significant difference between paroxetine and placebo in response (defined as the predefined primary outcome measure reported by the RCT) after 8–12 weeks (3 RCTs, children and adolescents aged 7–18 years; 216/384 [56%] with paroxetine *v* 147/286 [51%] with placebo; OR 1.21, 95% CI 0.89 to 1.66; P = 0.23). [15] It found that paroxetine significantly increased treatment response measured by Clinical Global Impression Improvement score (CGI-I equal or less than 2) compared with placebo after 8–12 weeks (3 RCTs, children and adolescents aged 7–17 years, 227/384 [59%] with paroxetine *v* 139/286 [48%] with placebo; OR 1.49, 95% CI 1.09 to 2.03; P = 0.01). [15] The second review (search date 2005) identified the same RCTs as the first review, but at the time of the review's publication, some of the RCTs had not yet been fully published, and it included additional data supplied by the authors. [14] It found no significant difference in response (by predefined criteria) between paroxetine and placebo (3 RCTs, 216/368 [59%] with paroxetine *v* 147/278 [53%] with placebo; RR 1.09, 95% CI 0.95 to 1.26; P = 0.2). It found no significant difference between groups in symptom-severity scores for RCTs reporting Children's Depression Rating Scale scores (1 RCT, P = 0.4) or Kiddie-Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS 9-item subscale) scores (2 RCTs, P = 0.10), or in function for RCTs using Global Assessment of Functioning measure (1 RCT, P = 0.40; absolute numbers in each analysis not reported). [14]

Paroxetine versus tricyclic antidepressants:
We found one systematic review. [13] The review found no significant difference between paroxetine (20–40 mg) and imipramine (gradual upward titration to 200–300 mg) in rates of remission (1 RCT, 188 people; RR of non-remission 0.77, 95% CI 0.55 to 1.06). The review found no significant difference between paroxetine and clomipramine in rates of clinical improvement (score of 2 [much improved] or 1 [very much improved] on Clinical Global Impressions scale) after 8 weeks (1 RCT; 121 people aged 12–20 years with major depression; numbers achieving clinical improvement: 35/59 [59%] with paroxetine *v* 32/55 [58%] with clomipramine; P = 0.71). [13]

Harms:

Paroxetine versus placebo:
The first systematic review did not report on harms. [15] The second systematic review found that adverse events were significantly more common with paroxetine compared with placebo (3 RCTs, 277/376 [74%] with paroxetine *v* 186/282 [66%] with placebo; RR 1.14, 95% CI 1.03 to 1.27). [14] It reported that headaches were common adverse effects in both groups, as were nausea and dizziness; somnolence, insomnia, and emotional lability were also noted (statistical analysis for

individual adverse effects between groups not reported). One other systematic review (search date 2004) which included similar RCTs to the first two reviews found that paroxetine increased serious adverse events after 8–12 weeks compared with placebo (2 RCTs, 455 people; RR of serious adverse events 2.55, 95% CI 1.23 to 5.30). [13] The review found no evidence that paroxetine increased suicidal behaviour/ideation after 7–12 weeks (3 RCTs, 662 people; RR 2.15, 95% 0.71 to 6.52). [13]

Comment:

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of paroxetine to children and adolescents. Given its unfavourable risk–benefit profile, paroxetine would usually only be considered after an adequate trial of fluoxetine had proved unsuccessful, or if fluoxetine had been poorly tolerated. [13]

OPTION SERTRALINE IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with placebo Sertraline may be no more effective at improving remission/response at 10 weeks in people aged 6–17 years, but we don't know about depression symptom severity (low-quality evidence).

Compared with CBT Sertraline may be less effective at increasing the rate of improvement from depression (defined as a reduction in symptoms or symptoms absent for 8 weeks) after 12 weeks treatment in adolescents aged 12–18 years, but may be no less effective at decreasing the proportion of people depressed at 9 months (very low-quality evidence).

Compared with sertraline plus CBT (in adolescents) We don't know whether sertraline alone is more effective at improving depressive symptoms in adolescents aged 12–18 years (very low-quality evidence).

Functional status
Compared with placebo Sertraline seems no more effective at improving functional status at 10 weeks in people aged 6–17 years (moderate-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Sertraline versus placebo:
We found three systematic reviews (search date 2004; [13] search date 2005; [14] search date 2007) [15] which identified the same two RCTs and reported a slightly different analysis. The first review found no significant difference in remission rates with sertraline versus placebo after 10 weeks (2 RCTs, 376 people aged 6–17 years; RR of non-remission 0.92, 95% CI 0.62 to 1.38). [13] The review also found no significant difference in depressive symptoms after 10 weeks (SMD in Children's Depression Rating Scale score –0.28, 95% CI –0.49 to +0.08). The review found no significant difference between sertraline and placebo in functional status after 10 weeks (SMD in Children's Global Assessment Scale score 0.09, 95% CI –0.11 to +0.30). [13] The second review found no significant difference between sertraline and placebo in response (defined as the predefined primary outcome measure reported by the RCT) after 10 weeks (127/189 [67%] with sertraline *v* 105/187 [56%] with placebo; RR 1.63, 95% CI 0.90 to 2.96; P = 0.11). [15] The third review found no significant difference in response (by predefined criteria) between sertraline and placebo (2 RCTs, 128/185 [69%] with sertraline *v* 106/179 [59%] with placebo; RR 1.17, 95% CI 1.00 to 1.36; P = 0.05; reported as no statistical difference between groups). It found that sertraline significantly improved depression symptom severity (measured by Children's Depression Rating Scale score) compared with placebo (2 RCTs, mean difference –3.56, 95% CI –6.69 to –0.42; P = 0.03; absolute number in analysis not reported), however the clinical importance of this is unclear. [14]

Sertraline versus CBT (in adolescents):
We found one RCT (73 adolescents aged 12–18 years) comparing sertraline, either alone or in combination with CBT, versus CBT alone. [32] The primary outcome measured was depressive diagnosis, which combined response and remission rates. The RCT found that rate of improvement from depression (defined as a reduction in symptoms or absence of symptoms for 8 weeks) was significantly lower with sertraline alone compared with CBT alone (logistical regression analysis) after 12 weeks' treatment (odds of having depressive disorder [sertraline *v* CBT]: OR 6.86, 95% CI 1.12 to 41.48). However, there was no significant difference between groups in proportion of people depressed at 9 months (OR 84.94, 95% CI 0.83 to 8718.04; absolute numbers not reported).

Sertraline alone versus CBT plus sertraline (in adolescents):
See benefits of sertraline plus CBT in adolescents, p 21 .

Harms:

Sertraline versus placebo (in children or adolescents):
The first review found no evidence that sertraline increased serious adverse events or suicidal behaviour/ideation after 10 weeks (2 RCTs, 373 people; RR of serious adverse event 1.14, 95% CI 0.39 to 3.32; RR for suicidal behaviour/ideation 2.16, 95% 0.48 to 9.62). [13] The second review did not report on adverse events. [15] The third review reported that nausea was commonly reported in both groups and that diarrhoea, vomiting, and insomnia were reported relatively frequently, but did not report a statistical analysis for adverse effects between groups. [14]

Sertraline versus CBT (in adolescents):
The RCT found 4/26 (15%) of people receiving sertraline monotherapy experienced at least one episode of suicidality compared with 1/22 (5%) of people receiving combined therapy (significance not assessed: OR not reported).

Sertraline alone versus CBT plus sertraline (In adolescents):
See harms of sertraline plus CBT in adolescents, p 21 .

Comment:

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of sertraline to children and adolescents. Given a less favourable risk–benefit profile, sertraline would usually only be considered after an adequate trial of fluoxetine had proved unsuccessful, or if fluoxetine had been poorly tolerated. [13]

OPTION TRICYCLIC ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with placebo Oral tricyclic antidepressants (amitriptyline, imipramine, and nortripytline) seem to be no more effective at improving remission rates at 8–10 weeks or depressive symptoms at 6–10 weeks in young people aged 5–18 years (moderate-quality evidence).

Compared with paroxetine We don't know whether imipramine is more effective at improving remission rates. We don't know whether clomipramine is more effective at increasing rates of clinical improvement (measured by Clinical Global Impressions scores) in people aged 12–20 years with major depression (low-quality evidence).

Compared with fluoxetine Nortriptyline may be less effective at improving depression scores at 8 weeks in young people aged 7–16 years, but we don't know whether it is more effective at increasing remission rates (very low-quality evidence).

Functional status
Compared with placebo Oral tricyclic antidepressants (amitriptyline, imipramine, and nortripytline) may be no more effective at improving functional status at 10 weeks in young people aged 5–18 years (low-quality evidence).

Note
Tricyclic antidepressants have rarely been associated with toxicity and mortality from overdose. Although very rare, any such risk has been considered unacceptable when there are safer alternatives.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Oral tricyclic antidepressants versus placebo:
We found one systematic review (search date 2004). [13] The review found no significant difference between oral tricyclic antidepressants (amitriptyline, imipramine, and nortriptyline) and placebo in rates of remission (reduction in scores on the Children's Depression Rating Scale or Hamilton Depression Rating Scale) after 8–10 weeks (5 RCTs, 331 people aged 5–18 years with depression; RR of non-remission 0.90, 95% CI 0.76 to 1.06). The review also found no significant difference between treatment and placebo in depressive symptoms (change in the Children's Depression Rating Scale or Hamilton Depression Rating Scale) after 6–10 weeks (6 RCTs, 352 people aged 5–18 years; SMD in depression score –0.12, 95% CI –0.33 to +0.09). [13] The review found no significant difference in functional status between oral tricyclic antidepressants (amitriptyline, clomipramine, imipramine, and nortriptyline) and placebo after 8 weeks (5 RCTs, 170 people aged 5–18 years; SMD in Children's Global Assessment Scale or Global Assessment of functioning score –0.04, 95% CI –0.34 to +0.26). [13]

Oral tricyclic antidepressants versus paroxetine:
See benefits of paroxetine, p 8 .

Oral tricyclic antidepressants versus fluoxetine:
See benefits of fluoxetine, p 3 .

Harms:

Oral tricyclic antidepressants versus placebo or versus each other:
We found one systematic review. [13] The review found evidence of a higher mean adverse-effect score for desipramine than for placebo during 6 weeks of treatment (42 people aged 15–19 years; SMD 0.72, 95% CI 0.08 to 1.36), but no evidence that imipramine was associated with more severe adverse events than was placebo during 8 weeks of treatment (182 people aged 12–18 years; RR of harm 2.29, 95% CI 0.46 to 11.50). [13] We found single case reports and case series of toxicity and mortality from tricyclic antidepressants in overdose and therapeutic doses. [33] Mortality has been estimated at 0.4/100,000 prescriptions. [34] Although rare, any such risk has been considered unacceptable when there are safer alternatives.

Oral tricyclic antidepressants versus paroxetine:
See harms of paroxetine, p 8 .

Oral tricyclic antidepressants versus fluoxetine:
See harms of fluoxetine, p 3 .

Comment:

Clinical guide:
Tricyclic antidepressants are not recommended for the treatment of depression in children and adolescents because they are unlikely to have beneficial effects and are potentially lethal in overdose.

OPTION VENLAFAXINE IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with placebo Venlafaxine may be more effective at improving symptoms of depression at 6–8 weeks in young people aged 6–17 years (low-quality evidence).

Adverse effects
Compared with placebo Venlafaxine seems to be associated with a higher rate of suicidal behaviour/ideation over 6–8 weeks of treatment (moderate-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Venlafaxine versus placebo:
We found one systematic review (search date 2004) comparing venlafaxine with placebo. [13] The review found that venlafaxine significantly improved symptoms of depression after 6–8 weeks compared with placebo (2 RCTs, 367 people aged 6–17 years with depression; SMD in Children's Depression Rating Scale score –0.24, 95% CI –0.45 to –0.03). [13]

Harms:

Venlafaxine versus placebo:
The review found that venlafaxine was associated with higher rates of suicidal behaviour/ideation over 6–8 weeks of treatment compared with placebo (2 RCTs, 361 people; RR of harm 8.84, 95% CI 1.12 to 69.51). [13]

Comment:

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of venlafaxine to children and adolescents. Given its unfavourable risk–benefit profile, venlafaxine would usually only be considered after an adequate trial of fluoxetine had proved unsuccessful, or if fluoxetine had been poorly tolerated. [13]

QUESTION What are the effects of psychological treatments for depression in children and adolescents?

OPTION INTERPERSONAL THERAPY IN ADOLESCENTS

Symptom improvement
Compared with waiting list control Interpersonal therapy may be more effective at increasing remission rates and improving clinician-rated or self-rated depressive symptoms after 12 weekly sessions of treatment in adolescents aged 12–18 years (low-quality evidence).

Compared with standard care Interpersonal therapy may be no more effective than standard care (not further defined) at increasing remission rates or improving clinician-rated or self-rated depressive symptoms in adolescents aged 12–18 years (low-quality evidence).

Compared with individual CBT We don't know whether interpersonal therapy is more effective at improving remission rates or depressive symptoms at the end of treatment (duration not specified) in people aged 13–17 years (low-quality evidence).

Functional status
Compared with standard care Interpersonal therapy may be less effective than standard care (not further defined) at improving functional status (low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Interpersonal therapy versus waiting list control:
We found one systematic review. [13] The review found that interpersonal therapy significantly increased remission rates (reduced score on self-rated Beck Depression Inventory [BDI] or Children's Depression Inventory [CDI]) compared with waiting list control after 12 weekly sessions of treatment (2 RCTs, 94 people aged 12–17 years with depression; RR of non-remission 0.50, 95% CI 0.28 to 0.88). One RCT included in the review found limited evidence that interpersonal therapy was more likely to induce remission (defined as no longer meeting clinician-rated DSM criteria for depression after 12 weekly sessions) than waiting list control (48 people, aged 12–18 years; RR of non-remission 0.30, 95% CI 0.09 to 0.96). [13] The review found limited evidence that interpersonal therapy improved clinician-rated depressive symptoms (using Hamilton Rating Scale for Depression [HRSD]) compared with waiting list control (1 RCT, 48 people aged 12–18 years with major depressive disorder; SMD –0.65, 95% CI –1.23 to –0.07). [13] Two RCTs included in the review found that interpersonal therapy improved self-rated depressive symptoms (as measured by self-rated BDI or CDI) compared with waiting list control after 12 weeks of treatment (2 RCTs, 85 people aged 12–18 years with depression; SMD in BDI or CDI –0.69, 95% CI –1.13 to –0.25). [13]

Interpersonal therapy versus standard care:
The systematic review found no significant difference between interpersonal therapy and standard care in remission rates (reduced score on clinician-rated HRSD) or clinician-rated depressive symptoms (as measured by clinician-rated HRSD) after treatment (treatment duration not specified; 1 RCT, 63 people aged 12–18 years; RR of non-remission 0.76, 95% CI 0.50 to 1.17; SMD on HRSD score –0.45, 95% CI –1.00 to +0.01). One RCT found no significant difference in self-rated depressive symptoms (as measured by self-rated BDI or CDI) between interpersonal therapy and standard care (1 RCT, 63 people; SMD in BDI or CDI score –0.37, 95% CI 0.87 to 0.13). The RCT provided limited evidence that interpersonal therapy (34 people) was inferior to standard care (29 people) in improving functional status as measured by the Global Assessment of Functioning (SMD in Global Assessment of Functioning score 0.54, 95% CI 0.03 to 1.04). [13]

Interpersonal therapy versus group CBT:
See benefits of group CBT, p 12 .

Interpersonal therapy versus individual CBT:
See benefits of individual CBT, p 13 .

Harms:

The systematic review did not report any adverse effects. [13]

Comment:

Clinical guide:
Some guidelines have recomended interpersonal therapy as a first-line treatment for depression of any severity. [1] Substantially impaired individuals may not, however, be able to participate in the treatment.

OPTION CBT (GROUP) IN CHILDREN AND ADOLESCENTS WITH MILD TO MODERATE DEPRESSION

Symptom improvement
Compared with waiting list control Group CBT may be more effective at improving clinician-rated depressive symptoms in people aged 4–18 years. Group CBT may be more effective than waiting list control/standard care/no treatment at improving self-rated depressive symptoms in people aged 10–18 years. Group CBT may be more effective than waiting list control/standard care/no treatment at increasing the rate of remission after treatment, but not at increasing remission rates compared with waiting list control, or at maintaining remission at 12 or 24 months compared with standard care in people aged 13–18 years (very low-quality evidence).

Compared with placebo medication and clinical management Group CBT may be no more effective at increasing remission rates or at improving depressive symptoms after 12 weeks of treatment in people aged 12–17 years (low-quality evidence).

Functional status

Compared with waiting list control Group CBT may be no more effective at improving functional status after treatment (treatment duration not stated) in people aged 13–18 years (low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Group CBT versus waiting list control:
We found one systematic review (search date 2004). [13] The review found no significant difference in remission rates between group CBT and waiting list control (reduced score on self-rated Beck Depression Inventory [BDI] or Children's Depression Inventory [CDI]) after treatment (treatment duration not specified; 1 RCT, 48 people aged 13–17 years; RR of non-remission: 0.75, 95% CI 0.38 to 1.48). [13] However, the review found that group CBT increased the rate of remission (no longer meeting clinician-rated DSM criteria for depression) after treatment compared with waiting list control, standard care, or no treatment (3 RCTs, 217 people aged 13–18 years; treatment duration not specified; RR of non-remission: 0.78, 95% 0.62 to 0.98). [13] The review found no significant difference in maintained remission rates with group CBT compared with standard care at 12 or 24 months' follow-up (1 RCT, 81 people aged 13–18 years; RR for non-remission at 12 months 1.56, 95% CI 0.69 to 3.55; RR for non-remission at 24 months 1.31, 95% CI 0.28 to 6.08). [13] The review found that group CBT significantly improved clinician-rated depressive symptoms (as measured by clinician-rated Children's Depression Rating Scale [CDRS] or Hamilton Depression Rating Scale [HRSD]) compared with waiting list control (3 RCTs, 197 people aged 4–18 years; SMD in CDRS or HRSD –0.30, 95% CI –0.59 to –0.01). The review found that group CBT significantly improved self-rated depressive symptoms (as measured by self-rated BDI or CDI) compared with waiting list control, standard care, or no treatment (4 RCTs, 186 people aged 10–18 years; SMD –0.82, 95% CI –1.12 to –0.51). [13] The review found no significant difference between group CBT and placebo in functional status (as measured by the Global Assessment of Functioning) compared with waiting list control after treatment (treatment duration not stated; 2 RCTs, 149 people aged 13–18 years; SMD in Global Assessment of Functioning score –0.26, 95% CI –0.79 to +0.28). [13]

Group CBT versus placebo medication and clinical management:
We found one systematic review (search date 2004) comparing CBT versus placebo medication and clinical management. [13] The review found no significant difference between CBT and placebo in remission rates (no longer meeting criteria for major depression on the clinician-rated Kiddie-Schedule for Affective Disorders and Schizophrenia interview) or depressive symptoms (as measured by clinician-rated CDRS) after 12 weeks of treatment (1 RCT, 223 people aged 12–17 years; RR of non-remission 0.87, 95% CI 0.70 to 1.08; SMD in CDRS score 0.03, 95% CI –0.23 to +0.30). [13]

Harms:

The systematic review did not report any adverse effects. [13]

Comment:

The conclusions drawn here about treatment efficacy differ slightly from those found in the referenced review. [13] Here, we focused on a smaller number of key outcome measures, and considered effect size as determined by relative risk and standardised mean difference, not by area under the curve analyses. In studies of psychological interventions, it is difficult to blind raters to treatment condition. In addition, some RCTs select participants on the basis of screening with depression rating scales rather than through clinical interview.

Clinical guide:
Some guidelines have recomended group CBT as a first-line treatment for depression of any severity. [1] Substantially impaired individuals may not, however, be able to participate in the treatment.

OPTION CBT (INDIVIDUAL) IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with waiting list control Individual CBT may be more effective at improving self-rated depressive symptoms at the end of treatment (duration not specified) in people aged 13–17 years (very low-quality evidence).

Compared with placebo medication and clinical management Individual CBT may be no more effective at improving remission rates or at improving depressive symptoms at 12 weeks in people aged 12–17 years (low-quality evidence).

Compared with interpersonal therapy We don't know whether individual CBT is more effective at improving remission rates or depressive symptoms at the end of treatment (duration not specified) in people aged 13–17 years (low-quality evidence).

Compared with family therapy Individual CBT may be more effective at increasing remission rates at the end of treatment (treatment duration not specified), but not at improving self-reported depressive symptoms in people aged 13–18 years (low-quality evidence).

Compared with non-directive supportive therapy Individual CBT may be more effective at increasing remission rates at the end of treatment (treatment duration not specified) in people aged 8–18 years, but may be no more effective at maintaining remission at 9 or 24 months in people aged 8–17 years, or in improving self-rated depressive symptoms in people aged 13–18 years (low-quality evidence).

Compared with sertraline CBT may be more effective at increasing the rate of improvement from depression (defined as a reduction in symptoms or symptoms absent for 8 weeks) after 12 weeks' treatment in adolescents aged 12–18 years, but may be no more effective at decreasing the proportion of people depressed at 9 months (very low-quality evidence).

Compared with CBT plus sertraline (in adolescents) We don't know whether sertraline plus CBT is more effective than CBT alone at improving depressive symptoms in adolescents aged 12–18 years (very low-quality evidence).

Compared with CBT plus fluoxetine (in adolescents) CBT alone may be less effective at improving depressive symptoms at 12–24 weeks in adolescents, but not at improving remission rates at 16 weeks (very low-quality evidence).

Compared with fluoxetine CBT seems to be less effective at improving depressive symptoms at 12 and 18 weeks in people aged 12–17 years with major depression, but not at 24, 30, or 36 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Individual CBT versus waiting list control:
We found one systematic review. [13] The review found that individual CBT significantly improved depressive symptoms (as measured by self-rated Beck Depression Inventory [BDI] or Children's Depression Inventory [CDI]) compared with waiting list control at the end of treatment (treatment duration not specified; 1 RCT, 39 people aged 13–17 years; SMD in BDI or CDI score: –0.34, 95% CI –0.98 to –0.29). [13]

Individual CBT versus placebo medication and clinical management:
We found one systematic review (search date 2004) comparing CBT versus placebo medication and clinical management. [13] The review found no significant difference between CBT and placebo in remission rates (no longer meeting criteria for major depression on the clinician-rated Kiddie-Schedule for Affective Disorders and Schizophrenia interview) or improved depressive symptoms (as measured by clinician-rated CDRS) after 12 weeks of treatment (1 RCT, 223 people, aged 12–17 years; RR of non-remission 0.87, 95% CI 0.70 to 1.08; SMD in CDRS score 0.03, 95% CI –0.23 to +0.30). [13]

Individual CBT versus interpersonal therapy:
We found one systematic review comparing individual CBT versus interpersonal therapy. [13] The review found no significant difference in remission rates (score less than 17 on self-rated CDI) or improved depressive symptoms by the end of treatment (treatment duration not specified; 1 RCT, 48 people aged 13–17 years; RR of non-remission 1.38, 95% CI 0.58 to 3.27; SMD in CDI score 0.34, 95% CI –0.28 to +0.97). [13]

Individual CBT versus family therapy:
We found one systematic review comparing individual CBT versus family therapy. The review found limited evidence that CBT significantly increased remission rates (remission defined as no longer meeting criteria for major depression on the clinician-rated Kiddie-Schedule for Affective Disorders and Schizophrenia interview) but did not significantly improve self-reported depressive symptoms (as measured by self-report BDI) after treatment (treatment duration not specified; 1 RCT, 72 people aged 13–18 years; RR of non-remission 0.58, 95% CI 0.38 to 0.88; SMD in BDI score –0.38, 95% CI –0.88 to +0.12). [13]

Individual CBT versus non-directive supportive therapy:
We found one systematic review comparing individual CBT versus non-directive supportive therapy. [13] The review found limited evidence that individual CBT significantly increased remission rates (remission defined as no longer meeting criteria for major depression on the clinician-rated DSM) compared with non-directive supportive therapy after treatment (treatment duration not specified; 2 RCTs, 129 people aged 8–18 years; RR of non-remission 0.63, 95% CI 0.42 to 0.96). It found no significant difference between individual CBT and non-directive supportive therapy in maintenance of remission 9 or 24 months after treatment (1 RCT, 56 people aged 8–17 years; RR of non-remission at 9 months: 1.14, 95% CI 0.48 to 2.72; RR of non-remission at 24 months: 1.75, 95% CI 0.58 to 5.29). [13] The review found no significant difference between individual CBT and non-directive

supportive treatment in self-rated depressive symptoms (as measured by self-report BDI) after treatment (treatment duration not specified; 1 RCT, 68 people aged 13–18 years; SMD in BDI score –0.40, 95% CI –0.88 to +0.08). [13]

CBT versus sertraline:
See benefits of sertraline, p 9 .

CBT plus sertraline versus CBT alone (in adolescents):
See benefits of CBT plus sertraline, p 21 .

CBT plus fluoxetine versus CBT alone (in adolescents):
See benefits of fluoxetine plus CBT in adolescents, p 19 .

CBT versus fluoxetine:
See benefits of fluoxetine, p 3 .

Harms:

The systematic review gave no information on adverse effects. [13] One retrospective study analysed data from a comparative trial of four psychotherapeutic modalities. [35] The study (107 people aged 13–18 years with DSM-III-R diagnosis of major depressive disorder) found that of the 88 people who reported no suicidality at the randomisation to treatment, 11/88 (13%) developed suicidality at 12–16 weeks of active treatment. [35]

CBT versus sertraline:
See harms of sertraline, p 9 .

CBT plus sertraline versus sertraline alone:
See harms of CBT plus sertraline, p 21 .

CBT plus sertraline versus CBT alone (in adolescents):
See harms of CBT plus sertraline, p 21 .

CBT plus fluoxetine versus CBT alone (in adolescents):
See harms of fluoxetine plus CBT in adolecents, p 19 .

CBT versus fluoxetine:
See harms of fluoxetine, p 3 .

Comment:

Clinical guide:
The evidence for the benefits of individual CBT is less robust than it is for group CBT. The reasons for this remain uncertain. However, where group therapy is unavailable, individual therapy is indicated as a first-line treatment for mild to moderate depression in children and adolescents.

OPTION GROUP THERAPEUTIC SUPPORT (OTHER THAN CBT) IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with group social skills training We don't know whether group therapeutic support is more effective at increasing remission rates in people aged 13–17 years with major depression (low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Group therapeutic support versus group social skills training:
We found no systematic review but found one RCT comparing group therapeutic support versus group social skills training. [37] The RCT found no significant difference in numbers achieving remission (defined as a score of less than 4 on Kiddie-Schedule for Affective Disorders and Schizophrenia dysphoria and anhedonia symptoms) after treatment between group therapeutic support and group social skills training (26 adolescents aged 13–17 years with major depression; 8/16 [50%] with group therapeutic support *v* 4/10 [40%] with group social skills training; RR and P value not reported). [37]

Harms:

The RCT gave no information on adverse events. [37]

Comment:

None.

OPTION INTERPERSONAL THERAPY IN CHILDREN

We found no direct information about interpersonal therapy in the treatment of depression in children under the age of 12 years.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: We found no systematic review or RCTs.

Harms: We found no systematic review or RCTs.

Comment: None.

OPTION GUIDED SELF-HELP IN CHILDREN AND ADOLESCENTS

We found no direct information about guided self-help on symptoms of depression or remission in the treatment of depression in children and adolescents.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: We found no systematic review or RCTs examining the effectiveness of guided self-help interventions for treating depression in children and adolescents.

Harms: We found no evidence on harms.

Comment: None.

OPTION INDIVIDUAL PSYCHODYNAMIC PSYCHOTHERAPY IN CHILDREN AND ADOLESCENTS

Symptom improvement
Compared with waiting list control Psychodynamic psychotherapy may be more effective at reducing global impairment scores in people aged 5–17 years with major depression or dysthymia (very low-quality evidence).

Compared with family therapy We don't know whether individual psychodynamic psychotherapy is more effective at increasing remission or improving self-rated depressive symptoms after treatment (treatment duration not specified) in people aged 10–15 years with major depression (low-quality evidence).

Functional status
Compared with family therapy We don't know whether individual psychodynamic psychotherapy is more effective at improving functional status after treatment (treatment duration not specified) in people aged 10–15 years with major depression (very low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Psychodynamic psychotherapy versus waiting list control:
We found one quasi-randomised controlled study (20 people aged 5–17 years with major depression or dysthymia) comparing 25 sessions of individual psychodynamic psychotherapy with waiting list control. [38] The study found a significant reduction in global impairment scores (as measured by the Impairment Score for Children and Adolescents) in the psychodynamic psychotherapy group compared with the waiting list control group (mean score for psychodynamic psychotherapy group at baseline 11.40, at end point 9.10 *v* mean score for waiting list control group at baseline 11.70, at end point 11.70; P less than 0.05).

Psychodynamic psychotherapy versus family therapy:
See benefits of family therapy, p 17 .

Harms: The RCT gave no information on adverse effects. [38]

Comment:

Clinical guide:
Absence of a specific measure of depression symptoms limits the inferences that may be drawn from the study comparing psychodynamic psychotherapy with waiting list control. [38]

OPTION CBT (FOR RELAPSE PREVENTION) IN CHILDREN AND ADOLESCENTS

Symptom improvement
Group CBT compared with standard care Group CBT may be no more effective than standard care (not further defined) at maintaining remission at 12 and 24 months in people aged 13–18 years (low-quality evidence).

Individual CBT compared with non-directive supportive therapy We don't know whether individual CBT is more effective than non-directive supportive therapy at maintaining remission at 9 or 24 months after treatment in people aged 8–17 years (low-quality evidence).

Booster CBT compared with assessment only A booster session of group CBT may be no more effective than assessment only at improving remission in people aged 10–17 years or at maintaining remission at 12 or 24 months in people aged 14–18 years (low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Group CBT versus standard care:
We found one systematic review (search date 2004) comparing group CBT versus standard care. [13] The review found no significant difference between group CBT and standard care in maintenance of remission (defined as no longer meeting clinician-rated DSM criteria for depression) at 12 and 24 months (1 RCT, 81 people aged 13–18 years; RR for non-remission at 12 months 1.56, 95% CI 0.69 to 3.55; RR for non-remission at 24 months 1.31, 95% CI 0.28 to 6.08).

Individual CBT versus non-directive supportive therapy:
We found one systematic review (search date 2004) comparing individual CBT versus non-directive supportive therapy. [13] The review found no significant difference between individual CBT and non-directive supportive therapy in maintenance of remission 9 or 24 months after treatment (1 RCT, 56 people aged 8–17 years; RR of non-remission at 9 months 1.14, 95% CI 0.48 to 2.72; RR of non-remission at 24 months 1.75, 95% CI 0.58 to 5.29).

Booster CBT versus assessment only:
We found one systematic review (search date 2004) comparing a booster session of CBT versus assessment only. [13] The review found no significant difference between a booster session of group CBT 6 months after initial treatment compared with assessment only (1 RCT, 29 people aged 10–17 years; RR of non-remission 0.35, 95% CI 0.11 to 1.14). [13] Another small RCT included in the review found no evidence that booster group CBT maintained remission compared with assessment only at 12 or 24 months (40 people aged 14–18 years; RR of non-remission at 12 months 3.33, 95% CI 0.69 to 16.06; RR of non-remission at 24 months 2.08, 95% CI 0.76 to 5.67). [13]

Harms:

The systematic review gave no information on adverse events. [13]

Comment:

Clinical guide:
Limited evidence suggests that CBT is no more effective than other forms of psychological treatment and is as effective as inactive treatments in reducing the likelihood of relapse of depression. Booster sessions seem not to add any additional benefit.

OPTION FAMILY THERAPY IN CHILDREN AND ADOLESCENTS

Symptom improvement

Compared with waiting list control Attachment-based family therapy may be more effective at increasing remission after 6 weeks, but not before 6 weeks, in people aged 13–17 years with major depression. Attachment-based family therapy may be more effective at improving self-rated depressive symptoms, but may be no more effective at improving clinician-rated depressive symptoms (low-quality evidence).

Compared with non-specific supportive therapy We don't know whether systemic behavioural family therapy is more effective at increasing remission or improving self-rated depressive symptoms in people aged 13–18 years (low-quality evidence).

Compared with individual psychodynamic psychotherapy We don't know whether family therapy is more effective at increasing remission or improving self-rated depressive symptoms after treatment (treatment duration not specified) in people aged 10–15 years with major depression (low-quality evidence).

Compared with non-directive supportive therapy We don't know whether family therapy is more effective at increasing remission or improving self-rated depressive symptoms after treatment (treatment duration not specified) in people aged 13–18 years with major depression (low-quality evidence).

Family therapy plus usual care compared with usual care alone We don't know whether family therapy plus usual care is more effective than usual care alone at improving depressive symptom scores (measured by Reynolds Adolescent Depression Scale) in people aged 13–18 years (low-quality evidence).

Compared with individual CBT Family therapy may be less effective at increasing remission rates at the end of treatment (treatment duration not specified), but not at improving self-reported depressive symptoms in people aged 13–18 years (low-quality evidence).

Functional status

Compared with individual psychodynamic psychotherapy We don't know whether family therapy is more effective at improving functional status after treatment (treatment duration not specified) in people aged 10–15 years with major depression (very low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Family therapy versus waiting list control:
We found one systematic review comparing attachment-based family therapy with waiting list control. The review found no significant difference in rates of remission (defined as no longer meeting criteria for major depression on clinician-rated Kiddie-Schedule for Affective Disorders and Schizophrenia interview) between attachment-based family therapy and waiting list control at 6 weeks (search date 2004; 1 RCT, 32 people aged 13–17 years with major depression; RR of non-remission 0.33, 95% CI 0.11 to 1.01). [13] However, the review found that attachment-based family therapy was significantly more likely to induce remission (defined as a reduced score on the self-rated Beck Depression Inventory [BDI]) compared with waiting list control after 6 weeks (RR of non-remission 0.46, 95% CI 0.24 to 0.91). [13] The review found no significant difference between attachment-based family therapy and waiting list control in clinician-rated depressive symptoms (SMD in clinician-rated Hamilton Rating Scale for Depression –0.63, 95% CI –1.34 to +0.08). [13] The review found a significant improvement with family therapy when depressive symptoms were measured by the self-report BDI (SMD in self-report BDI –0.75, 95% CI –1.47 to –0.03). [13]

Family therapy versus non-specific supportive therapy:
We found one systematic review comparing systemic behavioural family therapy versus non-specific supportive therapy. The review found no evidence that systemic behavioural family therapy induced remission (defined using clinician-rated DSM-III-R criteria for major depression) or improved self-rated depressive symptoms (measured by self-report BDI) after treatment compared with non-specific supportive therapy (70 people aged 13–18 years; treatment duration not specified; RR of non-remission 1.13, 95% CI 0.83 to 1.54; SMD in BDI –0.07, 95% –0.57 to +0.43). [13]

Family therapy versus individual psychodynamic psychotherapy:
We found one systematic review comparing family therapy versus individual psychodynamic psychotherapy. The review found no evidence that family therapy was more likely to induce remission (defined as no longer meeting criteria for major depression on the clinician-rated Kiddie-Schedule for Affective Disorders and Schizophrenia interview) or improve self-rated depressive symptoms (as measured by self-report Children's Depression Inventory) after treatment compared with individual psychodynamic psychotherapy (1 RCT, 72 people aged 10–15 years with major depression; treatment duration not specified; RR of non-remission 0.63, 95% CI 0.19 to 2.05; SMD in BDI –0.51, 95% CI –0.98 to –0.04). [13] The review found no evidence that family therapy improved functional status (as measured by the Children's Global Assessment Scale) after treatment compared with individual psychodynamic psychotherapy (treatment duration not specified; SMD in the Children's Global Assessment Scale: –0.10, 95% CI –0.55 to +0.37).

Family therapy versus non-directive supportive therapy:
We found one systematic review comparing family therapy versus non-directive supportive therapy. [13] The review found no evidence that family therapy was more likely than non-directive supportive therapy to induce remission (defined as no longer meeting criteria for major depression on the clinician rated Kiddie-Schedule for Affective Disorders and Schizophrenia interview) after treatment compared with non-directive supportive therapy (1 RCT, 70 people aged 13–18 years with major depression; treatment duration not specified; RR of non-remission 1.13, 95% CI 0.83 to 1.54). The RCT included in the review found no evidence that family therapy improved self-rated depressive symptoms (as measured by the self-report BDI) after treatment compared with non-directive supportive therapy (62 people; treatment duration not specified; SMD in BDI –0.07, 95% CI –0.57 to +0.43). [13]

Family therapy plus usual care versus usual care alone:
We found one RCT (31 people aged 13–18 years, mean age 15.9 years). [39] All adolescents included in the study were offered usual treatments, which included individual or group counselling and/or pharmacological treatment with supportive case management. The RCT found a statistically non-significant trend towards improvement in Reynolds Adolescent Depression Scale scores at 3 months for those receiving usual care plus family psychoeducation compared with those receiving usual care alone (mean change in RADS score –5.7 with family psychoeducation plus usual care *v* –2.6 with usual care alone; P = 0.052).

Family therapy versus individual CBT:
See benefits of individual CBT, p 13 .

Harms: The systematic review did not report any adverse events. [13] The RCT assessing effects of adjunctive family psychoeducation gave no information on adverse effects. [39]

Family therapy versus individual CBT:
See harms of individual CBT, p 13 .

Comment: **Clinical guide:**
In contrast to NICE recommendations, [13] the data we report, of sufficient methodological quality to be included in this review, do not support family therapy as a first-line treatment for depression in children and adolescents.

QUESTION What are the effects of combination treatments for depression in children and adolescents?

OPTION FLUOXETINE PLUS CBT IN ADOLESCENTS

Symptom improvement
Compared with placebo Fluoxetine plus CBT seems more effective at improving depressive symptoms at 12 weeks in people aged 12–17 years with major depression (moderate-quality evidence).

Compared with fluoxetine alone We don't know whether fluoxetine plus CBT is more effective at improving depressive symptoms at 12 weeks in people aged 11–17 years with major depression (very low-quality evidence).

Compared with CBT alone Fluoxetine plus CBT may be more effective at improving depressive symptoms at 12–24 weeks in adolescents, but not at improving remission rates at 16 weeks (very low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: **Fluoxetine plus CBT versus placebo:**
We found one systematic review (search date 2004) comparing combined therapy (fluoxetine plus CBT) with placebo. [13] The review found that combined therapy (CBT plus fluoxetine) significantly improved depressive symptoms after 12 weeks compared with placebo (1 RCT, 219 people aged 12–17 years with major depression; SMD in the Children's Depression Rating Scale [CDRS] score –0.98, 95% CI –1.26 to –0.70). [13]

Fluoxetine plus CBT versus fluoxetine alone:
The RCT included in the review found that combined therapy significantly improved depressive symptoms compared with fluoxetine alone, although the benefit was modest (216 people aged 12–17 years with major depression, SMD in the CDRS score –0.30, 95% CI –0.57 to –0.04). [13] We found an extended follow-up report of the RCT included in the review. [18] In the follow-up report, out of 216 participants initially randomised to the two arms, at 36 weeks 163 (75%) remained in the study and 123 (57%) remained in the treatment condition to which they had been initially randomised. [18] However, the RCT reported an intention-to-treat analysis, which we have reported here. It found no significant difference between combined therapy and fluoxetine alone in the CDRS score at 18–36 weeks (18 weeks: P = 0.19; 36 weeks: P = 0.65). [18] One subsequent RCT (208 people aged 11–17 years with major or probable major depression, not improved after brief intervention of routine care) found no significant difference between fluoxetine plus CBT and fluoxetine alone in improvement in depressive symptoms at 12 weeks (measured by CDRS score; mean effect over follow-up period +1.42, 95% CI –0.71 to +3.57, P = 0.19). [30]

Fluoxetine plus CBT versus CBT alone:
The RCT included in the review found that combined therapy significantly improved depressive symptoms compared with CBT alone (218 people aged 12–17 years with major depression; SMD in the CDRS score –0.94, 95% CI –1.22 to –0.66). [13] We found an extended follow-up report of the RCT included in the review. [18] In the follow-up report, out of 218 participants initially randomised in the two arms, at 36 weeks 166 participants (76%) remained in the study and 123 participants (56%) remained in the treatment condition to which they had been initially randomised. [18] However, the RCT reported an intention-to-treat analysis, which we have reported here. It found that combination treatment significantly improved the CDRS score compared with CBT alone at 18 weeks (P less than 0.001) and 24 weeks (P = 0.02), but found no significant difference between groups at 30 weeks (P = 0.23) or 36 weeks (P = 0.70). [18] One subsequent RCT (126 people aged 13–19 years with depression, comorbid substance abuse disorder and conduct disorder) found no significant difference between fluoxetine plus CBT and CBT plus placebo in remission rates for depression (CDRS score 28 or less) after 16 weeks of treatment (70% with combined treatment *v* 52% with CBT alone, P = 0.07). [36] It found that combined treatment significantly improved depressive symptoms (measured by CDRS) compared with CBT alone (effect size 0.78; P = 0.04). [36]

Harms:

The systematic review did not report on harms associated with combined therapy. [13] Harms data from the RCT included in the systematic review have been subsequently reported. [40]

Fluoxetine plus CBT versus placebo:
The RCT found no significant difference in reduction of self-reported physical symptoms for fluoxetine plus CBT compared with placebo after 12 weeks of treatment (mean Physical Symptom Checklist [PSC] scores: 11.0 with combination therapy *v* 12.3 with placebo; reported as not significant; P value not reported; PSC scores at start of treatment not reported). [40] The RCT found similar numbers of treatment-emergent physical adverse effects for fluoxetine plus CBT compared with placebo (61 with combination therapy *v* 60 with placebo; significance not assessed). It found no significant differences in the number of people reporting adverse effects between the three treatment groups receiving pills (37 with combination treatment *v* 35 with fluoxetine *v* 34 with placebo; reported as not significant; significance not assessed). There was a significant reduction in suicidal ideation scores for fluoxetine plus CBT compared with placebo at 12 weeks (mean Suicidal Ideation Questionnaire [SIQ] scores: 10.9 with combination treatment *v* 14.5 with placebo; P = 0.02; scores at start of treatment not reported). The RCT found that a smaller proportion of people reported emergence of, or worsening of suicidality (measured as an increase in SIQ scores) with fluoxetine plus CBT compared with placebo, although the difference between groups did not reach statistical significance (2/93 [2%] with combination treatment *v* 7/92 [8%] with placebo; reported as not significant; P value not reported).

Fluoxetine plus CBT versus fluoxetine alone:
The RCT included in the review found no significant difference in reduction of self-reported physical symptoms for fluoxetine plus CBT compared with fluoxetine alone after 12 weeks of treatment (mean PSC scores: 11.0 with combination therapy *v* 13.0 with fluoxetine; reported as not significant; P value not reported; PSC scores at start of treatment not reported: significance not assessed). [40] The RCT found lower numbers of treatment-emergent physical adverse effects for fluoxetine plus CBT compared with fluoxetine alone (61 with combination therapy *v* 81 with fluoxetine; significance not assessed). It found no significant differences in the number of people reporting adverse effects between the three treatment groups receiving pills (37 with combination treatment *v* 35 with fluoxetine *v* 34 with placebo; reported as not significant). There was a significant reduction in suicidal ideation scores for fluoxetine plus CBT compared with fluoxetine alone at 12 weeks (mean SIQ scores: 10.9 with combination treatment *v* 13.7 with fluoxetine alone; P = 0.004; scores at start of treatment not reported). The RCT found that a smaller proportion of people reported emergence of or worsening of suicidality (measured as an increase in SIQ scores) with fluoxetine plus CBT compared with fluoxetine alone, although the difference between groups did not reach statistical significance (2/93 [2%] with combination treatment *v* 7/96 [7%] with fluoxetine alone; reported as not significant; P value not reported). The subsequent RCT reported that there were no significant differences between groups in adverse effects (65/103 [62%] with combined treatment *v* 61/103 [59%] with fluoxetine alone; OR 1.05, 95% CI 0.59 to 1.91). [30] It reported that there was one fit, possibly related to medication, in a participant in the fluoxetine-alone group. [30]

Fluoxetine plus CBT versus CBT alone:
The RCT found a significantly greater reduction in self-reported physical symptoms for fluoxetine plus CBT compared with CBT alone after 12 weeks of treatment (mean PSC scores: 11.0 with combination therapy *v* 18.5 with CBT alone; P = 0.0036; PSC scores at start of treatment not reported). [40] The RCT found higher numbers of treatment-emergent physical adverse effects for fluoxetine plus CBT compared with CBT alone (61 with combination therapy *v* 9 with CBT alone; significance not assessed). There was a significant reduction in suicidal ideation scores for fluoxetine plus CBT compared with CBT alone at 12 weeks (mean SIQ scores: 10.9 with combination treatment *v* 11.3 with CBT alone; P = 0.04; scores at start of treatment not reported). The RCT found no significant difference in the proportion of people reporting emergence of, or worsening of suicidality (measured as an increase in SIQ scores) for fluoxetine plus CBT compared with CBT alone (2/93 [2%] with combination treatment *v* 2/93 [2%] with CBT alone; reported as not significant; P value not reported).The subsequent RCT-reported adverse events were generally mild and transient, and there was no significant difference between groups (P value not reported). [36]

Comment:

Clinical guide:
Combining CBT with fluoxetine is likely to be only marginally more effective than fluoxetine monotherapy in reducing depressive symptoms, but patients who receive combined therapy may experience fewer adverse events. Combining CBT with fluoxetine is more effective than cognitive therapy alone in reducing depressive symptoms but is associated with greater adverse events. UK guidelines recommend commencing with CBT and adding fluoxetine if there is a lack of treatment response, but this strategy has not been tested under experimental conditions. [13]

OPTION FLUOXETINE PLUS CBT IN CHILDREN

We found no direct information about whether fluoxetine plus CBT is better than no active treatment in the treatment of depression in children.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Fluoxetine plus CBT versus placebo:
We found no systematic review or RCTs.

Harms:

Fluoxetine plus CBT versus placebo:
We found no systematic review or RCTs.

Comment:

Clinical guide:
In the light of emerging evidence and consensus on harms data, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of fluoxetine to children, whether or not it is prescribed in combination with CBT.

OPTION SERTRALINE PLUS CBT IN ADOLESCENTS New

Symptom severity
Compared with sertraline alone We don't know whether sertraline plus CBT is more effective at improving depressive symptoms in adolescents aged 12–18 years (very low-quality evidence).

Compared with CBT alone We don't know whether sertraline plus CBT is more effective at improving depressive symptoms in adolescents aged 12–18 years (very low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits:

Sertraline plus CBT versus placebo:
We found no systematic review or RCTs.

Sertraline plus CBT versus sertraline alone:
We found one RCT (73 adolescents aged 12–18 years). [32] The primary outcome measured was depressive diagnosis, which combined response and remission rates. The RCT found no significant difference between sertraline plus CBT and sertraline monotherapy in rate of improvement from depression (defined as a reduction in symptoms or absence of symptoms for 8 weeks) after 12 weeks' treatment (OR [sertraline alone *v* combination] 1.31, 95% CI 0.31 to 5.48). [32] A separate analysis of the proportion of people in each group reaching full remission (absence of symptoms for 8 weeks) found no significant difference between treatments at 9 months (OR [sertraline alone *v* combination] 3.0, 95% CI 0.68 to 13.31; absolute numbers not reported).

Sertraline plus CBT versus CBT alone:
We found one RCT (73 adolescents aged 12–18 years). [32] The primary outcome measured was depressive diagnosis, which combined response and remission rates. The RCT found no significant difference in odds of depression between sertraline plus CBT and CBT alone after 12 weeks' treatment (OR [CBT alone *v* combination] 0.19, 95% CI 0.03 to 1.16). [32] A separate analysis of the proportion of people in each group reaching full remission (defined as absence of symptoms for 8 weeks) found no significant difference between treatments at 9 months (OR [CBT alone *v* combination] 2.7, 95% CI 0.60 to 12.14; absolute numbers not reported).

Harms:

Sertraline plus CBT versus placebo:
We found no RCTs.

Sertraline plus CBT versus sertraline alone:
The RCT found that 15% (4/26) of people receiving sertraline monotherapy experienced at least one episode of suicidality compared with 5% (1/22) of people receiving combined therapy (significance not assessed: OR not reported). [32]

Sertraline plus CBT versus CBT alone: The RCT gave no information on the adverse effects of combination therapy compared with CBT alone. [32]

Comment:

Clinical Guide:
Combining CBT with sertraline is unlikely to be more effective than sertraline monotherapy or CBT alone in reducing depressive symptoms, but the population size may have been too small to detect

clinically important differences. Patients who receive combined therapy may experience fewer suicide-related behaviours than those who receive sertraline monotherapy.

QUESTION **What are the effects of complementary treatments for depression in children and adolescents?**

OPTION **OMEGA 3 POLYUNSATURATED FATTY ACIDS (FISH OIL)** New

We found no direct information about omega 3 polyunsaturated fatty acids in the treatment of depression in children or adolescents.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: We found one systematic review (search date 2004) on the effects of omega 3 polyunsaturated acids on mental health. [41] The review identified no RCTs on the effects of omega 3 polyunsaturated fatty acids in the treatment of depression in children or adolescents that met *Clinical Evidence* inclusion criteria.

Harms: We found no RCTs.

Comment: At present there is insufficient evidence to support the use of omega 3 polyunsaturated fatty acids in the treatment of depression in children and adolescents.

OPTION **ST JOHN'S WORT (HYPERICUM PERFORATUM) IN CHILDREN AND ADOLESCENTS**

We found no direct information about St John's Wort (*Hypericum perforatum*) in the treatment of depression in children or adolescents.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: At present, there is insufficient evidence to support the use of St John's Wort in the treatment of depression in children and adolescents.

QUESTION **What are the effects of treatments for refractory depression in children and adolescents?**

OPTION **ELECTROCONVULSIVE THERAPY IN CHILDREN AND ADOLESCENTS**

We found no direct information about electroconvulsive therapy in the treatment of depression in children and adolescents.

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: We found no systematic review and no RCTs.

Harms: We found no specific evidence on harms in children and adolescents. Known adverse effects in adults include memory impairment. See electroconvulsive therapy under depression in adults.

Comment: **Clinical guide:**
Controlled trial evidence is unlikely to be gathered for electroconvulsive therapy in children and adolescents. However, electroconvulsive therapy is indicated for a severely obtunded child or adolescent with depression who may, for example, have prolonged psychotic symptoms, and fails to hydrate or maintain caloric intake. Such treatment would usually be delivered in a specialist centre.

OPTION **LITHIUM IN CHILDREN AND ADOLESCENTS**

Symptom severity
Compared with placebo Lithium may be no more effective at improving global assessment or depression scores at 6 weeks in children aged 6–12 years with non-bipolar depression and a family history of bipolar affective disorder (low-quality evidence).

For GRADE evaluation of interventions for depression in children and adolesents, see table, p 28 .

Benefits: We found no systematic review but found one RCT comparing lithium with placebo. [42] The RCT found no significant difference between lithium and placebo after 6 weeks (30 children aged 6–12 years with non-bipolar depression and family history of bipolar affective disorder; global assessment: P = 0.07; 9 depression items of the Kiddie-Schedule for Affective Disorders and Schizophrenia interview: P = 0.91). [42] The RCT may have lacked power to rule out a clinically important difference.

Harms: The RCT reported that out of the 17 children randomised to lithium treatment, four were withdrawn because of adverse effects (three had confusion, one had nausea and vomiting). [42]

Comment: **Clinical guide:**
It is not routine practice to give lithium alone to depressed children. Lithium is sometimes used to augment antidepressants and to prevent mania from developing with antidepressant use.

GLOSSARY

Interpersonal therapy A standardised form of brief psychotherapy (usually 12–16 weekly sessions) intended primarily for outpatients with unipolar non-psychotic depressive disorders. It focuses on improving the individual's interpersonal functioning and identifying the problems associated with the onset of the depressive episode. [44] In children and adolescents, interpersonal therapy has been adapted for adolescents to address common adolescent developmental issues — for example, separation from parents, exploration of authority in relationship to parents, development of dyadic interpersonal relationships, initial experience with the death of a relative or friend, and peer pressure.
Non-directive supportive therapy Helping people to express feelings, and clarify thoughts and difficulties; therapists suggest alternative understandings and do not give direct advice but try to encourage people to solve their own problems.
Pseudo-continuous outcome measure The strict definition of a continuous outcome is one measured on a scale that is continuously variable, good examples being height or systolic blood pressure. In addition, there is an assumption that an increase in 1 unit in one region is equivalent to an increase of 1 unit in another region of the scale. In the case of psychometric scales made up of a series of questions, the latter assumption is not always valid, in which case the scale may be referred to as a pseudo-continuous measure. Caution needs to be applied in interpreting the magnitude of change reported on such measures.
Psychodynamic psychotherapy Psychological interventions, derived from a psychodynamic or psychoanalytic model, in which (1) the patient and therapist explore and gain insight into conflicts and how these are represented in current situations and relationships, including the therapy relationship; (2) patients are given the opportunity to explore feelings and conscious and unconscious conflicts originating in the past, with the technical focus on interpreting and working through the conflicts; (3) therapy is non-directive and patients are not taught specific skills.
Systemic behavioural family therapy A combination of two treatment approaches that have been used effectively for dysfunctional families. In the first phase of treatment, the therapist clarifies the concerns that brought the family into treatment, and provides a series of reframing statements designed to optimise engagement in therapy and identification of dysfunctional behaviour patterns (systemic therapy). In the second phase, the family members focus on communication and problem solving skills and the alteration of family interactional patterns (family behavioural therapy).
Attachment-based family therapy A brief structured psychotherapy directed to adolescents and their parents or caregivers. It aims to repair attachment while promoting the autonomy of the adolescent. The treatment has five specific tasks; the focus of the family is shifted from “fixing” the individual to improving family relationships; an alliance is established with the individual; parental empathy for the individual is enhanced by exploring the parents' own stressors and history of attachment failure; the individual is encouraged to express previously unexpressed anger about core conflicts; and the individual is encouraged to make successful connections outside the home (e.g. at school, with peers, and at work).
Cognitive behavioural therapy (CBT) A brief structured treatment (20 sessions over 12–16 weeks) aimed at changing the dysfunctional beliefs and negative automatic thoughts that characterise depressive disorders. [43] Cognitive behavioural therapy requires a high level of training for the therapist, and has been adapted for children and adolescents suffering from depression. A course of treatment is characterised by 8–12 weekly sessions, in which the therapist and the child collaborate to solve current difficulties. The treatment is structured and often directed by a manual. Treatment generally includes cognitive elements, such as the challenging of negative thoughts, and behavioural elements, such as structuring time to engage in pleasurable activity.
Guided self-help A self-administered intervention designed to treat depression, which makes use of a range of books, self-help manuals, or internet material, that is based on an evidence based intervention and is designed specifically for the purpose.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Sertraline plus CBT in adolescents New option categorised as Unknown effectiveness; we found one small RCT that found no significant difference between sertraline plus CBT and sertraline or CBT alone in rates of remission. [32]

Omega 3 polyunsaturated fatty acids New option categorised as Unknown effectiveness; we found no systematic review or RCTs on the effects of omega 3 polyunsaturated fatty acids on depression in children and adolescents.

CBT (for relapse prevention) in children and adolescents Two new comparisons added reported in one systematic review: group CBT versus standard care, and individual CBT versus non-directive supportive therapy. [13] The review found no significant difference in relapse rates between treatments in either comparison. Categorisation of "CBT (for relapse prevention) in children and adolescents" unchanged (Unlikely to be beneficial).

CBT (individual) in children and adolescents One longer-term follow-up report of an RCT in adolescents included in a systematic review added comparing CBT versus fluoxetine, and CBT plus fluoxetine versus CBT alone, which reports follow-up results at 36 weeks. [18] One RCT subsequent to the review added, comparing fluoxetine plus CBT versus CBT alone. [36] Categorisation of "CBT (individual) in children and adolescents with mild to moderate depression" unchanged (Unknown effectiveness).

Citalopram/escitalopram in children and adolescents Option title altered from "citalopram in children and adolescents" to "citalopral/escitalopram in children and adolescents" to clarify that data on escitalopram is also included in the option. One systematic review comparing both citalopram and escitalopram versus placebo added to the benefits and harms section. [15] It found no significant difference between citalopram and placebo or between escitalopram and placebo in response rates. [15] Data from one further systematic review added to the harms section to increase harms data reporting. [14] Existing categorisation unchanged, and "citalopram/escitalopram in children and adolescents" categorised as Unknown effectiveness.

Fluoxetine in children and adolescents Two systematic reviews added comparing fluoxetine versus placebo [15] [14] which included similar RCTs and found similar results to one systematic review already reported. One RCT added comparing fluoxetine versus nortriptyline [17] which found weak evidence that fluoxetine may improve symptoms of depression after 8 weeks compared with nortriptyline. One longer-term follow-up report of an RCT included in a systematic review added, comparing fluoxetine versus CBT in adolescents, which reported follow-up results up to 36 weeks. [18] One subsequent RCT to the review added comparing fluoxetine plus CBT versus fluoxetine alone. [30] Categorisation of "fluoxetine (improves remission rates and prevents relapse) in children and adolescents" unchanged (Beneficial).

Fluoxetine plus CBT in adolescents One RCT added; [40] harms data enhanced; RCT added is an analysis of the harms data from a large RCT. The RCT found lower numbers of treatment-emergent physical adverse effects for fluoxetine plus CBT compared with fluoxetine alone. One extended follow-up report of an RCT in adolescents included in a systematic review added which compares fluoxetine plus CBT versus fluoxetine alone and versus CBT alone, and reports outcomes up to 36 weeks. [18] Two subsequent RCTs to the review added, one comparing fluoxetine plus CBT versus fluoxetine alone, [30] and one comparing fluoxetine plus CBT versus CBT alone. [36] Categorisation of "fluoxetine plus CBT in adolescents" unchanged (Beneficial).

Paroxetine in children and adolescents Two systematic reviews added comparing paroxetine versus placebo which identify similar RCTs. [15] [14] Neither review found evidence of a consistent benefit with paroxetine compared with placebo. Categorisation of "paroxetine in children and adolescents" unchanged (Unlikely to be beneficial).

Sertraline in children and adolescents Two systematic reviews added comparing sertraline versus placebo, which identified the same two RCTs as an already reported systematic review. [14] [15] The two additional systematic reviews came to similar conclusions as the already reported review. One RCT comparing sertraline versus CBT added. [32] The RCT found weak evidence that sertraline is associated with a lower overall improvement in depression (primary outcome included response and remission), but there was no difference in the proportion of people depressed at end of assessment. Categorisation of "sertraline in children and adolescents" unchanged (Unlikely to be beneficial).

Family therapy in children and adolescents One RCT added comparing family therapy plus usual care versus usual care alone; [39] the RCT found a trend towards improvement in symptoms of depression for those receiving usual care plus family psychoeducation compared with those receiving usual care, but the difference did not reach statistical significance. Categorisation of "family therapy in children and adolescents" changed from Unlikely to be beneficial to Unknown effectiveness.

Interpersonal therapy in adolescents Existing evidence re-evaluated and categorisation for "interpersonal therapy (in adolescents with mild to moderate depression)" changed from Beneficial to Likely to be beneficial.

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TABLE 1 **Summary of outcome measures commonly used in trials of treatments for depression in children and adolescents (see text).**

Outcome measure	Description	Scoring system
Children's Depression Rating Scale (Revised)	Semi-structured interview with child, supplemented with information from parents or significant others; assesses 17 symptoms, including those that serve as DSM criteria for depressive disorders; based on how the child has felt over previous 2 weeks. Can be used as a depression screening instrument, a confirmatory diagnostic tool, and a measure of treatment response in children. Good interrater (0.74–0.96) and test–retest (0.80–0.96) reliability, sound internal consistency (0.70), insensitive to age of child.	Items scored on a scale of 1 (least difficulties) to 5 or 7 (greatest difficulties). The summary score (range 17–113) is then transformed into a t score. Scores below 55 are unlikely to be associated with depressive disorder, scores 55–64 indicate possible risk, and scores above 65 are likely to be associated with depressive disorder.
Children's Depression Inventory	Self-report questionnaire (administrator may read aloud while child fills in) consisting of 27 items. For each item, the child chooses one of three statements describing how they have felt over the previous 2 weeks. Covers most DSM criteria for depressive disorder. Can be used as a depression screening instrument, a confirmatory diagnostic tool, and a measure of treatment response in children. Variable test–retest reliability (0.38–0.87) but sound internal consistency (0.59–0.88).	Items scored on a scale of 0 (least difficulties) to 2 (greatest difficulties). An aggregate score (range 0–54) of 11 or greater is associated with depressive disorder (sensitivity 0.67, specificity 0.60). Items load onto five factors: dysphoric mood, acting out, loss of personal and social interest, self-depreciation, and vegetative symptoms.
Hamilton Rating Scale for Depression (Revised)	Designed to assess adult depressive symptomatology but has been widely used with adolescent populations. Clinician rating based on interview with person and a sef-report problem inventory. Can be used as a depression screening instrument, a confirmatory diagnostic tool, and a measure of treatment response. Excellent interrater reliability (0.90+), and moderate to good internal consistency (0.45–0.90).	Items are scored on a 3–5 point scale of 0 (absent) to 2 or 4 (clearly present/severe). An aggregate score (range 0–64) of 11 is regarded as indicative of a diagnosis of depression.
Children's Depression Inventory for Parents	Modified version of the Child Depression Inventory completed by parents, which describes the child over the previous 2 weeks. May be used as a confirmatory diagnostic tool and is sensitive to treatment response. Moderate test–retest reliability (0.54–0.75), sound internal consistency (0.82–0.85). Generally moderate to good mother–father total score correlation (0.54–0.64), but variable parent–child correlation (0.03–0.74).	Items scored on a scale of 0 (least difficulties) to 2 (greatest difficulties). An aggregate score (range 0–54) of 12 or greater is associated with depressive disorder but does not discriminate well between depression and presentations of other psychiatric conditions (sensitivity 0.87; specificity 0.24).
Kiddie-Schedule for Affective Disorders and Schizophrenia (Kiddie-SADS)	Semi-structured diagnostic interview for children and adolescents, completed with child and parents. Covers most childhood disorders. Current and lifetime assessment versions available. Used in research trials as a standard method of diagnostic assessment. Good interrater reliability (0.86–0.89) and moderate to good test–retest reliability of individual items (0.41–0.81), and for categorical depression diagnosis (0.54). Moderate internal consistency of depression items (0.60–0.84)	Items are scored on a 2 or 3 point scale (not present, subthreshold, threshold). Some versions include a 0–6 point scale to assess severity (not at all/normal to extreme).
Clinical Global Impressions Scale	Clinician ratings to assess overall severity of symptoms in reference to baseline functioning. Interrater reliability high when clinicians are trained, and it has moderate to good test–retest reliability.	Consists of three global measures which include severity of illness (scale 1–7; “normal” to “extremely ill”); global improvement (scale 1–7; “very much improved” to “very much worse”); and the efficacy index (scale 1–4; compares improvement in symptoms to adverse effects, from “none” to “outweighs therapeutic effect”). Higher scores indicate greater symptomatology and impairment; or not much change from baseline (before treatment).
Depression Checklist Scores	Includes 10 major symptoms of depression, as used by DSM III, and as appropriate for children. Each symptom category is anchored by characteristic behaviours of that symptom. The symptom category is checked as positive if any of the presentations are evident. Has been used as a confirmatory diagnostic tool and a measure of treatment response. No information available regarding reliability or consistency.	Total scores (range 0–10) reflect the number of depressive symptoms evident. Follows a DSM approach to diagnosis: if a child has enough symptoms reaching threshold for a period of 1 month, and these represent a change from usual behaviour, then the child can be given a diagnosis of depression.
Longitudinal Interval Follow-up Evaluation Interview for DSM-III-R	Clinician-rated semistructured interview with patient, which assesses the longitudinal course of mental illness. Excellent interrater reliability for the psychiatric symptom ratings and the global assessment scores (0.90).	Sections are rated on various scales that range from 1 and have variable end points. Low scores indicate no symptomatology/high functioning, and high scores indicate severe symptomatology/diagnostic criteria met/low functioning.

Outcome measure	Description	Scoring system
Children's Global Assessment Scale	Clinician rating of the subject's most impaired level of functioning over the previous month on a hypothetical continuum of health illness, irrespective of treatment or prognosis. Test–retest reliability is high, making the instrument a good measure of change over time. Interrater reliability is only modest.	A single score is made in the range 100–1, with 0 indicating inadequate information. A score in the range 100–91 indicates superior functioning, 90–81 good functioning in all areas, 80–71 no more than slight impairment, 70–61 difficulties in a single area, 60–51 variable functioning with sporadic difficulties in several areas, 50–41 moderate degree of impairment in most or severe impairment in one area of functioning, 40–31 major impairment in functioning in several areas or unable to function in one, 30–21 unable to function in most areas, 20–11 needs considerable supervision to prevent harm to self or others, 10–1 needs constant supervision because of severely aggressive or self-destructive behaviour, or other disorder. The use of intermediary levels (e.g. 35, 58, 62) is encouraged to reflect finer grading of impairment.
Global Assessment of Functioning Scale	Clinician rating of psychological, social, and occupational functioning on a hypothetical continuum of health illness. Does not include impairment in functioning due to physical or environmental limitations. Psychometric data on children and adolescents are limited for this instrument.	A singe score is made in the range 100–1, with 0 indicating inadequate information. The scoring ranges are similar to those for the Children's Global Assessment Scale.

DSM, diagnostic and statistical manual

TABLE GRADE evaluation of interventions for depression in children and adolescents

Important outcomes			Symptom improvement, functional status, adverse effects						
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of pharmacological treatments for depression in children and adolescents?									
3 (536) [13] [14] [15] [16]	Symptom improvement	Fluoxetine *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for unclear clinical importance of some outcomes
2 (286) [13]	Functional status	Fluoxetine *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (40) [17]	Symptom improvement	Fluoxetine *v* other antidepressant	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for uncertainty about method of randomisation. Directness point deducted for uncertainty about generalisability of results
1 (220) [13] [18]	Symptom improvement	Fluoxetine *v* CBT	4	−1	0	0	0	Moderate	Quality point deducted for low follow-up
2 (422) [15]	Symptom improvement	Citalopram *v* placebo	4	0	0	−1	0	Moderate	Directness point deducted for narrow range of outcomes reported
1 (268) [15]	Symptom improvement	Escitalopram *v* placebo	4	0	0	−1	0	Moderate	Directness point deducted for narrow range of outcomes reported
2 (164) [13]	Symptom improvement	Mirtazapine *v* placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (20) [31]	Symptom improvement	MAOIs *v* placebo	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of comorbid conditions
3 (670) [15] [14]	Symptom improvement	Paroxetine *v* placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results for response depending on measure used
3 (658) [13] [14]	Adverse effects	Paroxetine *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (309) [13]	Symptom improvement	Paroxetine *v* tricyclic antidepressants	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for narrow range of comparators
2 (376) [13] [15] [14]	Symptom improvement	Sertraline *v* placebo	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results for depressive symptoms
Not clear (not clear) [13]	Functional status	Sertraline *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (73) [32]	Symptom improvement	Sertraline *v* CBT	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for different results at different end points.
6 (3521) [13]	Symptom improvement	Tricyclic antidepressants *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes			Symptom improvement, functional status, adverse effects						
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
5 (170) [13]	Functional status	Tricyclic antidepressants *v* placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (367) [13]	Symptom improvement	Venlafaxine *v* placebo	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for narrow range of comparators
2 (361) [13]	Adverse effects	Venlafaxine *v* placebo	4	−2	0	−1	+2	Moderate	Quality point deducted for incomplete reporting of results and unclear outcome assessment. Directness point deducted for narrow range of outcomes reported. Effect-size points added for RR above 5
What are the effects of psychological treatments for depression in children and adolescents?									
6 (at least 94) [13]	Symptom improvement	Interpersonal therapy *v* waiting list control (in adolescents)	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for subjective outcome measure
1 (63) [13]	Symptom improvement	Interpersonal therapy *v* standard care	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (63) [13]	Functional status	Interpersonal therapy *v* standard care	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 4 (at least 217) [13]	Symptom improvement	Group CBT *v* waiting list control	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness point deducted for different results for different outcome measures (remission) and combined comparison groups
2 (149) [13]	Functional status	Group CBT *v* waiting list control	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (223) [13]	Symptom improvement	Group CBT *v* placebo medication and clinical management	4	−2	0	0	0	Low	Quality point deducted for incomplete reporting of results and for unclear comparator
1 (39) [13]	Symptom improvement	Individual CBT *v* waiting list control	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for narrow range of comparators
1 (223) [13]	Symptom improvement	Individual CBT *v* placebo medication and clinical management	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for unclear comparison group
1 (48) [13]	Symptom improvement	Individual CBT *v* interpersonal therapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and unclear treatment duration
1 (72) [13]	Symptom improvement	Individual CBT *v* family therapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and unclear treatment duration
4 (256) [13]	Symptom improvement	Individual CBT *v* non-directive supportive therapy	4	−1	0	−1	0	Low	Quality point deducted for unclear treatment duration. Directness points deducted for inconsistent results for different outcomes
1 (26) [37]	Symptom improvement	Group therapeutic support *v* group social skills training	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

Important outcomes			Symptom improvement, functional status, adverse effects						
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (20) [38]	Symptom improvement	Psychodynamic psychotherapy *v* waiting list control	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results and for quasi-randomisation. Directness point deducted for narrow range of comparators
1 (81) [13]	Symptom improvement	Group CBT *v* standard care	4	−2	0	0	0	Low	Quality points deducted for sparse data and unclear comparator
1 (56) [13]	Symptom improvement	Individual CBT *v* non-directive supportive therapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting (results/included population)
2 (69) [13]	Symptom improvement	Booster CBT *v* assessment only	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting (results/included population)
1 (32) [13]	Symptom improvement	Family therapy *v* waiting list control	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for different results for different timeframes and different outcomes (clinician rated or self-reported)
1 (70) [13]	Symptom improvement	Family therapy *v* non-specific supportive therapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and unclear treatment duration
1 (72) [13]	Symptom improvement	Family therapy *v* individual psychodynamic pyschotherapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and unclear treatment duration
1 (72) [13]	Functional status	Family therapy *v* individual psychodynamic pyschotherapy	4	−3	0	0	0	Very low	Quality points deducted for sparse data, unclear treatment duration, and incomplete reporting of results
1 (70) [13]	Symptom improvement	Family therapy *v* non-directive supportive therapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and unclear treatment duration
1 (31) [39]	Symptom improvement	Family therapy plus usual care *v* usual care alone	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow range of comparators
What are the effects of combination treatments for depression in children and adolescents?									
1 (219) [13]	Symptom improvement	Fluoxetine plus CBT *v* placebo (in adolescents)	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (424) [30] [18] [13]	Symptom improvement	Fluoxetine plus CBT *v* fluoxetine alone (in adolescents)	4	−2	−1	0	0	Very low	Quality points deducted for incomplete reporting of results and low follow-up. Consistency point deducted for conflicting results between RCTs
2 (344) [18] [13] [36]	Symptom improvement	Fluoxetine plus CBT *v* CBT alone (in adolescents)	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and low follow-up. Directness point deducted for inclusion of comorbid disorders
1 (73) [32]	Symptom improvement	Sertraline plus CBT *v* sertraline alone (in adolescents)	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for composite outcome
1 (73) [32]	Symptom improvement	Sertraline plus CBT *v* CBT alone (in adolescents)	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for composite outcome
What are the effects of complementary treatments for depression in children and adolescents?									
No studies found									

Important outcomes			Symptom improvement, functional status, adverse effects						
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for refractory depression in children and adolescents?									
1 (30) [42]	Symptom improvement	Lithium *v* placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

Type of evidence: 4 = RCT
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio