

Depression in children and young people

Evidence Update June 2013

A summary of selected new evidence relevant to NICE clinical guideline 28 'Depression in children and young people: identification and management in primary, community and secondary care' (2005)

Evidence Update 42



Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NICE Evidence Services topic page for [depression](#).

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Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

- [Depression in children and young people](#). NICE clinical guideline 28 (2005).

A search was conducted for new evidence from 17 August 2010 to 14 January 2013. A total of 3164 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 8 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An [Evidence Update Advisory Group](#), comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Feedback







If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

Key point	Potential impact on guidance	
	Yes	No
Care of all children and young people with depression <ul style="list-style-type: none"> Limited evidence suggests that a range of factors (for example, gender, level of oppositionality, history of physical abuse) and family contextual issues (for example, parental marital discord) may moderate the effects of treatment. A modular approach to delivery of therapy may be a promising way to provide evidence-based treatments with the flexibility required for management of young people with multiple mental health problems. 		 
Step 3: Mild depression <ul style="list-style-type: none"> A group cognitive behaviour therapy (CBT) programme for preventing depression, delivered universally in a school setting, may not reduce symptoms of depression in young people at high risk of depression, and could increase reporting of symptoms. Computerised CBT may be a valid treatment option for young people with mild depression. 	 	
Steps 4 and 5: Moderate to severe depression <ul style="list-style-type: none"> Combining CBT and newer antidepressants may bring some limited benefits in the short term over either therapy alone, particularly with regard to global functioning. When medication is used for children and young people, fluoxetine is the antidepressant of choice, because it is the only antidepressant licensed for this use. There remains little evidence to inform views on the relative value of other antidepressants. 		

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods. For further details of this evidence in the context of current guidance, please see the full commentary.

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the ‘key references’ (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

1.1 Care of all children and young people with depression

Impact on treatment response of parental marital discord, abuse and other factors

NICE clinical guideline 28 ([NICE CG28](#)) recommends that when a child or young person has been diagnosed with depression, consideration should be given to the possibility of parental depression, parental substance misuse, or other mental health problems and associated problems of living, as these may have a negative impact on the success of treatment.

[Amaya et al. \(2011\)](#) reported a subgroup analysis of a randomised controlled trial (RCT), the ‘Treatment for Adolescents with Depression Study’ (TADS), to assess the impact of parental marital discord on treatment response. It is not clear if this was a pre-specified or post-hoc analysis. In the original trial, 439 young people (age 12–17 years) meeting diagnostic criteria for major depression were included. Participants were randomly assigned to treatment with fluoxetine¹ alone, cognitive behaviour therapy (CBT) alone, both fluoxetine and CBT (combination), or placebo tablets. The trial was double-blind (participant and evaluator) for the fluoxetine-only and placebo groups, and single-blind (evaluator only) for the CBT-only and CBT plus fluoxetine groups.

The present subgroup analysis examined young people (n=260, 47% female) from households with 2 parents, and included 60 participants treated with fluoxetine alone, 67 with CBT, 67 with combination therapy and 66 with placebo. Parents completed the Dyadic Adjustment Scale to measure the quality of the couple’s relationship; the score on this scale was used to define groups of low and high marital discord. Parents also completed the Conners’ Parent Rating Scale–Revised Short Version to assess the extent of young people’s oppositionality (that is, externalising behaviour); the score on this scale was used to define groups of low and high oppositionality. Independent evaluators used the Clinical Global Impressions–Improvement (CGI-I) scale to assess change in young people’s depression relative to baseline after 12 weeks of treatment, with the last observation carried forward if data were missing. Treatment response was defined as a CGI-I rating of ‘very much improved’ or ‘much improved’. Non-response was defined as a rating of ‘minimally improved’, ‘no change’, or ‘worse’. Logistic regression was used to assess the impact on treatment response of parental marital discord, and gender and oppositionality at baseline of young people, and interactions between these factors.

¹ Since publication of NICE CG28, fluoxetine has been licensed for use in children and young people aged 8 years and older to treat moderate to severe major depression that is unresponsive to psychological therapy after 4–6 sessions, only in combination with a concurrent psychological therapy. See notes at the beginning of section 1.6 on the use of antidepressants in children and young people.

In families with low parental marital discord (52 males and 66 females):

- There was a significantly greater response to combination treatment (fluoxetine plus CBT) compared with placebo in both males (71.4% versus 26.3%, $p=0.01$) and females (72.2% versus 35.7%, $p=0.04$).
- Males showed no significant response to treatment with either CBT alone or fluoxetine alone, compared to placebo.
- Females had a particularly poor response to CBT alone (20%); significantly lower than the response seen with combination treatment ($p=0.005$) or fluoxetine alone (57.9%, $p=0.03$), or CBT alone in females from families with high parental marital discord (60%, $p=0.02$).
- Young people with depression and high oppositionality showed a significantly greater response to combination treatment (94.1%) compared with fluoxetine alone (56.3%, $p=0.03$) or placebo (42.1%, $p=0.006$). There was a particularly poor response to CBT alone (20%); significantly lower than the response seen with combination treatment ($p=0.0006$) or fluoxetine alone ($p=0.05$).

In families with high parental marital discord (69 males and 73 females):

- Males showed a significantly greater response to combination therapy than placebo (84.6% versus 21.4%, $p=0.003$), and to fluoxetine alone than placebo (58.8% versus 21.4%, $p=0.04$).
- Females also showed a significantly greater response to combination therapy than placebo (72.7% versus 36.8%, $p=0.02$) and to fluoxetine alone than placebo (83.3% versus 36.8%, $p=0.02$). CBT alone resulted in no significantly improved response versus placebo in either males or females.
- Young people with depression and high oppositionality showed a significantly improved response to treatments that included fluoxetine (combination treatment 73.7% versus placebo 17.6%, $p=0.002$; fluoxetine alone 79.2% versus CBT 45%, $p=0.02$; fluoxetine versus placebo $p=0.0004$). CBT alone did not significantly improve response compared with placebo.

The chief limitations of the study were that the numbers in each subgroup were small (because of sub-divisions into 4 treatment groups, then further division by parental marital harmony, gender, and oppositionality), so this secondary analysis may not have been powered for these subanalyses. The authors therefore stated that results should be considered exploratory. Furthermore, treatment was for a short duration. An additional limitation may have been the scale used to assess parental conflict, as although this captures some dimensions of marital relationships, other areas not assessed (for example, frequency and level of verbal or physical hostility) may better predict responses. Finally, TADS included non-clinical referrals of young people so may be comparable to UK primary care cases, but not necessarily those referred to Child and Adolescent Mental Health Services.

Within its limitations, the analysis suggests that young people with depression in families with high levels of parental marital discord may benefit from treatments that include medication (fluoxetine alone or combined with CBT). In contrast, in families with low parental marital discord, treatment of young people with depression with fluoxetine alone or CBT alone was no more effective than placebo.

[Shamseddeen et al. \(2011\)](#) reported a post-hoc analysis of data from the 'Treatment of Resistant Depression in Adolescents' (TORDIA) study. TORDIA included 334 young people with clinically significant depression that had not responded to at least 4 weeks of treatment with fluoxetine 20 mg or equivalent selective serotonin reuptake inhibitor (SSRI), with the final 4 weeks at a dosage equivalent to 40mg of fluoxetine, unless this dose could not be tolerated.

Reasons for exclusion included: previous treatment with 7 or more sessions of CBT; a history of completing 2 or more prior adequate SSRI trials or non-response to venlafaxine²; diagnoses of bipolar spectrum disorder, psychosis, autism, eating disorders, substance misuse or dependence; and not living with the primary caregiver. Participants were randomised to 1 of 4 treatment groups: monotherapy with a different SSRI from that previously used (citalopram, fluoxetine or paroxetine²); monotherapy with venlafaxine; combination therapy with SSRI and CBT; or combination therapy with venlafaxine and CBT. CBT consisted of 12 weekly sessions, 3–6 of which were family sessions. An adequate response to treatment was defined as a CGI-I score of ≤ 2 and a 50% reduction in score on the Child Depression Rating Scale–Revised (CDRS-R). A history of physical abuse was reported by 43 (13.1%) participants, and 55 (16.9%) had a history of sexual abuse; of these, 17 participants (5.2%) were both physically and sexually abused. Logistical regression was used to assess the impact of physical and sexual abuse on the response to treatment.

Among participants with no history of abuse, the response to treatment was significantly higher with combination therapy (62.8%) than medication alone (37.6%; odds ratio [OR]=2.8, 95% confidence interval [CI] 1.6 to 4.7, $p < 0.001$). In young people with a history of sexual abuse, the response to combination treatment (42.3%) and medication alone (48.3%) were similar (OR=0.8, 95% CI 0.3 to 2.3, $p = 0.66$). Sexual abuse alone had no significant moderating effect on treatment response. Young people with a history of physical abuse showed significantly lower response to combination treatment (18.2%) than medication alone (52.4%; OR=0.2, 95% CI 0.1 to 0.8, $p = 0.02$). Excluding those with a history of both physical and sexual abuse, physical abuse alone was found to moderate response to treatment with combination therapy relative to those without a history of such abuse ($p = 0.001$) whereas for those with a history of sexual abuse, there was no significant effect ($p = 0.18$). Young people with a history of physical abuse were less likely to have an adequate response to combined treatment compared with non-physically abused participants (OR=0.08; 95% CI 0.02 to 0.36), even after controlling for demographic and baseline characteristics.

TORDIA was not designed to examine treatment for young people with depression with a history of abuse, so the number of such participants ($n = 81$) was small relative to the total population in the study. Furthermore, details about the abuse and other traumatic or stressful life events were not collected. Young people not living with a primary caregiver were excluded so the results may not be generalised to children with active protective services involvement. Within the limitations of a post-hoc analysis, the results suggest that physical abuse may reduce responsiveness to depression-focused CBT in young people with depression.

Taken together, and within the limitations indicated, findings from these studies suggest that a range of individual characteristics and family contextual issues may moderate the effects of treatment, consistent with [NICE CG28](#) guidance.

Key references

Amaya MM, Reinecke MA, Silva SG et al. (2011) [Parental marital discord and treatment response in depressed adolescents](#). *Journal of Abnormal Child Psychology* 39: 401–11

Shamseddeen W, Asarnow JR, Clarke G et al. (2011) [Impact of physical and sexual abuse on treatment response in the Treatment of Resistant Depression in Adolescent Study \(TORDIA\)](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 50: 293–301

² NICE CG28 states that venlafaxine and paroxetine should not be used for the treatment of depression in children and young people. At the time of publication of this Evidence Update, venlafaxine, paroxetine and citalopram did not have UK marketing authorisation for use in depression in children and young people under the age of 18 years, and it is stated by their summary of product characteristics that they are not recommended, or should not be used, for this indication. See notes at the beginning of section 1.6 on the use of antidepressants in children and young people.

Modular approach to psychotherapeutic interventions

[NICE CG28](#) recommends that comorbid diagnoses and developmental, social and educational problems should be assessed and managed, either in sequence or in parallel, with the treatment for depression.

[Weisz et al. \(2012\)](#) reported an RCT involving 10 US outpatient clinical centres to assess standard treatment versus the 'Modular Approach to Therapy for Children with Anxiety, Depression or Conduct Problems' (MATCH). MATCH was designed to address the need for flexibility when managing children with multiple problems and shifting treatment needs (distinct from separate evidence-based treatments for depression, anxiety and conduct problems in young people, which are usually based on a predetermined sequence of prescribed sessions). It comprises a menu of free-standing modules to treat anxiety (CBT), depression (CBT) and disruptive conduct (Behavioural Parent Training). Healthcare professionals can then select the appropriate therapy to meet individual needs.

The 84 participating community clinicians were randomly assigned to 1 of 3 strategies: MATCH, standard treatment (that is, 3 established treatments for anxiety, depression and conduct problems), or usual care. Participants (n=174) included in the study were representative of the clinical, social and ethnic diversity seen at the clinics. Age ranged from 7–13 years, 70% were male, 45% were white, 53% lived in single-parent households and diagnoses included mood disorder (44%), anxiety disorder (57%), conduct disorder (66%) and attention deficit hyperactivity disorder (58%). Standardised diagnostic assessment was conducted before and after treatment. Outcomes were assessed weekly using the Top Problems Assessment that measures the severity of problems identified by children and parents as most important, and the Brief Problem Checklist that measures internalising, externalising and total problems. Mixed effects regression analyses were used to identify the trajectories of change, reported as coefficient estimates by time (measured in log days).

Young people receiving modular treatment showed significantly faster improvement in outcomes than both usual care (Brief Problems estimate -0.346 , $p=0.004$, effect size 0.59; Top Problems estimate -0.226 , $p=0.003$, effect size 0.62) and standard care (Brief Problems estimate -0.416 , $p=0.001$, effect size 0.71; Top Problems estimate -0.183 , $p=0.014$, effect size 0.50). There was no significant difference in rate of improvement in young people receiving usual and standard care. After treatment, the mean number of diagnoses (that is, any diagnosis from the Diagnostic and Statistical Manual of Mental Disorders IV) was significantly fewer among young people receiving modular treatment (1.23) than those given usual care (1.86; $p=0.01$). There was no significant difference in mean number of diagnoses with standard versus modular care ($p=0.27$), or usual versus standard care ($p=0.16$).

Limitations of the study included the sample size, which imposed constraints on the level of analysis. The authors concluded that the modular approach may be a promising way to build on the strengths of evidence-based treatments, which is consistent with the current recommendations of [NICE CG28](#). However, if the findings are supported in studies in a European or UK setting, the resource and client implications arising from the more rapid response with a modular approach may have an impact on service design.

Key reference

Weisz JR, Chorpita BF, Palinkas LA et al. (2012) [Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth](#). *Archives of General Psychiatry* 69: 274–82

1.2 [Stepped care](#)

No new key evidence was found for this section.

1.3 [Step 1: Detection, risk profiling and referral](#)

No new key evidence was found for this section.

1.4 [Step 2: Recognition](#)

No new key evidence was found for this section.

1.5 [Step 3: Mild depression](#)

Classroom-based CBT in young people at high risk of depression

[NICE CG28](#) recommends that after up to 4 weeks of watchful waiting, children and young people with mild depression should be offered a course of non-directive supportive therapy, group CBT or guided self-help. It is recommended that these interventions are delivered by appropriately trained professionals in tier 1 (which includes teachers and primary care services). However, the guideline does not currently specify, or advise against, any particular types of group CBT for young people with mild depression.

[Stallard et al. \(2012\)](#) conducted a pragmatic cluster RCT to assess reduction in depressive symptoms following a classroom-based CBT depression prevention programme in young people at high risk of depression. Of 66 mixed sex, urban and rural comprehensive schools in the UK invited to join the study, 8 agreed to participate. A total of 5030 young people aged 12–16 years were recruited to the study (91.4% of the 5503 eligible students at participating schools). Depressive symptoms were assessed using the Short Mood and Feelings Questionnaire, which was completed by all participants at screening and 2 weeks later (baseline). Those scoring ≥ 5 on both occasions were considered at high risk of depression ($n=1064$, 21.2%).

Year groups in each participating school were randomised to 1 of 3 interventions that were delivered during personal, social and health education (PSHE) lessons. Classroom-based CBT (the resourceful adolescent programme used successfully in Australia and New Zealand) was delivered by 2 trained facilitators working alongside the class teacher. Attention control consisted of the class teacher delivering the usual school provision for PSHE lessons alongside 2 facilitators not involved in delivering CBT. A final group received usual school provision, where the class teacher delivered PSHE lessons without assistance.

After 12 months, the Short Mood and Feelings Questionnaire score was assessed, with data available for 846 (79.5%) of those initially identified at high risk of depression. The adjusted mean scores on the questionnaire showed no significant difference from baseline between classroom-based CBT and attention control (-0.63 , 95% CI -1.85 to 0.58 , $p=0.41$) or usual school provision (0.97 , -0.20 to 2.15 , $p=0.12$). It was not possible to rule out a potential small clinical harm from classroom-based CBT compared with usual school provision. A further analysis of attendance at allocated lessons suggested that those in the classroom-based cognitive behavioural therapy group had a higher mean Short Mood and Feelings Questionnaire score at 12 months (that is, more symptoms of low mood) compared with usual school provision (adjusted difference= 1.43 , 95% CI 1.22 to 1.64 , $p<0.001$).

Limitations included the reliance on self-report of symptoms, which could have failed to capture important changes in the diagnostic status. Additionally, although delivering group CBT to all children (versus targeted therapy) might be perceived as being easier to implement, those with more symptoms may have found it difficult to engage fully in a programme dominated by peers with fewer symptoms. Finally, the study related to a depression prevention programme, but the authors did not appear to test prevention of depression, instead measuring its effect on the pooled, average, depression symptom score of classes of young people.

The evidence suggests that a group CBT programme for preventing depression, delivered universally in a school setting, may not reduce symptoms of depression in young people at high risk of depression, and could increase reporting of symptoms. The study authors therefore suggest that this approach is not pursued without further research and evaluation.

[NICE CG28](#) does not currently recommend, or advise against, any specific types of group CBT for young people with mild depression. However these data suggest that there may be potential harms associated with universal group CBT provision in schools. This evidence may, therefore, have a potential impact on [NICE CG28](#), although the details of any impact are outside the scope the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

Key reference

Stallard P, Sayal K, Phillips R et al. (2012) [Classroom based cognitive behavioural therapy in reducing symptoms of depression in high risk adolescents: pragmatic cluster randomised controlled trial](#). *British Medical Journal* 345: e6058

Computerised CBT for young people with depressive symptoms

The interventions recommended by [NICE CG28](#) for mild depression do not include computer-based therapies, although a [research recommendation](#) was made on computerised CBT.

Among trials conducted on computerised CBT since publication of [NICE CG28](#) is a study by [Merry et al. \(2012\)](#). This non-inferiority study compared the effectiveness of SPARX (Smart, Positive, Active, Realistic, X-factor thoughts) with usual care for young people seeking help for depressive symptoms. SPARX is an interactive fantasy game designed to deliver CBT for the treatment of clinically significant depression. The study was conducted in 24 primary healthcare sites in New Zealand. It included 187 participants (aged 12–19 years), who were not at major risk of self-harm and were deemed by their primary healthcare clinician to need treatment. Participants were randomised to SPARX (n=94) or usual care (n=93). Care was taken to ensure allocation concealment. Data on the nature of usual care were available for 83 (89%) participants: it primarily consisted of counselling (89.2%), with 85.5% of sessions lasting at least 30 minutes.

The primary outcome measure was rating on the CDRS-R, which has a range of 17–113. Non-inferiority was defined as not worse than 5.5 units inferior change on the CDRS-R. Assessment was conducted by researchers who were blind to the treatment allocation. A total of 170 participants (91%) were assessed after the intervention and 168 (90%) at the 3-month follow-up. Of the 94 young people allocated to SPARX, 80 returned questionnaires reporting the number of modules completed; 69 (86%) completed at least 4 of the 7 SPARX modules.

SPARX was not inferior to usual care in the primary, per protocol analysis (participants completing at least 4 of the SPARX modules), as shown by the difference in mean reduction in CDRS-R score (2.73, 95% CI -0.31 to 5.77, p=0.079). Similar findings for SPARX versus usual care were reported in the intention-to-treat population (1.60, 95% CI -1.21 to 4.41, p=0.264). There was also no significant difference in the rate of response to treatment (defined as a 30% decrease in symptoms on the CDRS-R) with SPARX and usual care in the primary analysis (66.2% versus 58.3%; difference=7.9%, 95% CI -7.9 to 24%, p=0.332). However, there was a significantly higher remission rate (score less than 30 on the CDRS-R) with SPARX than usual care (43.7% versus 26.4%; difference=17.3%, 95% CI 1.6 to 31.8%, p=0.03).

Limitations included missing data on adherence to treatment in the usual care group (not all clinicians supplied complete records to the study), and that some young people expressed dislike of computers. Nevertheless, as exemplified by this study, computerised CBT may be a valid treatment option for young people with mild depression. Consequently, this study (and

others published prior to the search period for this Evidence Update) may have a potential impact on [NICE CG28](#), although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

Key reference

Merry SN, Stasiak K, Shepherd M et al. (2012) [The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: a randomised controlled non-inferiority trial](#). *British Medical Journal* 344: e2598

1.6 Steps 4 and 5: Moderate to severe depression

Prescribing antidepressants for children and young people

At the time [NICE CG28](#) was published, there were no antidepressant treatments licensed in the UK for use in children or young people. Since publication of the guideline, fluoxetine has been licensed for use in children and young people aged 8 years and older to treat moderate to severe major depression that is unresponsive to psychological therapy after 4–6 sessions, only in combination with a concurrent psychological therapy.

[NICE CG28](#) notes that unlicensed medicines may be legally prescribed where there are no suitable alternatives and where the use is justified by a responsible body of professional opinion ([Royal College of Paediatrics and Child Health, 2010](#)). Prescribers should refer to the [summary of product characteristics](#) for full and up-to-date details of licensing. Informed consent should be obtained and documented for the use of any drug outside the licensed indications, in line with the [guidance from the General Medical Council](#).

[NICE CG28](#) also notes particular cautions when considering the use of antidepressants for children and young people. In particular the Committee on Human Medicinal Products (CHMP) of the European Medicines Agency has advised that SSRIs and serotonin noradrenaline reuptake inhibitors (SNRIs) should not be used in children and adolescents except within their approved indications – not usually depression – because of the risk of suicide-related behaviour and hostility. This advice is reflected in summaries of product characteristics. However, the CHMP also made it clear that doctors may make decisions based on the individual clinical needs of a child or a young person to use these products for the treatment of depression or anxiety. The Committee on Safety of Medicines had previously advised that child and adolescent psychiatrists are able to prescribe SSRIs other than fluoxetine in certain circumstances; for example, where drug treatment is indicated but a person cannot tolerate fluoxetine. When SSRIs or SNRIs are prescribed, the CHMP recommended that patients should be monitored carefully for the appearance of suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment. Further advice is given in section 1.6.4 of [NICE CG28](#).

Treatment with psychological or antidepressant therapy, alone or in combination

[NICE CG28](#) recommends that children and young people with moderate to severe depression should be assessed by healthcare professionals in Child and Adolescent Mental Health Services and offered, as a first-line treatment, a specific psychological therapy (individual CBT, interpersonal therapy or shorter-term family therapy) of at least 3 months duration. If there is no response after 4 to 6 sessions, the child or young person should be reviewed by a multidisciplinary team and considered for alternative or additional psychological therapy or combined psychological therapy and fluoxetine (cautiously in younger children). [NICE CG28](#) also advises that antidepressant medication should not be offered to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy.

A Cochrane review by [Cox et al. \(2012\)](#) evaluated the use of psychological therapies compared with antidepressant medication, alone and in combination, for the treatment of depression in children and young people. RCTs included in the review involved participants aged 6–18 years with a diagnosis of major depressive disorder using standardised criteria. A total of 10 RCTs (n=1235) were included in the review. Primary outcomes assessed in the review were remission of depressive disorder, acceptability of treatment as measured by dropouts, and suicide-related serious adverse outcomes.

Psychological therapies were compared with antidepressant medication in 2 studies (n=220). There was limited evidence that antidepressant medication was more effective than psychotherapy on clinician-defined remission post-intervention (OR=0.52, 95% CI 0.27 to 0.98), but not on other measures of remission. Significantly fewer participants experienced suicidal ideation in the group receiving psychological therapy than with medication, both post-intervention (OR=0.26, 95% CI 0.09 to 0.72; 1 study) and after 6–9 months (OR=0.26, 95% CI 0.07 to 0.98; 1 study). Combined psychological therapy and antidepressant medication was compared with antidepressant medication alone in 4 studies (n=618). There were no significant differences in remission rates, dropouts or suicidal ideation, post-intervention or after 6–9 months. Combined psychological therapy and antidepressant medication was compared with psychological therapy alone in 2 studies (n=265). There were no significant differences in remission rates, dropouts or suicidal ideation, post-intervention or after 6–9 months. The 4 studies (n=249) comparing combination therapy with psychological therapy plus placebo targeted comorbid diagnoses rather than depression in isolation (with some trials including only participants with alcohol or other substance-use disorders). This comparison is therefore difficult to interpret and not relevant to [NICE CG28](#).

The authors concluded that the relative effectiveness of the therapies could not be established. The analysis was limited by the heterogeneity of the included studies in terms of comorbid conditions and severity of depression. Only 1 study (ADAPT) reported by [Goodyer et al. \(2008\)](#) was conducted in the UK, and 1 study used tricyclic antidepressants (which are not used in practice), limiting the relevance of the findings. Furthermore, the analysis did not include the TORDIA study as it contained a 'treatment resistant' population. This study was included in an earlier meta-analysis conducted by [Dubicka et al. \(2010\)](#), together with 4 other RCTs that compared newer-generation antidepressants alone and in combination with CBT in young people (n=1206). This meta-analysis found no evidence of a significant benefit of combined medication and CBT compared with antidepressants alone for depressive symptoms, suicidality and global improvement after acute treatment or at follow-up. There was a significant advantage of combined treatment after 12 weeks when assessed by the Child Global Assessment Schedule (CGAS, weighted mean difference [MD]=−2.32, 95% CI −3.91 to −0.74, p=0.004) but not when assessed with the Health of the Nation Outcome Scale in Children and Adolescents.

[Calati et al. \(2011\)](#) conducted a meta-analysis comparing 12 weeks of treatment with combined CBT and antidepressant medication with the same antidepressant alone. A total of 5 RCTs (n=1621) were included, comprising 4 studies of major depressive disorder (ADAPT, TADS, TORDIA and a study that was included in the Cochrane review by Cox et al. discussed above) and 1 study (n=488) of anxiety disorder. Outcomes were assessed using CGAS, CGI-I and CDRS-R.

Treatment with combination therapy was associated with significantly improved CGAS score (MD=−2.79, 95% CI −4.10 to −1.48, p<0.0001; 5 studies, n=1146); a sensitivity analysis of those with major depressive disorder only also showed a significant difference (p=0.002). Treatment with combination therapy was associated with significant improvement on the CGI-I scale (OR=0.59, 95% CI 0.36 to 0.98, p=0.04; 4 studies, n=1025); the sensitivity analysis of those with major depressive disorder only did not show a significant difference (p=0.08). No difference in depressive symptoms was found between combination therapy and

antidepressant alone using the CDRS-R scale (possible range 17–113, MD=0.94, 95% CI -1.56 to 3.43, p=0.46; 3 studies, n=749).

Although the meta-analysis was limited by the pooling of 4 studies on depression with 1 on anxiety, the sensitivity analyses conducted allowed effects in major depressive disorder to be considered separately. Other limitations include differences in the kinds and duration of CBT offered, differences in age range of subjects, and the measurement of outcomes after acute treatment (12 weeks) only.

Overall, these meta-analyses suggest that there may be little difference in efficacy between monotherapy with psychological or antidepressant treatment for moderate or severe depression in the populations of young people studied (although there was some evidence to suggest a greater effect with antidepressant monotherapy as measured by clinician-defined remission). There is an increased risk of suicidal ideation from antidepressant monotherapy compared with psychological treatment alone. Combining CBT with antidepressants may be beneficial with regard to some measures of global functioning, although benefits in other measures are less clear. Combining CBT with antidepressants has not been convincingly shown to mitigate the risk of suicidal ideation from antidepressants.

Evidence from these reviews may have a potential impact on [NICE CG28](#), although the details of any impact are outside the scope the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

Additional information about the meta-analysis by Calati et al. (2011) is also available in an independent [critical appraisal](#) report produced for the Centre for Reviews and Dissemination's Database of Abstracts of Reviews of Effects.

Key references

Calati R, Pedrini L, Alighieri S et al. (2011) [Is cognitive behavioural therapy an effective complement to antidepressants in adolescents? A meta-analysis](#). *Acta Neuropsychiatrica* 23: 263–71

Cox GR, Callahan P, Churchill R et al. (2012) [Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents](#). *Cochrane Database of Systematic Reviews* issue 11: CD008324

Supporting references

Centre for Reviews and Dissemination (2012) [Is cognitive behavioural therapy an effective complement to antidepressants in adolescents? A meta-analysis](#). *Database of Abstracts of Reviews of Effects*

Dubicka B, Elvins R, Roberts C et al. (2010) [Combined treatment with cognitive-behavioural therapy in adolescent depression: meta-analysis](#). *British Journal of Psychiatry* 197: 433–40

Goodyer IM, Dubicka B, Wilkinson P et al. (2008) [A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial](#). *Health Technology Assessment* 12: 14

Choice of antidepressant medication

[NICE CG28](#) recommends that when an antidepressant is prescribed to a child or young person with moderate to severe depression, it should be fluoxetine³ as this is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks. If treatment with fluoxetine is unsuccessful or is not tolerated because of side effects, consideration should be given to the use of another antidepressant. Sertraline or citalopram are the recommended second-line treatments⁴ (see notes at the beginning of section 1.6).

[NICE CG28](#) also states that paroxetine and venlafaxine should not be used for the treatment of depression in children and young people⁴.

A Cochrane review by [Hetrick et al. \(2012\)](#) evaluated newer generation antidepressants for depressive disorders in children and young people aged 6–18 years. A total of 19 placebo-controlled studies were included in the analysis, with the number of participants randomised to the treatment arms ranging from 23 to 367 (median 188). Studies included treatments that are licensed in the UK for use in children and young people (5 trials of fluoxetine) and not currently licensed for this age group (2 trials of sertraline, 2 trials of citalopram, 4 trials of paroxetine, 2 trials of venlafaxine, 2 trials of escitalopram⁴ and 2 trials of mirtazapine⁴). All but 3 of the studies excluded young people at high risk of suicide, and 10 trials excluded those who had not responded to previous antidepressant treatment. The primary efficacy outcome for the analysis was resolution of a depressive episode and the primary safety outcome was suicide completion. Secondary outcomes evaluated included depressive symptom severity (using the CDRS-R, possible range 17–113), remission or response to treatment, functioning (using the CGAS, possible range 1–100) and suicide-related outcomes. Remission was measured in a variety of ways both across and within trials. Most often it was defined by the trial authors as a level of improvement in depression symptoms on clinician-rated scales. The scale and the cut-point used to define this level of improvement varied between trials. The scale and cut-point used to define response was also variously defined between trials and usually, but not always, was of a smaller magnitude compared with remission. Suicide-related outcomes (such as suicide ideation) were also classified and reported in various ways in each of the trials.

No studies provided data that allowed assessment of the primary outcomes (efficacy or safety), but it was noted that no completed suicides were reported in any of the trials. Compared with placebo, treatment with antidepressant significantly improved depressive symptoms as measured by CDRS-R (MD=-3.51, 95% CI -4.55 to -2.47, $p<0.00001$; 14 studies, $n=2490$). The authors noted however that the observed improvement in symptom score was relatively small (on a scale with a range from 17 to 113). There was also a significant increase in rates of remission or response to therapy (risk ratio [RR]=1.18, 95% CI 1.08 to 1.28, $p=0.00014$; 16 studies, $n=2924$), and functioning (MD=2.20, 95% CI 0.90 to 3.49, $p=0.0009$; 9 studies, $n=1593$). Compared with placebo, treatment with antidepressant increased the risk of suicide-related outcomes (RR=1.58, 95% CI 1.02 to 2.45; $p=0.041$; 17 studies, $n=3229$). There was also a significant increase in the risk of all adverse events compared with placebo (RR=1.11, 95% CI 1.05 to 1.17, $p=0.00011$; 11 studies, $n=2136$),

³ Since publication of NICE CG28, fluoxetine has been licensed for use in children and young people aged 8 years and older to treat moderate to severe major depression that is unresponsive to psychological therapy after 4–6 sessions, only in combination with a concurrent psychological therapy. See notes at the beginning of section 1.6 on the use of antidepressants in children and young people.

⁴ At the time of publication of this Evidence Update, citalopram, escitalopram, mirtazapine, paroxetine, sertraline and venlafaxine did not have UK marketing authorisation for use in depression in children and young people under the age of 18 years, and it is stated by their summary of product characteristics that they are either not recommended, or should not be used, for this indication. See notes at the beginning of section 1.6 on the use of antidepressants in children and young people.

although adverse events were reported differently in each study. There was no evidence that the individual drug class modified the effect for any of these outcomes ($p=0.22$).

Subgroup analyses of individual therapies found a significant impact of treatment with fluoxetine with regard to reduction in depressive symptoms (MD=-5.63, 95% CI -7.39 to -3.86, $p<0.00001$; 3 studies), remission or response (RR=1.47, 95% CI 1.03 to 2.08, $p=0.032$; 4 studies) and functioning (MD=3.08, 95% CI 0.14 to 6.02, $p=0.04$; 2 studies) but not suicide-related outcomes (RR=1.77, 95% CI 0.85 to 3.69, $p=0.13$; 2 studies). The risk of adverse events was greater in those taking fluoxetine compared with placebo (RR=1.19; 95% CI 1.05 to 1.35; 2 studies). Treatment with citalopram, mirtazapine or paroxetine did not have a significant impact on any of the measures reported. For sertraline, the only outcome among those discussed above to show a significant impact of treatment was CDSR-R (MD=-3.52, 95% CI -6.64 to -0.40, $p=0.027$; 2 studies). For escitalopram, significant effects were seen for reducing depressive symptoms (MD=-2.67, 95% CI -4.85 to -0.48, $p=0.02$; 2 studies) and improvement in functioning (MD=2.28, 95% CI 0.23 to 4.32, $p=0.029$; 2 studies), but in no other outcomes. For venlafaxine, there was no evidence of a beneficial effect but an increased risk of suicide-related outcomes (RR=12.93, 95% CI 1.71 to 97.82, $p=0.013$; 1 study).

Limitations of the evidence included methodological differences between and low quality of some studies. Additionally, the authors judged none of the trials to be at low risk of bias, with limited information about many aspects of risk of bias, high drop-out rates and issues regarding measurement instruments and the clinical usefulness of outcomes. The participants in the trials included in the analysis may also represent a population that is less unwell than that seen in clinical practice.

Overall, the evidence is consistent with the recommendation of [NICE CG28](#) that fluoxetine is the antidepressant of choice, when medication is used. There remains little evidence to inform views on the relative value of other antidepressants in children and young people.

Key reference

Hetrick SE, McKenzie JE, Cox GR et al. (2012) [Newer generation antidepressants for depressive disorders in children and adolescents](#). Cochrane Database of Systematic Reviews issue 11: CD004851

1.7 [Transfer to adult services](#)

No new key evidence was found for this section.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Steps 4 and 5: Moderate to severe depression

- [Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents](#)
- [Newer generation antidepressants for depressive disorders in children and adolescents](#)

Further evidence uncertainties for depression can be found in the [UK DUETs database](#) and in the [NICE research recommendations database](#).

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- [Depression in children and young people](#). NICE clinical guideline 28 (2005).

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 17 August 2010 (the end of the search period for [the latest review of the need to update NICE clinical guideline 28](#)) to 14 January 2013:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used (based on the search strategy for the reference guidance), which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network [search filters for RCTs and systematic reviews](#).

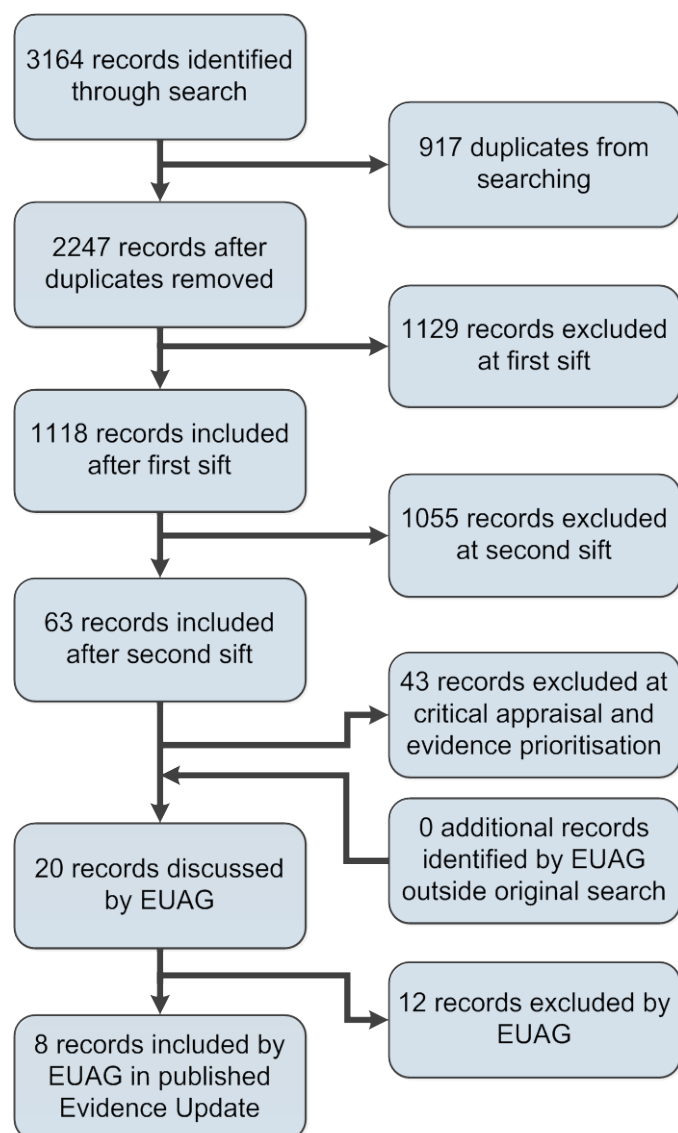
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about [how NICE Evidence Updates are developed](#) on the NICE Evidence Services website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Depression/	7	exp Adolescent/
2	exp Depressive Disorder/	8	exp Pediatrics/
3	(depressi\$ or dysthymi\$).ti,ab.	9	(child\$ or adolescen\$).ti,ab.
4	"seasonal affective disorder".ti,ab.	10	6 or 7 or 8 or 9
5	1 or 2 or 3 or 4	11	5 and 10
6	exp Child/		

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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