

Clinical review

Recent developments in the treatment of major depressive disorder in children and adolescents

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Conflicts of interest

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Disclosure: licence fee from Lundbeck for use of brief psychosocial intervention manual

ABSTRACT

Major depressive disorder in adolescents is an important public health concern. It is common, a risk factor for suicide and is associated with adverse psychosocial consequences. The UK NICE guidelines recommend that children and young people with moderate to severe depression should be seen within Child and Adolescent Mental Health Services and receive specific psychological interventions, possibly in combination with antidepressant medication. Cognitive-behavioural therapy (in some studies) and interpersonal psychotherapy have been demonstrated to be more effective than active control treatments for depressed adolescents. For children with depression, there is some evidence that family focused approaches are more effective than individual therapy. Fluoxetine is the antidepressant with the greatest evidence for effectiveness compared with placebo. Treatment with antidepressants and/or psychological therapy is likely to reduce suicidality, although in some young people, SSRIs lead to increased suicidality. There is limited evidence that combination of specific psychological therapy and antidepressant medication is better than treatment with monotherapy. There are methodological limitations in the published literature that make it difficult to relate study findings to the more severely ill clinical population in Child and Adolescent Mental Health Services. Young people should have access to both evidence based psychological interventions and antidepressants for paediatric depression. Collaborative decisions on treatment should be made jointly by young people, their carers and clinicians, taking into account individual circumstances and potential benefits, risks and availability of treatment.

INTRODUCTION

Major depressive disorder is common in adolescence; lifetime prevalence rates vary from 11-20%(1–3). Major depressive disorder is an important risk factor for suicide(4), a leading cause of death in young people(5–7) and co-morbidity with other psychiatric disorders is common(8).

This paper will give an overview of recent developments in the treatment of depression in children and adolescents. Almost all studies only included adolescents, and it will be specifically stated if a study included children.

WHAT DO DEPRESSIVE DISORDERS LOOK LIKE IN CHILDREN AND ADOLESCENTS?

Feeling sad or irritable is a normal reaction to stress. However, depression is an illness and is more than feeling sad: low mood becomes enduring (two weeks or more), and is commonly accompanied by other symptoms, such as sleep difficulties, not wanting to eat, negative thoughts and feeling tired. It commonly interferes with everyday life and is associated with functional impairment at home, school and in relationships. The core features of depression are similar in children, adolescents and adults (see table 1).

Table 1: Criteria for ICD-10 depressive episode(9)	
<p>Key symptoms:</p> <ul style="list-style-type: none"> • Depressed mood • Loss of interest and enjoyment in activities • Decreased energy and fatigability <p>Associated symptoms:</p> <ul style="list-style-type: none"> • Reduced ability to concentrate • Loss of self-esteem or self confidence • Excessive thoughts of guilt or worthlessness • Despairing and pessimistic view of the future • Thoughts or acts of self-harm or suicide • Disrupted sleep • Loss of appetite 	<p>Depression Severity</p> <p>For an episode of depression symptoms need to be present for a duration of at least 2 weeks in all three grades of severity.</p> <p>Mild:</p> <p>2 key symptoms 2 associated symptoms</p> <p>Moderate:</p> <p>2 key symptoms 3-4 associated symptoms</p> <p>Severe:</p> <p>3 key symptoms 4 associated symptoms</p>

What treatments are effective for depressive disorders in children and adolescents?

It has been shown that contact with mental health services is beneficial for adolescents with depressive symptoms(10). It is important that services offer treatments with the best evidence base.

Psychological interventions

The NICE guidelines(11) for the treatment of mild depression recommend a period of 4 weeks watchful waiting and after this period non-directive supportive therapy, group cognitive behavioral therapy (CBT) or guided self-help. If there has been no response for 2-3 months using these treatment modalities, then a referral should be made to specialist Child and Mental Health (CAMH). Young people with moderate to severe depression should be offered a specific psychological therapy as a first-line treatment: individual CBT, interpersonal psychotherapy (IPT) or family therapy (FT). The NICE guidelines suggest that such a therapy should be given for at least 3 months duration. A recent meta-analysis of psychological therapies for depression in children/adolescents found a standardized effect size of 0.29(12). Given the higher cost and lower availability of the specialist therapies recommended by NICE in comparison to non-specific treatment as usual (TAU) or counselling, it is important that they are shown to have significantly different efficacy.

Cognitive Behavioural Therapy

CBT is the treatment most studied for adolescent depression. It aims to increase helpful behaviours (such as going out more) and modify negative thinking. Earlier studies suggested a very high effect size, but more recent studies (with more active control treatment and more robust methodology) demonstrate more modest effect sizes. A meta-analysis of CBT studies versus controls reported a standardized mean difference (SMD) in favour of CBT of 0.53 ($p < 0.01$). However, the methodology of many of these studies was poor, and limiting inclusion to studies with better methodology revealed much smaller effects (eg SMD for studies using intention to treat analysis was 0.26, $p < 0.05$; SMD for studies with active control groups was 0.11, $p < 0.01$)(13). The CBT used in RCTs has at times been criticised for being too rigid and not being totally focused on each individual's problems. A modular(14) approach to CBT, with flexible application of manualised focused treatment for the problems a young person (including depression, anxiety and behaviour problems) has been shown to be more effective than treatment as usual.

Interpersonal Therapy (IPT)

IPT aims to reduce depressive symptoms by improving relationships, using techniques such as communication analysis and building up positive social networks. The only study of IPT for depression in adolescents with an active control group (TAU) found an SMD in favour of IPT of 0.50 ($p=0.04$)(15). This study also showed that the IPT-TAU difference was significantly higher in those with moderate, as opposed to mild/sub-threshold depression. However, this study requires replication.

Family Therapy (FT)

FT examines family relationships and tries to improve conflicts and other dysfunction, however, it has not been found to be more effective than control treatments for adolescent depression, whether as a single therapy or combined treatment(16–18). A more recent trial compared FT to individual psychodynamic psychotherapy (PPT) and found no significant difference(19). However, this study did not have a TAU control group. Psychodynamic Psychotherapy (PPT) has not been demonstrated to be more effective than a brief psychosocial intervention (BPI)(20). A pilot study of Attachment-Based Family Therapy (ABFT) suggested it may be effective for depression, but a fully powered study showed no significant difference in depressive symptoms between ABFT and TAU(21). Taking these studies together, family therapy does not appear to be any more effective than TAU for depression in adolescents.

Only one small ($n=42$) Randomised Controlled Trial (RCT) of psychological therapy for depression has targeted children (age 7-12), rather than adolescents. IPT was adapted so there was much greater parental involvement - family-based interpersonal therapy (FB-IPT). FB-IPT was more effective than more individually-based client-centred therapy for 38 7-12-year olds with a depressive disorder (remission rates 66% vs 31%, $p = 0.04$)(22) (Dietz 2015). A recent moderate-sized ($n=154$) study showed FT to be more effective than individual therapy for 7-14-year olds with depression(23). Thus,

a family-based approach may be more effective than individual therapy in children/younger adolescents.

Psychodynamic psychotherapy (PPT)

PPT focuses on interpersonal relationships, attachment and life stresses, and explicitly works on the therapeutic relationship between the client and therapist. A recent large UK based RCT (IMPACT, n=465) compared PPT, CBT and a manualized brief psychosocial intervention (BPI)(20). There was no difference between treatments over 86 weeks follow-up. This suggests that both PPT and BPI are as effective as CBT, up to now the most-widely supported and used treatment for adolescent depression.

Network Meta-Analysis Comparing Psychological Therapies

Network meta-analysis (NMA) allows two-way comparisons to be inferred from the results of other studies comparing treatments (24). A recent NMA of psychological therapies for child and adolescent depression found IPT and CBT both to be significantly more effective than treatment as usual, placebo and waiting-list(25). IPT and CBT were not significantly different from each other at post-intervention or short-term follow-up; IPT was significantly better than CBT at long-term follow-up. FT, problem-solving therapy and supportive therapy were significantly better than waiting-list but did not differ from placebo or TAU. Play therapy did not differ from waiting-list. PPT did not significantly differ from other interventions, although this NMA did not include the later IMPACT study. Of note, this NMA did include older studies with less-robust methodology (such as not using intention-to-treat) and merged all studies using the same treatment model, although they could vary in terms of delivery (eg group/individual, internet/face-face).

Pharmacological interventions

NICE do not recommend antidepressant medication for the initial treatment of mild depression in the paediatric population. The updated guidelines indicate that fluoxetine can be considered in

combination with specific psychological therapy for young people (age 12-18) in the initial treatment of moderate to severe depression. In children (aged 5-11) the combination of fluoxetine with psychological treatment should be considered with caution and only after 4-6 sessions of psychological therapy. The starting dose of fluoxetine is 10mg once daily increasing to a standard dose of Fluoxetine 20mg once daily for 4-6 weeks with review at each stage of the treatment pathway(11). The British National Formulary (BNF) suggests that fluoxetine can be given to a maximum dose of 60mg; there is no evidence to indicate that using such a high dose is effective or not effective in adolescents; dosage should be governed by individual response, tolerance of any adverse effects, and should be kept to the lowest possible dose required to achieve an adequate response. These guidelines suggest sertraline or citalopram as second line treatment. They recommend that venlafaxine, paroxetine and tricyclic antidepressants should not be used due to significant side-effects. The most recent Cochrane review on tricyclic antidepressants for paediatric depression(26) found no benefit on remission or response rates, when compared with placebo. There was a small reduction in depression scores amongst adolescents treated with tricyclics compared with placebo. Adverse effects were more notable in the tricyclic, versus placebo, group. The most recent Cochrane meta-analysis on newer generation antidepressants(27) demonstrated that the drug-placebo difference is greatest for fluoxetine, with an absolute mean difference between treatments of 5.63 on the CDRS-R and a risk ratio for response of 1.47. The largest (and non-drug company funded) RCT of fluoxetine (Treatment for Adolescents with Depression Study) had a response rate of 61% in the fluoxetine group and 35% in the placebo group at 12 weeks. The Cochrane review also demonstrated that escitalopram and sertraline were significantly superior to placebo. However, other SSRIs, venlafaxine and mirtazapine were not significantly better than placebo.

A recent network meta-analysis (NMA) compared antidepressants, based on indirect comparisons across studies, again found the drug-placebo difference to be greatest for fluoxetine (SMD 0.51)(28).

The study did not find a significant difference between fluoxetine and other NGAs, although these findings are constrained by methodological issues(29). Head-head comparisons also found escitalopram and sertraline to be superior to placebo, although this did not remain significant in the more conservative random-effects analysis used in the NMA.

There were justified concerns about risk of bias from the authors, due to limited information, high dropout rates and no details on allocation concealment across studies. The population used in the trials were unlikely to be representative of clinic populations, as those with co-morbid psychiatric disorders and high suicide risk were generally excluded from individual studies.

Evidence and guidance on how long to continue antidepressants for is not clear. Guidelines for adult depression suggest that they should be continued for six-nine months after remission in first episode cases with lower risk of relapse, and a longer duration in higher risk/recurrent cases(30).

Potential Harms from Antidepressants

The most recent Cochrane review on NGAs reported that adverse effects were greater in those taking antidepressants (11 trials N=2136 RR 1.11, 95% CI 1.05 to 1.17). The most commonly noted physical side-effects were headaches, abdominal pain, dizziness and nausea. Emotional lability was more often associated with paroxetine, fluoxetine and sertraline. In addition, mirtazapine was reported to increase metabolic side effects (increased appetite, weight gain and hyperlipidaemia)(26). TADS found that emotional and behavioral disinhibition and non-psychiatric adverse events were greater in the Fluoxetine treated groups(31). The risk of conversion to mania/manic symptoms with SSRIs is higher for depressed adolescents than adults, although there is no clear evidence that the conversion to full mania/hypomania is more common with SSRIs than placebo in depressed adolescents (32).

In 2003, The USA Food and Drugs Administration (FDA), followed soon by the Medicines & Healthcare Products Regulatory Agency United Kingdom (MHRA UK), released warnings about

increased risk of suicidality from SSRIs in paediatric patients. They advised that clinicians balance the risk of suicidality with clinical need in antidepressant treatment for pediatric patients. They recommend that fluoxetine be the first-line drug treatment for pediatric major depressive disorder. The meta-analysis by the FDA on suicide related adverse events included 4582 patients from 24 pediatric trials. Data for SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram) showed a modest increased risk of suicidality in 20 trials (RR 1.66 95% CI 1.02-2.68)(33).

However, although it has been shown that suicidality does increase in some individual young people taking SSRIs, on average it reduces across samples of young people, when measured prospectively(31). Of note, Gibbons and colleagues carried out a recent and more robust meta-analysis using individual-level data (as opposed to aggregate results from studies) from published and unpublished studies on adolescent depression. Suicidality reduced in both fluoxetine and placebo groups, and there was no significant difference between groups. On the other hand, depressive symptoms improved more in the fluoxetine group. While this study does not support the hypothesis that SSRIs increase suicidality more than placebo, it also suggests that reduction of depression is not the sole mechanism for reducing suicidality(34). Also, non-controlled but larger and more representative community-based studies have suggested that higher rates of SSRI prescribing are associated with lower suicide rates; and that suicide attempts are more common before SSRI prescribing than after it(35).

In view of this small risk of a very important adverse event, antidepressant medication initiation and adverse outcomes need to be monitored carefully by appropriately-trained doctors, such as child and adolescent psychiatrists. The risk of increased suicidality needs to be weighed against the risk of inadequately-treated depression.

It is difficult to extrapolate the results from these trials to the more severely depressed and complex patients seen in clinics, as studies usually excluded patients with severe depression, co-morbidity and/or suicidality and the drug-placebo difference may be greater in more severe depression (as

seen in both adolescents and adults(36,37)). Most importantly, the effects of antidepressants on suicidality in people with pre-existing suicidal thoughts is unknown, as these individuals are usually excluded from medication trials.

Potential Harms from psychological intervention

Little consideration has been given to date of the potential harms of psychotherapy in the adolescent population which could be a result of either ineffective practice, ineffective engagement or specific adverse events(38). Examples of adverse effects could include dependence on the therapist, poor quality therapy which could also deter future acceptance of therapy; and feelings of failure for not 'succeeding' in psychological tasks.

Comparisons/Combinations of Psychological and Pharmacological Interventions

The most recent Cochrane review on psychological therapies versus antidepressant medication, alone and in combination, for child/adolescent depressive disorder identified 11 trials(39). However, given that the meta-analyses for antidepressants demonstrated differential efficacy for different SSRIs, it may not be appropriate to combine studies using different antidepressants. 2 studies were found comparing SSRIs to psychological therapy (CBT), and the pooled odds ratio for remission was non-significantly in favour of SSRI (0.62, CI 0.28-1.35). However, the study that compared fluoxetine to CBT demonstrated that fluoxetine (response rate = 61%) was significantly better than CBT (response rate 43%, OR 0.49, CI 0.28-0.84)(30), while the study comparing sertraline to CBT showed CBT to be non-significantly better than sertraline(40).

Outcome data from 3 trials comparing combination therapy and antidepressant medication showed that combination treatment was more likely to lead to remission than antidepressant medication alone, but this difference was not statistically significant (OR 1.50, 95% CI 0.99 to 2.27). There was no significant difference overall when the two studies comparing combination therapy and CBT were

pooled. However, again this may have been due to clinical heterogeneity: combined treatment with fluoxetine and CBT was significantly better than CBT alone (TADS, OR = 2.94, 95% CI 1.67 to 5.18) and combined treatment was better than fluoxetine alone on some outcome measures only(31); whilst combined treatment with sertraline and CBT was non-significantly worse than CBT alone(40).

One RCT looked at treatments for depressed adolescents who had not responded to treatment with one SSRI(41). Participants were randomized in two ways: to another SSRI or venlafaxine; and to CBT or non-CBT. The addition of CBT was more effective on some outcome measures (eg response rate, 54.8% vs 40.5%, $p = 0.009$), but not others (including continuously measured depression severity, SMD 0.09 at 12 weeks).

Given the evidence that NGAs increase suicidality compared to placebo, it is important to compare this adverse outcome between different treatments. TADS randomized 439 depressed adolescents to fluoxetine alone, CBT alone, combined CBT and fluoxetine or placebo. Suicidality (measured on a continuous scale) reduced in all treatment groups. At 12 weeks, this reduction was significantly greater in the combined treatment group than either fluoxetine alone or CBT alone; there was no significant difference between fluoxetine alone and CBT alone. There was no significant difference in suicide-related events at 12 weeks(31). However, at 36-week follow-up, suicidal events were significantly greater in the fluoxetine alone (15%) than the CBT alone (6%) group, which was statistically significant ($p = 0.04$)(41). There was no statistically significant difference between combined treatment and either monotherapy. However, the p-values have not been corrected for all treatment contrasts for suicidal events across the four treatment groups (fluoxetine alone, CBT alone, combined CBT and fluoxetine or placebo).

In the UK, the ADAPT study compared CBT plus SSRI against SSRI alongside specialist clinical care over 28 weeks. There was no evidence of a protective effect of CBT as there were no significant differences in suicidal thoughts or self-harm events between SSRI alone and combined

treatment(43). Similarly, in the TORDIA study for adolescents with treatment-resistant depression, there was no evidence of a protective effect of CBT(41).

Sleep and depression

Sleep disturbance in adolescent depression is common, with 92% [n=427] of depressed adolescents in the IMPACT study reporting sleep problems(20). Loss of sleep can increase the likelihood of developing depressive symptomatology and risk taking behaviours(44). Sleep disturbance worsens the course of depression in depressed adolescents(45). The assessment and management of sleep problems is an important component of the treatment of adolescent depression. Specific treatments for insomnia may involve psychological or pharmacological interventions, although studies are limited for the adolescent population(46).

Moderators of treatment response

When the difference between treatment groups is significantly different for patients with and without a baseline variable, that variable acts as a moderator. The identification of moderators helps us to target the appropriate treatment for individual patients. TADS demonstrated that milder depressive symptoms and greater cognitive distortions each led to the difference between combined fluoxetine plus CBT and fluoxetine alone to be significantly greater; and also that the difference between CBT and placebo was significant in young people from high income families only(47). In TORDIA, the addition of CBT was more likely to be effective in adolescents with more co-morbid disorders, and less likely to be effective in young people who had experienced child maltreatment(48).

Social Interventions

The NICE guidelines emphasise the importance of managing the context of depression:

‘Comorbid diagnoses and developmental, social and educational problems should be assessed and managed, either in sequence or in parallel, with the treatment for depression. Where appropriate

this should be done through consultation and alliance with a wider network of education and social care. Attention should be paid to the possible need for parents' own psychiatric problems (particularly depression) to be treated in parallel'(11).

Long-Term Outcome and Relapse prevention

Long-term follow-up of the TADS sample showed that 91.5% of adolescents met criteria for recovery within 2 years and 96.4% recovered within 63 months. 46.6% of those who recovered had a recurrence of depression. Initial treatment group had no effect on recovery nor recurrence. This lack of non-difference at follow-up was also found in a smaller earlier study, which demonstrated CBT to be better than FT and supportive therapy in the short-term(17); there was no difference between groups at 2-year follow-up(49). As stated above, the IMPACT trial demonstrated no difference between CBT, PPT and BPI over 86 weeks; there was no significant difference between treatments at any time(20). A separate pooled analysis consisting of three studies compared antidepressant treatment against placebo, and reported that antidepressants were significantly better for relapse/recurrence prevention (OR = 0.34, 95% CI 0.18-0.64)(26).

There is also evidence that the risk of relapse may be reduced by adding sequential CBT, as opposed to continuation pharmacotherapy alone, after a successful antidepressant response. Of 144 children and adolescents who had responded to fluoxetine treatment, only 9% relapsed with continuation treatment combined with CBT, versus 26.5% who were treated with fluoxetine alone after 30 weeks(50).

Preventative strategies

The most recent Cochrane review on interventions for preventing depression in children and adolescents included psychological only interventions. The updated review identified 83 trials in a

qualitative synthesis. The population selected were children and adolescents aged 5 to 19, who had not yet received a primary diagnosis of depression with no restrictions on setting. The evidence-based psychological interventions included were IPT-orientated, CBT-orientated and third-wave CBT. The latter is a group of psychotherapy approaches; which in this updated review included dialectical behavioural therapy (DBT), positive psychology, mindfulness, acceptance and commitment therapy (ACT) and behaviour therapy). Data from 32 trials revealed a reduction of risk of diagnosis with depression in the medium term (up to 12 months) for those receiving psychological evidence-based interventions (CBT, third-wave CBT and IPT) compared with no intervention (Risk Difference -0.03, 95% CI -0.05 to -0.01 p=0.01). This effect was not maintained at longer term follow-up. Whilst there were small benefits of depression prevention, the quality of evidence was rated as low and results heterogenous(51).

Online interventions

There is an exponential growth in the development of mobile apps and computerised technologies, however, there is limited evidence base for the use of apps for mental health disorders in adolescents(52). It has been suggested that the use of Digital Health Interventions (DHIs) for mental health problems is accessible, efficient and effective. A systemic and meta-review on DHIs in young people, yielded 6 RCTs for depression, however, 5 trials excluded participants with severe depression. There was some support for the use of Computerised Cognitive Behavioural Therapy (cCBT) in young people with mild depression and anxiety. There were significant methodological limitations, effectiveness was found to be inconclusive, and there was lack of data on cost-effectiveness of treatment(53).

Implications for clinical practice

It is not easy to draw conclusions that apply to clinic populations from the literature. This is partly due to methodological limitations which apply to studies of both antidepressants and psychological therapies; in particular, the use of waiting-lists or inactive controls as comparators makes it

impossible to tell whether the therapy is specifically effective, or if improvement is a result simply of time spent with a caring therapist. In addition, psychological treatment trials rarely examine adverse effects although there is a growing literature about potential harms. The evidence base has suggested that both IPT and CBT are more effective than treatment as usual, however, the IMPACT study reported no difference between PT, CBT and a brief manualised psychosocial intervention both in the short and longer term. Family based interventions are likely to be effective for younger children. With regards to antidepressants, there is evidence from several studies (the largest one of which was not funded by a drug company) that fluoxetine is more effective than placebo, with weaker evidence in favour of sertraline and escitalopram. There is limited evidence that combined treatment is better than monotherapy. Continuation treatment with antidepressants significantly reduces the risk of relapse, and sequential treatment with CBT in fluoxetine responders may be of additional benefit in preventing relapse. All treatments should be given within a psychosocial framework with a considered formulation of risk and protective factors. The major limitation of all these studies is that almost all excluded patients with severe depression, co-morbid disorders and/or suicidality. These are precisely the complex patients seen in CAMHS that need a robust evidence base for treatment.

The NICE guidelines recommend starting treatment with a specific psychological therapy in moderate to severe adolescent depression, however combined treatment with fluoxetine and psychological therapy may be considered as a first-line approach in more severe cases. This is based partly on risk of side-effects with medication. Weighing up the benefits and risks of treatment options for each young person is complex and made harder by the long waiting-lists for psychological therapies in many places. Young people and their families should be told of the potential benefits and, harms, as well as waiting-lists, for treatments and be enabled to make fully informed, collaborative decisions about the most appropriate treatment choice for them. Future research needs to focus on the most impaired and suicidal young people, as well as those that do

not respond to first-line treatments and evaluate the potential benefits and harms of both antidepressants and psychological therapies.

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