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GUIDELINES

Diagnosis and management of depression in children and young people: summary of updated NICE guidance

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On behalf of the Clinical Guidelines Update Committee B

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Depression affects around 2.8% of children under the age of 13 and 5.6% of 13-18 year olds.[1] Effective treatment is important because persistent depression is associated with serious complications, including poor school performance and social functioning,[2] recurring depression in adulthood,[3] and suicide.[4] This article summarises recommendations from the updated National Institute for Health and Care Excellence (NICE) guideline on depression in children and young people.[5] The update had a narrow remit—only recommendations on the choice of psychological therapy and the combination of antidepressant treatment with psychological therapy were considered.

Recommendations

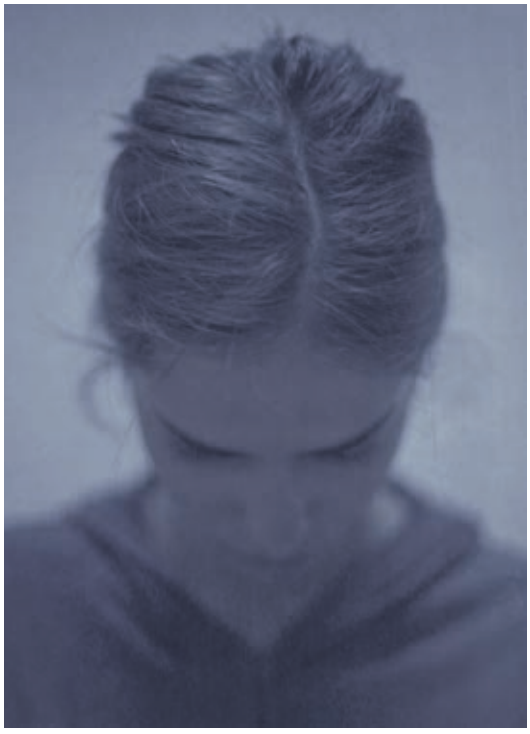
NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. Where the evidence was minimal, recommendations in the original guidance were based on the guideline development group's experience and opinion of what constitutes good practice. Changes to the original recommendations were based on evidence from updated systematic reviews on clinical and cost effectiveness. Evidence levels for the recommendations are in the full version of this article on thebmj.com.

Assessment and detection

- When assessing a child or young person with depression, routinely consider and record in the patient's notes potential comorbidities and the social, educational, and family context for the patient and family members. This information should include the quality of interpersonal relationships between the patient and other family members and between the patient and his or her friends and peers.
- Healthcare professionals in primary care, schools, and other relevant community settings should be trained to detect symptoms of depression and to assess children and young people who may be at risk of depression. Training should include the evaluation of recent and past psychosocial risk factors, such as age; sex; family discord; bullying; physical, sexual, or emotional abuse; comorbid disorders, including drug and alcohol use; and a history of parental depression. They should also be aware of the natural course of single loss events; the importance of multiple risk factors; ethnic and cultural factors; and factors known to be associated with a high risk of depression and other health problems, such as homelessness, refugee status, and living in institutional settings.
- In assessing a child or young person with depression, always ask the patient and the parent(s) or carer(s) directly about the child or young person's alcohol and drug use, any experience of being bullied or abused, self harm, and ideas about suicide. Offer the young person the opportunity to discuss these issues initially in private.
- If a child or young person with depression presents acutely having self harmed, immediate management should follow a previous NICE guideline that applies to children and young people,[6] paying particular attention to the guidance on consent and capacity. Further management should then follow the current depression guideline.
- Assess and manage comorbid diagnoses and developmental, social, and educational problems, either in sequence or in parallel with treatment for depression. Where appropriate this should be done through consultation and alliance with a wider network of education and social care.
- Pay attention to the possible need for parents' own psychiatric problems (particularly depression) to be treated in parallel if the child or young person's mental health is to improve. If such a need is identified, a plan for obtaining such treatment should be made, bearing in mind the availability of adult mental health provision and other services.

THE BOTTOM LINE

- There is little clear evidence to favour one psychological therapy over another for the treatment of depression in children and young people. Clinicians should discuss this uncertainty when recommending treatments
- For initial treatment of moderate to severe depression in young people (12-18 years), antidepressants and psychological therapy may be started concurrently as an alternative to offering a trial of psychological therapy first and starting antidepressants only if this trial is unsuccessful



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- Diagnosis and management of community and hospital acquired pneumonia in adults (*BMJ* 2014;349:g6722)
- Intrapartum care of healthy women and their babies (*BMJ* 2014;349:g6886)
- Identification, assessment, and management of overweight and obesity (*BMJ* 2014;349:g6608)

- Child and Adolescent Mental Health Services (CAMHS) tier 2 or 3 should work with health and social care professionals in primary care, schools, and other relevant community settings to provide training and develop ethnically and culturally sensitive systems for detecting, assessing, supporting, and referring children and young people who are depressed or at high risk of becoming depressed. (Tier 2 services comprise CAMHS specialists working in community and primary care settings; tier 3 comprises a multidisciplinary team or service working in a community mental health clinic or child psychiatry outpatient service.)
- Make training opportunities available for CAMHS professionals to improve the accuracy of diagnosing depressive conditions. The existing interviewer based instruments (such as Kiddie-Sads (K-SADS) and child and adolescent psychiatric assessment (CAPA)) could be used for this purpose but will require modification for regular use in busy routine CAMHS settings.

Psychological therapies

- Psychological therapies used in the treatment of children and young people should be provided by trained child and adolescent mental healthcare professionals.
- Discuss the choice of psychological therapies with children and young people and their family members or carers (as appropriate). Explain that there is no good quality evidence that one type of psychological therapy is better than others, especially more than 12 months after the end of therapy or for children (aged 5-11 years). (New recommendation.)

Mild depression

- Do not prescribe antidepressant drugs as initial treatment in children and young people.
- After up to four weeks of watchful waiting, offer individual non-directive supportive therapy, group cognitive behavioural therapy (CBT), or guided self help for a limited period (two to three months) to all children and young people with continuing mild depression and no serious comorbid problems or signs of suicidal ideation. This could be provided by appropriately trained professionals in primary care, schools, social services, and the voluntary sector or in tier 2 CAMHS. (Reviewed 2015, unchanged.)

Moderate to severe depression

- Offer children and young people a specific psychological therapy (individual CBT, interpersonal therapy, family therapy, or psychodynamic psychotherapy); it is suggested that this should be of at least three months' duration. (New recommendation.)
- Do not offer antidepressant drugs to a child or young person except in combination with a psychological therapy. Make specific arrangements for careful monitoring of adverse drug reactions, as well as for reviewing mental state and general progress—for example, weekly contact with the child or young person and their parent(s) or carer(s) for the first four weeks of treatment. The precise frequency will need to be decided on an individual basis and recorded in the notes. If psychological therapies are declined, drugs can still be given, but because the young person will not be reviewed at psychological therapy sessions, the prescribing doctor should closely monitor the child or young person's progress on a regular basis and focus particularly on emergent adverse drug reactions. (Reviewed 2015, unchanged.)
- For initial treatment in young people (12-18 years), consider combined therapy (fluoxetine and psychological therapy) as an alternative to psychological therapy followed by combined therapy (see next recommendation). Note that use of fluoxetine for the treatment of depression in young people without an unsuccessful trial period of psychological therapy is outside of the licensed indications. (New recommendation.)
- If depression in a child or young person does not respond to psychological therapy after four to six treatment sessions, undertake a multidisciplinary review.
- After multidisciplinary review:
  - If the child or young person's depression is not responding to psychological therapy because of coexisting factors, such as comorbid conditions, persisting psychosocial risk factors (for instance family discord), or parental mental ill health, consider alternative or additional psychological therapy for the parent or other family members, or alternative psychological therapy for the patient
  - Offer fluoxetine if depression in a young person (12-18 years) is unresponsive to a specific psychological therapy after four to six sessions. Note that fluoxetine is the only antidepressant licensed for use in depression in young people (Reviewed 2015, unchanged.)
  - Cautiously consider fluoxetine if depression in a child (5-11 years) is unresponsive to a specific psychological therapy after four to six sessions, although the evidence for fluoxetine's effectiveness in this age group is not established. Note that use of fluoxetine for the treatment of depression in children under 8 years is outside of the licensed indications. (Reviewed 2015, unchanged.)

Psychological therapies used in the treatment of children and young people should be provided by trained child and adolescent mental healthcare professionals

Overcoming barriers

The original 2005 guideline recommended offering antidepressants only if a trial of psychological therapy was ineffective. The main change will be that clinicians should now consider starting treatment with antidepressants and psychological therapy simultaneously for young people with moderate to severe depression. A possible barrier to implementation may be overcoming concerns about the safety of antidepressants in young people (relating to suicidal thoughts). However, the evidence reviewed by the committee did not show an increase in suicidal ideation in young people treated with antidepressants and psychological therapy compared with those treated with psychological therapy alone, but it did show that combined treatment had clear benefits. Unfortunately, difficulties in accessing psychological therapy still exist in the United Kingdom despite previous NICE guidelines on this topic.

UNCERTAINTIES

Adjunctive treatment with quetiapine for major depressive disorder: are the benefits of treatment worth the risks?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com

Quetiapine was approved in 2009 and 2010 for the adjunctive treatment of major depressive disorder (MDD) in several countries worldwide, including the European Union, Canada, the United States, and Australia. These approvals followed three industry sponsored trials of quetiapine versus placebo added to an antidepressant for depression in adults who had an inadequate response to at least six weeks of antidepressant treatment. All three trials showed statistically significant improvements in symptoms of depression compared with placebo.[1]

Pharmacoepidemiological studies in the United States and Canada have shown a shift in practice over the past decade in the use of antipsychotic drugs in the management of MDD. The US National Ambulatory Medical Care Survey found that the percentage of office visits in which a non-psychotic depression was diagnosed that included adjunctive antipsychotic treatment increased from 4.6% (95% confidence interval 2.9% to 6.3%) in 1999-2000 to 12.5% (9.7% to 15.3%) in 2009-10.[2] Quetiapine was the most frequently used antipsychotic drug for augmentation from 2007 to 2010. US data have also shown declining rates of psychotherapy among antidepressant users as the percentage of patients receiving antipsychotic drugs has increased.[3] Over the past decade, Canada has seen a large and preferential increase in the use of quetiapine, which has been the most commonly prescribed antipsychotic since 2007. In 2005, 3.2 prescriptions for quetiapine by family physicians were dispensed per 100 Canadians; by 2012 this had increased to 12.0 per 100.[4] Mood disorders were the most common diagnoses associated with quetiapine prescriptions.

With an estimated global point prevalence of 4.4%,[5] MDD is a frequently encountered problem in clinical practice. Approximately 33% of people in the STAR*D sample (a prospective study of 3671 people with MDD) entered remission after initial selective serotonin reuptake inhibitor treatment; this increased to 50% after a switch to a different antidepressant or augmentation with a second agent or cognitive therapy.[6] A proportion of patients with MDD fail to achieve remission and experience residual symptoms or early relapse, prompting clinicians to search for other treatment options. Quetiapine has been positioned as an alternative in this setting. The use of quetiapine, however, is associated with both short and long term nuisance and serious adverse effects, including weight gain, abnormal lipid profile, elevated glucose, thyroid abnormalities, sedation, and extrapyramidal side effects. Is the benefit associated with its use as an adjunctive treatment worth the risks?

What is the evidence of the uncertainty?

Efficacy data

Three randomized controlled trials, from six to eight weeks in duration, compared adjunctive quetiapine with placebo for MDD (total of 995 participants).[1] All three trials were rated at high risk of bias for incomplete outcome data and selective outcome reporting and at unclear risk of bias for random sequence generation, allocation concealment, and blinding.[7] Efficacy outcomes included the number of patients achieving remission, as defined by a Montgomery Asberg Depression Rating Scale (MADRS) score of 8 or less (possible total score 0-60) or a Hamilton Depression Scale (HAM-D) score of 7 or less (possible 0-50), and the score at endpoint. The number needed to treat (NNT) for remission was 9 (95% confidence interval 6 to 19)[1] for quetiapine compared with placebo over six to eight weeks of treatment.[7] The mean difference in the MADRS score at endpoint was −2.7 points (−4.0 to −1.3), and that for the HAM-D score at endpoint was −2.7 points (−3.8 to −1.6),[7] both favoring quetiapine. The associated effect sizes of these differences range from 0.26 to 0.33, indicating a small, difficult to detect clinical advantage of quetiapine.[8] The item with the largest contribution to quetiapine's 2.7 point advantage was sleep, followed by tension, pessimistic thoughts, sadness, and inability to feel.[9] The effect of quetiapine versus placebo on quality of

HOW LONG SHOULD QUETIAPINE BE CONTINUED AS ADJUNCTIVE TREATMENT FOR MDD?

No long term data on adjunctive quetiapine are available to guide clinicians on the optimal duration of treatment. Data from the placebo discontinuation study of quetiapine monotherapy for major depressive disorder show that after open label stabilization with quetiapine for 16-26 weeks, 34.4% of participants randomized to placebo had a relapse of their depression within 52 weeks of discontinuation, whereas the remaining 65.6% did not.[12] As patients using quetiapine as an adjunctive to an antidepressant would remain on an antidepressant after discontinuation of quetiapine, relapse rates may be lower. In the face of considerable uncertainty, attempting withdrawal of adjunctive therapy in stable patients with major depressive disorder after four to six months of successful treatment, and to monitor closely for signs of relapse, seems logical.

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- Does intensive medical treatment improve outcomes in aortic dissection? (*BMJ* 2014;349:g5288)

life was not significant (effect size 0.04, −0.09 to 0.18),[1] indicating no quality of life advantage with short term use.

The only trial comparing add-on quetiapine with other augmentation strategies, a six week randomized open label study of quetiapine versus lithium as add-on to antidepressants in MDD (n=688), suggested non-inferiority to lithium.[10] However, this finding needs to be confirmed in a double blind trial of longer duration.

Short term adverse effects

Quetiapine use was associated with a high, dose related rate of early discontinuation (8-28%) versus placebo (<2-7%).[9 11] Adverse effects associated with quetiapine in these short term studies included sedation, abnormal metabolic laboratory results (high glucose, total cholesterol, low density lipoprotein cholesterol, or triglycerides or low high density lipoprotein), and weight gain. For sedation, the number needed to harm (NNH) was 3 (2 to 3). The NNH for abnormal metabolic laboratory results was 6 (4 to 9). Mean weight gain was 0.9 (0.6 to 1.3) kg over six to eight weeks of treatment, with an NNH of 37 (12 to 594) for gaining more than 7% of baseline body weight.

Long term adverse effects

Data on the long term adverse effects associated with adjunctive quetiapine use in MDD are not available. In one trial in 776 people with MDD,[12] all participants received open label quetiapine treatment for four to eight weeks, followed by open label quetiapine stabilization for 12-18 weeks, and then were randomized to maintenance quetiapine monotherapy or placebo for up to 52 weeks. Increased weight was reported as an adverse event by 10.2% of participants during the open label phase: 9.7% of those randomized to quetiapine maintenance and 1.6% randomized to placebo. Clinically important shifts in triglycerides and high density lipoprotein cholesterol compared with baseline were reported in 15.3% and 10.6% of participants during the open label phase: 14% and 9.4% of those randomized to quetiapine maintenance treatment and 8% and 4.8% randomized to placebo. Extrapyramidal symptoms were seen in 8.2% during the open label phase: 2.8% of those randomized to quetiapine maintenance treatment and 1.8% randomized to placebo.

Both the short term and long term metabolic effects of quetiapine are of great concern, as data from the US National Health and Nutrition Examination Surveys (2005-10) have shown that both moderate to severe depressive symptoms and antidepressant use are associated with increased obesity.[13] Depression is also an independent risk factor for cardiovascular disease, with consistent evidence linking the presence of mood disorders to excess mortality from cardiovascular disease.[14]

What should we do in the light of the uncertainty?

Data on the use of quetiapine as an adjunctive treatment to antidepressants in people with MDD who have an inadequate response highlight several areas of concern. These include small absolute changes in scale scores associated with treatment, no difference between quetiapine and placebo in measures of quality of life, NNT for remission of 9 (6 to 19), NNT for adverse effect related discontinuation of 8 (6 to 11) (300 mg/day), NNH of 3 (2 to 3) for sedation and 6 (4 to 9) for abnormal metabolic laboratory results, and limited long term safety and efficacy data to inform clinical practice.

Data on the use of quetiapine as an adjunctive treatment to antidepressants in people with MDD who have an inadequate response highlight several areas of concern

Physicians considering the use of quetiapine for adjunctive treatment of MDD should inform patients that no evidence shows that the treatment improves quality of life and that it is associated with modest benefit in the short term and unknown effectiveness in the long term and is burdened by potential major adverse events with short and long term treatment. We have no way of telling who will experience benefit or adverse events at the time the decision about treatment must be made.

For patients with MDD who do not respond to initial selective serotonin reuptake inhibitor (SSRI) treatment, management options include adjunctive and switching strategies.[6 15] The National Institute for Health and Care Excellence (NICE) recommends switching antidepressants first, as using a single antidepressant is associated with fewer side effects, or considering augmentation with an antipsychotic such as quetiapine if the patient is informed about and prepared to tolerate the greater side effect burden. This requires monitoring of weight, lipid and glucose concentrations, and extrapyramidal side effects.[15]

On the basis of an overview of evidence based guidelines and systematic reviews on the treatment of resistant depression,[16] switching strategies include changing to a different SSRI or another antidepressant such as bupropion, mirtazapine, a serotonin norepinephrine (noradrenaline) reuptake inhibitor, or a tricyclic antidepressant. Switching from an SSRI to a non-SSRI agent is associated with a higher remission rate after unsuccessful SSRI treatment (28%) than switching to a second SSRI (23.5%).[17]

Augmentation strategies may include addition of psychotherapy, as well as drugs such as buspirone, lithium, or triiodothyronine. Compared with placebo, the NNT for a treatment response is 4.3 (2.4 to 22.2) with triiodothyronine and 5 (3 to 8) with lithium.[18 19] Adding psychotherapy to drug treatment for depressive symptoms in MDD is associated with a small mean effect size (Cohen's d) of 0.31 (0.20 to 0.43), with benefits shown for different types of psychological treatment, including cognitive behavioral therapy and interpersonal psychotherapy.[20] Weigh up and discuss the benefits and risks of each option with each patient before choosing an augmentation strategy.

Exercise great caution when prescribing quetiapine for MDD. If selecting this drug, monitor depressive symptoms with a validated scale as part of the evaluation. Carefully monitor for adverse effects, measuring weight gain, body mass index, and extrapyramidal symptoms, as well as cholesterol, triglycerides, glucose, and thyroid function.[21] We recommend clinical assessment of metabolic and extrapyramidal adverse effects at baseline, two weeks, one month, three months, six months, and 12 months and laboratory tests at baseline, three months, and 12 months.