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How do we Safely Treat Depression in Children, Adolescents and Young Adults?

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Abstract

Increasing concerns about the safety and efficacy of antidepressant drugs for children, adolescents and young adults have been countered by claims that reduced prescribing of antidepressants may have dangerous consequences. This leaves clinicians unsure as to how to weigh up the evidence and apply it to their patients. This paper promotes an approach of evaluating the evidence in each study according to the importance of the outcomes being measured in that study. It finds that on important measures such as mortality, hospitalization and quality of life, the evidence is unfavourable for antidepressants in this population. Here, an approach is suggested that primary care physicians might adopt with their depressed young patients. Through a combination of 'watchful waiting' and physical and emotional rehabilitation, physicians can actively intervene without reliance on medication or psychotherapy.

Until around 2003 the prevailing view was that selective serotonin reuptake inhibitor (SSRI) antidepressants were safe and effective treatments for depression in adolescents and probably also children. This view was held in spite of few studies having been carried out in this population, in the context of an acceptance that there was strong evidence to support the use of antidepressants in adults. Since then, findings have been published that question the role of antidepressants, particularly in children and adolescents. Although the conclusions of published studies of antidepressants in children were often favourable,[1-4] it emerged that investigators' conclusions exaggerated benefits and downplayed adverse effects.[5] Adding data from unpublished trials led to the conclusion that the benefit-harm ratio of all antidepressants except fluoxetine was unfavourable in children and adolescents.[6] In 2003 and 2004, regulatory agencies, first in the UK then in the US, raised concerns about increases in suicidal behaviour in children and adolescents on antidepressants – concerns that were subsequently confirmed.[7] In October 2004, the US FDA instructed manufacturers to include 'black box warnings' about the risks of suicidal thoughts and behaviours on all antidepressants, including fluoxetine. Subsequently, the use of antidepressants has been defended on the grounds that subsequent trials[8] and analyses[9] show better outcomes, that antidepressant use is associated with reduced suicide

rates,[10] and that non-treatment is also associated with risks that may be greater than those that arise from antidepressant treatment.[11]

This paper assesses the evidence for and against the use of antidepressants in children and adolescents with depression. It gives most weight to whether antidepressants impact on the most important outcomes: mortality, serious adverse outcomes and quality of life. Opinion is based on reviewing all published, and some unpublished, randomized controlled trials (RCTs) in childhood depression,[12] and relevant papers yielded by a PubMed search for ([child OR adolescen*] AND antidepressant AND suicide) up until October 2008.

The last part of the paper offers practical advice on primary care management of depressed young people within the frame of a 'watchful waiting' approach, whereby physicians can actively treat without reliance on medication or psychotherapy.

1. Hierarchy of Outcomes

It is usual to rank evidence for the benefit of antidepressants for depression according to the methodology that produced the data. RCTs are generally accepted as top of the hierarchy for producing valid evidence. But as the Vioxx® tragedy illustrates, mortality is the ultimate measure of the cost-benefit of a drug, over-riding performance on those outcomes that are designated primary in RCTs. Therefore, this review of the use of antidepressants for depression in children and adolescents gives priority to the importance of the outcomes addressed.[13] The feared endpoint of depression is suicide; although rare, all-cause mortality is the outcome at the top of the hierarchy (see table I). Next most important is serious misadventure, such as suicidal behaviour, hospitalization or dropout from school. Measures of quality of life improvement are rated next. Improvement on rating scales is at the foot of the hierarchy, judged less important than non-severe adverse outcomes. Scales commonly filled out by the treating physician in RCTs of antidepressants, such as the Hamilton Depression Rating Scale[18] and the Children's Depression Rating Scale,[19] cover a range of depressive symptoms. It is plausible that improvement on rating scales correlates with meaningful changes to the young person's life, but we have surprisingly little evidence to support this assumption. Drug evaluation experts caution against inferring substantial outcomes from rating-scale measures.[20] For each of the outcomes, both the consequences of untreated depression, and the positive and negative impact of treatment are considered.

Table I. Hierarchy of outcomes in antidepressant research in children and adolescents

Outcome (in order of importance)	Evidence for antidepressants
1. All-cause mortality	Possible suicide risk[10,14-16]
2. Serious adverse outcomes	Demonstrated to increase suicide-related events[7] (relative risk = 1.8); other serious adverse events also occur. Hospitalization rates unknown
3. Long-term developmental outcomes	Unknown
4. Quality-of-life measures	Unknown
5. Adverse events	5–15%[12] in randomized controlled trials
6. Medium-term outcome on depression scales	Similar outcomes for fluoxetine and placebo at 36 weeks[17]
7. Short-term outcome on depression scales	Evidence of lack of efficacy (disputed evidence of efficacy for fluoxetine)[5,8]

2. Mortality

2.1 Untreated Depression

The primary mortality concern for children and young adults with depression is suicide. Suicide is very rare in children, but is an important cause of mortality in older adolescents, and is often attributed to depression. However, there are no reliable estimates of the risk of suicide in untreated depression in this age group, and there is no one-to-one relationship between depression and suicide. One long-term follow-up study found quite a high suicide rate among those who had been depressed as adolescents and diagnosed with conduct disorder, but not among those who had only been diagnosed with depression; however, numbers of patients were small.[21] Studies

that have shown very high levels of depression among young people who have committed suicide have often lacked controls. Where there have been controls, the level of psychiatric diagnosis is around 60% in suicides and over 20% in controls.[22] The role of depression in suicide is not easy to tease out from other factors – most importantly the role of alcohol and other drugs.

2.2 Does Treatment Change Mortality Rates?

Given that depression makes an important contribution to suicide, establishing a role for antidepressants in suicide prevention requires that we demonstrate that those treated with antidepressants are less likely to commit suicide. It has been suggested that increased treatment with antidepressants is a marker of increased access to care and that the package of increased care and antidepressants has a beneficial effect. However, there is evidence that more drugs are being prescribed in the same number of consultations with healthcare professionals.[23] Thus, any effect of antidepressant prescribing on suicide rates is unlikely to be due to extra healthcare.

It is generally noted that RCTs are silent on the issue of suicide and antidepressants, because the numbers are too small, and the follow-up too brief. Other methodologies have therefore been used to test the relationship between antidepressant prescribing and suicide rates. Cohort studies compare suicide levels in patients with and without various treatments. Some appear to show protective effects from antidepressants.[14] A recent large case-control study found that suicide attempts (odds ratio [OR] 1.52; 95% CI 1.12, 2.07) and suicide deaths (OR 15.62; 95% CI 1.65, ∞) were more likely in children and adolescents treated with antidepressant drugs compared with placebo.[15] Ecological studies look for an association between suicide rates and antidepressant usage at a population level, and find relationships in both directions.[10,16]

In summary, population studies do not and cannot demonstrate cause and effect, and studies suggesting an inverse correlation between antidepressant prescribing and suicide are balanced by studies of similar methodology that show the opposite. RCTs show an increase in suicide-related events (but not completed suicide) in adolescents and young adults.[7] We can conclude that there is no demonstrated link between suicide and antidepressants in young people, but based on the data presented above there is reason to worry.

3. Serious Adverse Outcomes

Under this heading we need to consider unsuccessful suicide attempts, hospitalizations due to depression or other conditions, criminality, school or vocational dropout, severe substance misuse and serious adverse medication events.

3.1 Untreated Depression

Untreated depression in children and adolescents is associated with later depression, substance abuse, functional impairment and suicide-related events.[21,24]

3.2 Does Treatment Alter Serious Adverse Outcomes?

Because we do not have systematic data, we do not know whether treating depression alters these long-term outcomes. We do have some data about harm from antidepressants. An adverse drug experience is deemed serious if it is life-threatening, or results in hospitalization or prolongation of an existing hospitalization. RCTs show clinically significant increases in suicide-related events with antidepressant treatment. Two independent, FDA-commissioned reanalyses of RCT data showed that antidepressants almost doubled the risk of suicide-related events compared with placebo (risk ratio 1.81; 95% CI 1.24, 2.64).[7,25] While some authors have suggested that these analyses overestimated risk,[26] it appears that the reviewers were very cautious in their analysis. For example, Hammad et al.[7] only designated four patients in GSK's Study 329[2] as meeting the criteria for their primary outcome of 'suicidal behavior or ideation', allocating a further three cases to the secondary outcome of 'possible suicidal behavior or ideation'. Yet detailed

examination of the patient narratives in Study 329 shows that at least three more cases might have been included from that study. One patient "punched pictures, broke glass, and sustained lacerations that required six sutures. His anger subsided, but he expressed hopelessness and possible suicidal thoughts."[27] Two further cases where the patient had to be hospitalized for suicidal ideation were excluded by the reviewers because the serious suicidal acts occurred after the subjects had stopped taking medication, with the rationale that there was no way of knowing what might have happened once the subject left the study. However, both episodes occurred within a few days of ceasing medication and the withdrawal effects of paroxetine are well known.

A number of studies report serious adverse events (SAEs) to be more frequent in the drug arm of RCTs of antidepressants in young people than in the placebo arm.[1,28] For example, in the above study, 12% for those taking paroxetine experienced SAEs – including headache, worsening depression, aggression and euphoria – compared with 2.3% for placebo.[2]

In summary, we have no meaningful data on which to conclude that antidepressants prevent severe adverse outcomes from depression, but we know that SAEs occur in a significant proportion of patients; perhaps up to 10%. Suicidal thinking and behaviour is more likely to be problematic in the first weeks of taking antidepressants, and at the time of withdrawal.[29] Therefore, at these times, more frequent monitoring is required. If face-to-face monitoring is not feasible or appropriate, then patients and families must have ready telephone access to the prescriber.

4. Quality of Life, Functional Outcomes

Depression has a significant impact on quality of life. No RCT of antidepressants for children or young people that reported improvement on quality of life measures, or that described any functional outcome such as school attendance, hospitalization or mental health consultation could be found.

5. Adverse Events

Withdrawal from RCTs because of adverse events provides a conservative estimate of troublesome adverse events. Relevant data were provided for 12 of 15 published RCTs, totalling 2395 children and adolescents;[1-4,28,30-34] 8.1% (102/1253) withdrew because of adverse events in the drug groups, and 4.5% (51/1142) in the placebo groups[12] Adverse events that were frequent and occurred at least twice as often in the drug group in at least two RCTs included gastrointestinal symptoms, psychiatric adverse events and sleep disturbance. Yet suicide-related events are often the only harms considered in discussions of the adverse effects of antidepressants. For example, calculation by Bridge et al.[9] of the number needed to harm does not even include the FDA category of 'possible suicidal behaviour or ideation', and excluded other significant adverse effects.

6. Improvement in Depression Measures

6.1 Studies in Children and Adolescents

Measurements are restricted to scores on depression scales, and even then they are based on researcher ratings rather than self report or parent report. Of 42 measures reported in six studies reviewed in 2004,[5] only ten were measures relying on patient or parent report, and none of these ten showed significant advantage for active drug.

6.1.1 Long-Term Studies

The longest follow-up in an RCT for adolescents was 36 weeks in TADS (Treatment for Adolescents with Depression Study).[17] At week 36, all groups of subjects had similar outcome, yet a claim was made that "overall, combination therapy in the TADS proved robustly superior to CBT" (cognitive behavioural therapy), and that "short- and long-term data from TADS unequivocally confirm that fluoxetine is an effective treatment for adolescents with moderate to severe MDD." It is questionable whether speeding recovery in a minority of patients justifies the risk of pharmacological treatment.

6.1.2 Short-Term Studies

Two studies are often cited to counter scepticism about the effectiveness of antidepressants for children and adolescents. Firstly, a meta-analysis reported by Bridge et al.[9] concludes that likely benefits outweigh harms for antidepressant treatment of depression in children and adolescents. The claim for a favourable benefit-harm ratio is based on 60% response to drugs (50% to placebo) and a 1 in 100 excess rate of suicidal ideation/attempts. Clinicians should pay more attention to a small increase in risk than to a small short-term benefit on a depression scale, of little clinical significance. A more recent meta-analysis interpreted a similar data set as showing "limited efficacy."[35]

Secondly, short-term follow-up in TADS[8] is often cited as positive, but in fact in the study, fluoxetine differed statistically significantly from placebo on only one of two primary endpoints, and there were other methodological weaknesses.[36] The benefits of fluoxetine, like all other antidepressants, are of doubtful clinical importance for children.

6.2 Adult Studies

A recent paper[37] showing that drug trials do not support clinically meaningful effectiveness of antidepressants for adults in all but the most severe cases of depression has surprised many clinicians. It ought not to have, similar research having been published at least six years ago,[38] but the atmosphere has changed because other concerns about antidepressants have emerged in the meantime. The previously held belief that antidepressants are effective was largely attributable to publication bias[39] and selective reporting that has exaggerated benefit and under-reported harm. Even in those who have an initial positive response to antidepressants, the evidence base for maintenance therapy at 6–8 months is poor.[40]

7. Summary of Evidence

To summarise the evidence, we have no clear guidance as to whether antidepressants increase or decrease mortality; they cause clinically significant levels of serious adverse events; we have no useful evidence of impact on quality of life or hospitalization; we know that they cause troublesome adverse events in more than 5% of young people who take them; and we have some evidence that they do not improve outcome in the medium term. The balance of evidence is that they have no clinically significant impact on depression measures in the short-term, although experts present fluoxetine as an exception.

We have no clear-cut evidence that non-treatment is associated with risks of suicide. We cannot be confident about which patients, if any, should receive antidepressants, but we can be confident that many young people who are prescribed antidepressants should not be. We are therefore ethically obliged to exercise caution in prescribing to this population.[41]

8. What To Do?

Since we have grounds for concern about safety issues for antidepressants, and evidence-based psychotherapies may not be readily available, what should we do when faced by an apparently depressed adolescent? I believe that we should aim to exploit and enhance the 1-in-2 response in the placebo arm of RCTs (number needed to treat = 2). When acute risk is low, the UK National Institute for Clinical Excellence proposes 'watchful waiting',[42] whereby a doctor offers a brief explanation about depression, and arranges to see the patient again in about 2 weeks. In more severe cases, referral to or consultation with a child and adolescent mental health service or a child psychiatrist is recommended. The limited availability of such services is an indication for advocacy; it does not mandate prescribing against available evidence.

But in fact, general practitioners (GPs), who treat the majority of patients with depression, have considerably more than 'watchful waiting' to offer their patients. Primary care mental health should not be seen as a second-rate form of psychiatric intervention. GPs have extensive knowledge of a patient's community and often have prior knowledge of the patient and their family. This information and their capacity to build on a

relationship over time mean that GPs are well placed to provide optimal assessment and management of many primary care presentations of depression in young people.

It is helpful to conceptualize the task in managing depression as physical and emotional rehabilitation rather than as treatment of acute illness. The following rehabilitation guidelines are aimed to enhance natural pathways to recovery.

8.1 Exclude/Explore/Explain

Before adopting a rehabilitation approach, it is important to *exclude* acute dangers and indications for immediate psychiatric intervention. The patient should be asked about self-harm, use of alcohol and other drugs, and symptoms of acute anxiety or psychosis. The doctor should then *explore* possible reasons for the patient's misery, including grief and trauma but also less dramatic life events and circumstances.[43] The GP should then give an *explanation* to the patient of their symptoms, either in terms of the identified stressors or as manifestations of a depressive episode, with a natural history that predicts recovery within weeks.[44] The GP is helping the patient to develop a coherent narrative for their experience, thereby reducing anxiety and providing a rationale for intervention.

8.2 Neurovegetative Rehabilitation

In the absence of an acute severe psychiatric illness or a major recent loss or trauma, the approach should be one of rehabilitation. Neurovegetative features such as sleep and appetite disturbance and loss of energy and concentration are often very troublesome to patients. The knowledge that correcting sleep patterns can significantly enhance well-being can often lead doctors to prescribe. When prescribing is considered, we should be guided by what Moncrieff and Cohen[45] have described as a 'drug-centred' model. Rather than accepting the proposition, for which there is little evidence, that antidepressants work on the neurobiology of depressive disorders ('disease-centred' model), they suggest that psychotropic drugs create abnormal states that may be exploited to relieve symptoms. Drug-induced effects of antidepressants vary according to their chemical class, and include, for example, sedation, cognitive and emotional blunting, or mild stimulation. These effects might be exploited according to the requirements of a particular case.

But there are non-drug means that can be preferable when drugs are of unknown safety. Sleep hygiene can restore sleep patterns, as can management of caffeine and alcohol consumption. Exercise is shown to be effective in reducing depression in adults, and although the research base in children is poor, there is some support for its use.[46] Young people with depression will often have discontinued vocational and recreational activities. It should be explained to them that a gradual and graded return to healthy levels of activity is a step towards restoring their mood rather than something that must wait until 'I feel better'.

8.3 Managing Feelings

Young people may have an expectation that there is something wrong if they do not feel good most of the time. They might benefit from learning that being 'good at feelings' is as important as feeling good. What presents as depression can be a manifestation of avoiding uncomfortable feelings of anger, sadness, fear or shame. Often the GP will not immediately be able to identify the source of such feelings. Even so, there are a number of potentially productive interventions, including encouraging the patient to talk about these feelings with the doctor or a confidante, or to keep a journal. It has long been recognized that there is benefit from deliberately recalling uncomfortable memories and feelings, provided it does not progress to ''dwell[ing] persistently upon painful memories or anticipations, and brood[ing] upon feelings of regret and shame.''[47] I find it useful to suggest to patients that they talk only to me and one other person about their concerns, and feel free to put the memories out of their minds at other times; or if they are to write about them, to do it only at a specified time each day. The impact of such apparently benign interventions on physical and mental health is well documented.[48]

9. Conclusion

I have put forward an approach to the management of depression in young people that can be carried out in the general practice setting within the framework of a 'watchful waiting' approach where the patient is followed up regularly and encouraged to re-contact the treating practitioner if there are concerns. We need not feel impotent in the face of our need to be extremely cautious in antidepressant prescribing to young people.

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