Clinical review

Efficacy and safety of antidepressants for children and adolescents

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How safe and effective are antidepressants in children and adolescents? The authors of this review have found disturbing shortcomings in the methods and reporting of trials of newer antidepressants in this patient group

Antidepressants introduced since 1990, especially selective serotonin reuptake inhibitors and venlafaxine, have been used increasingly as first line treatment for depression in children.[1,2] The safety of prescribing antidepressants to children (including adolescents) has been the subject of increasing concern in the community and the medical profession, leading to recommendations against their use from government and industry (box 1). In this paper, we review the published literature on the efficacy and safety of newer antidepressants in children.

Summary points

Investigators' conclusions on the efficacy of newer antidepressants in childhood depression have exaggerated their benefits

Improvement in control groups is strong; additional benefit from drugs is of doubtful clinical significance

Adverse effects have been downplayed

Antidepressant drugs cannot confidently be recommended as a treatment option for childhood depression

A more critical approach to ensuring the validity of published data is needed

Methods

Having criticised the way in which Keller et al interpreted the results of their study,[3,4] we sought to check the quality of methods and reporting of other published trials of newer antidepressants in children (box 2). Of seven published randomised controlled trials of newer antidepressants for depressed children published in refereed journals, six used a placebo control.[3,5–9] We analysed each study's methods and the extent to which authors' conclusions were supported by data. The seventh study, which compared a newer antidepressant with a tricyclic antidepressant without finding significant difference,[10] was not included in the analysis but appears in the table on bmj.com.

Box 1: Warnings about antidepressants in children

June 2003—Letter from GlaxoSmithKline to all medical practitioners in the United Kingdom actively discouraging the use of paroxetine in patients less than 18 years of age, on the basis of recently disclosed trial results showing unacceptable risk of serious adverse effects, including hostility and suicidality. www.researchprotection.org/risks/PaxilRisks0603.html (accessed 17 Mar 2004)

June 2003—Warning from the UK Committee on Safety of Medicines against the use of paroxetine in children. www.mhra.gov.uk/news/2003/seroxat10603.pdf (accessed 1 Mar 2004)

August 2003—Warnings about venlafaxine, promulgated by the manufacturer. www.effexor.com/pdf/Wyeth_HCP.pdf (accessed 30 Dec 2003)

December 2003—UK Committee on Safety of Medicines bans all remaining selective serotonin reuptake inhibitors, except fluoxetine, for use in patients under 18 years of age. medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ssrioverview_101203.pdf (accessed 30 Dec 2003)

March 2004—FDA issues. Public Health Advisory on cautions for use of antidepressants in adults and children. www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html (accessed 27 Mar 2004)

Funding of trials

Pharmaceutical companies paid for the trials and otherwise remunerated the authors of at least three of the four larger studies (table).

A table showing details of studies reviewed is on bmj.com

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Box 2: Search strategies

Medline (1989 to February 2004) and Embase (1988 to 2004 week 04)
("Depressive Disorder"[MeSH]) AND ("Serotonin Uptake Inhibitors"[MeSH] OR "Antidepressive Agents"[MeSH] OR "Antidepressive Agents, Second-Generation"[MeSH] OR "Antidepressive Agents, Tricyclic"[MeSH] OR citalopram OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR moclobemide OR nefazodone OR paroxetine OR reboxetine OR sertraline OR trazodone OR venlafaxine) AND (randomized controlled trial[Publication Type]) AND ("Child"[MeSH] OR "Adolescent"[MeSH])

PsycLIT (1985 to February week 3 2004)
(exp Serotonin Reuptake Inhibitors/ or exp Antidepressant Drugs/ or exp Major Depression/ or exp PAROXETINE/ or exp FLUOXETINE/ or exp SERTRALINE/ or exp MOCLOBEMIDE/ or exp FLUVOXAMINE/ or exp CITALOPRAM/ or exp TRAZADONE/ or exp Imipramine/ or exp Antidepressant Drugs/ or exp TRICYCLIC ANTIDEPRESSANT DRUGS/ or exp Desipramine/ or (keywords) venlafaxine or duloxetine or escitalopram or milnacipran or mirtazapine or moclobemide or nefazodone or reboxetine) AND exp CHILD PSYCHIATRY/

Efficacy

The table on bmj.com summarises the trials reviewed. A total of 477 patients in the six studies were treated with paroxetine, fluoxetine, sertraline, or venlafaxine (≥23% dropouts), and 464 were treated with placebo (≥25% dropouts). Of 42 reported measures, only 14 showed a statistical advantage for an antidepressant. None of the 10 measures relying on patient reported or parent reported outcomes showed significant advantage for an antidepressant, so that claims for effectiveness were based entirely on ratings by doctors. No study presented data on rates of attempted self harm, presentations to emergency or mental health services, or school attendance.

Two small studies found no statistically significant advantage for antidepressants over placebo on any of the outcome measures reported.[5 6] Of the remaining four papers, two did[7 9] and two did not[3 8] show statistically significant advantages for antidepressants over placebo on primary outcome measures.

We meta-analysed the five published studies on selective serotonin reuptake inhibitors by using the standardised mean difference (Hedges' *g*) as the measure of effect.[3 5 7–9] We averaged relevant outcome measures within studies and then pooled them across studies by using a random effects model. We included all continuous outcome measures related to depression and health related quality of life. The effect size was small 0.26 (95% confidence interval 0.13 to 0.40). Assuming a standard deviation of scores of 11 to 14 on the revised children's depression rating scale in depressed children, an effect size of 0.26 is equivalent to a very modest 3 to 4 point difference on the scale, which has a range of possible scores from 17 to 113.

As regards unpublished studies, we note from a report from the US Food and Drug Administration Center for Drug Evaluation and Research that only one of nine showed a statistical advantage for drug over placebo.[10]

Funding sources for trials of antidepressants

Trial	Source of funding
Simeon et al (1990)[5]	Not disclosed
Mandoki et al (1997)[6]	Not disclosed
Emslie et al (1997)[7]	Attributed to National Institute of Mental Health, but FDA data show that study was sponsored by Eli Lilly[20]
Keller et al (2001)[3]	GlaxoSmithKline; two authors employees of GlaxoSmithKline
Emslie et al (2002)[9]	Eli Lilly; all authors employed by or otherwise contracted to Eli Lilly
Wagner et al (2003)[8]	Pfizer; all authors paid by Pfizer; two Pfizer employees; "study supervisor" held stock options in Pfizer

Adverse effects of treatment

Because the follow up period for the randomised controlled trials was short, and numbers were relatively small, serious adverse effects were likely to be few. When they do occur, we would therefore expect authors to draw attention to them, along with data available from other sources that suggest that serious adverse effects might occur. Of 93 patients treated with paroxetine by Keller et al, 11 had serious adverse events, compared with 2/87 in the placebo group.[3] The authors presented no statistical analysis, but the difference was significant (Pearson's $\chi^2=6.09$, df = 1, $P=0.01$). In spite of this striking difference in serious events between paroxetine and placebo, Keller et al concluded that, "paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious," even though seven patients were admitted to hospital during treatment with paroxetine.[3] Furthermore, despite five of these patients being admitted to hospital with events known to occur with the use of selective serotonin reuptake inhibitors, including suicidality, only one serious event (headache) was judged by the treating investigator to be related to paroxetine treatment. The criteria for determining causation of serious events were not stated.

Among 373 patients in the trial by Wagner et al, 9% (17/189) treated with sertraline withdrew because of adverse events, compared with 3% (5/184) in the placebo group.[8] These authors also published no statistical analysis of this outcome or details of the adverse effects, but the difference in withdrawal rates was significant (Pearson's $\chi^2=6.62$, df = 1, $P=0.01$). Wagner et al reported seven adverse effects that occurred in at least 5% of the sertraline group, at least twice as often as in the placebo. Despite these results they concluded that, "sertraline is an effective, safe, and well tolerated short-term treatment for children and adolescents."

Other sources of data support the view that adverse effects might be more frequent than the authors of these studies imply. For example, children and adolescents with obsessive compulsive disorder exhibit a variety of treatment emergent effects of fluoxetine, including an "activation syndrome" affecting up to half of young patients; self injurious ideation or behaviour was seen in 6/42 patients.[12] The failure of drug companies to disclose increased suicidal activ-

ity secondary to these drugs is also the subject of much debate.[13]

Study methods

Withdrawals

High rates of withdrawal occurred in all the studies, ranging from 17% to 32% for patients treated with selective serotonin reuptake inhibitors and from 17% to 46% for placebo treated patients. Such high rates of withdrawal over relatively short study periods (typically 8-10 weeks) raise concerns about the possible introduction of bias by the analytical method chosen. Most of these studies used an intention to treat, last observation carried forward approach. The last observation carried forward approach is based on the assumption (unlikely in childhood depression) that the condition of patients who have dropped out would have remained unchanged for the remainder of the study, had they continued in it. In none of these studies were the withdrawn patients assessed at the end of the trial to assess their outcome (a "true" intention to treat approach). The higher the drop-out rate the more likely a last observation carried forward approach is to produce unreliable results.

Use of categorical outcomes

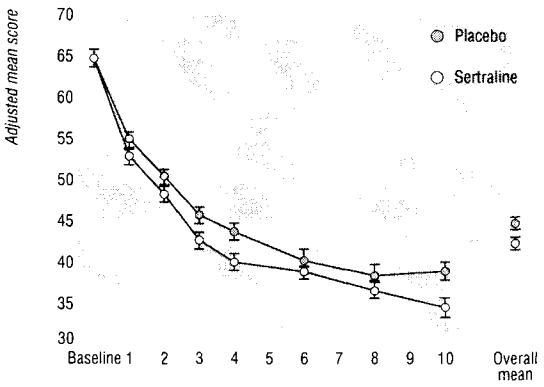
Categorical outcomes (such as response and remission) are likely to inflate small differences between groups.[14] As categorical outcomes are usually based on data from continuous measures, the difference in continuous measures should always be examined first and given priority. This approach has often not been followed in the childhood antidepressant literature, where three of six nominated primary outcome variables were categories created by dividing continuous measures.

Unblinding

The real proportion of effect attributable to a selective serotonin reuptake inhibitor may be less than apparent, given that the placebo versus drug difference is less where active placebo is used (that is, placebo with an active pharmacological principle that produces side effects).[15] This finding suggests that part of the impact of an active drug might be due to unblinding as a result of detection of side effects by patients and doctors. No data are given in any paper reviewed here on the effectiveness of blinding. Blinding was "essentially" maintained for a subset of the participants in the Emslie (1997) study.[7,16] However, the authors did not examine adverse events as a possible cause of unblinding, and they noted in their conclusions that "the role that minimal side effects for the active medication played undoubtedly contributes to these findings." Other work suggests that clinicians will have performed better than chance at predicting whether or not their patients were on the active drug,[17] so that unintended bias may be a contributing or decisive cause of observed differences between the drug and placebo groups.[18]

Doubtful clinical implications of statistical superiority to placebo

Given the large placebo effect in all six studies reviewed, the clinical significance of the drug effect should be questioned. For example, in spite of a one week placebo lead-in and exclusion of initial placebo responders, Emslie et al (2002) found that, for the measure showing the greatest advantage of fluoxetine over placebo (revised children's depression rating scale), the improvement in the placebo group was 70% of the improvement seen in the fluoxetine group (22 point decrease for fluoxetine *v* 15 points for placebo).[7] Similarly, the fact that 87% of the improvement in the sertraline group was reproduced in the placebo group casts some doubt on Wagner et al's claim,[9] and Varley's editorial support for that claim,[19] that their results are clinically, as well as statistically, significant. This is illustrated by the graph from their paper (fig), which shows that, although they found a significant difference at 10 weeks, it was very small in size and unlikely to be clinically important.



Weekly and overall adjusted mean scores on revised children's depression rating scale. Week 1, P=0.09; week 2, P=0.08; week 3, P=0.01; week 4, P=0.008; week 6, P=0.37; week 8, P=0.18; week 10, P=0.001; mean response, P=0.007. Reproduced, with permission, from *JAMA* 2003;290:1033-41

Quality of reporting

In discussing their own data, the authors of all of the four larger studies have exaggerated the benefits, downplayed the harms, or both. This raises the question of whether the journals that published the research reviewed the studies with a sufficient degree of scrutiny, given the importance of the subject. Despite the authors' initial claims, data reported by Keller et al showed no statistically significant advantage of drug over placebo.[2] Neither of the two pre-designated primary outcome measures (change from baseline in the score on the Hamilton rating scale (depression) and "response" defined as a fall in score below 8 or by 50%), were significantly different between paroxetine and placebo. Interpretation of these data was confused by an unexplained change in the definition of "response" to "reduction of HAM-D to below 8". Altering this definition enabled the authors to claim significance on a primary endpoint. The authors have subsequently modified that claim to having shown a "signal for efficacy."[20]

The two studies ultimately published by Emslie and colleagues in 1997 and 2002 (B1Y-MC-X065 and B1Y-MC-HCJE) were the subject of a "statistical review" by the US Center for Drug Evaluation and Research.[21]

That document showed that the prespecified primary outcome measure in the first Emslie study was proportion of completing patients who achieved recovery. The original definition of recovery in the study protocol was a score of ≤ 28 on the revised children's depression rating scale ("remission") and a clinical global impression-improvement score of 1 or 2. Two things are clear: firstly, this measure did not reach statistical significance (P = 0.339); secondly, when the study was published, new primary outcome measures were used (see table on bmj.com).

The authors chose a reduction from baseline of ≥ 30% on the revised children's depression rating scale (shown on post hoc analysis of the first study to show favourable advantage to fluoxetine[21]) as the single primary endpoint for the second study (B1Y-MC-HCJE).[8] However, they found no statistical difference between fluoxetine and placebo on this measure. Although Emslie et al did state in the results section that significance was not reached on "response," they did not make it explicit that this meant a failure to show change on their stated primary outcome, and they make much more of the secondary endpoints that did favour fluoxetine. Whenever the failure to show superiority of fluoxetine over placebo in achieving 30% reduction from baseline on the rating scale is reported, mean improvement and "remission" are given equal weight in the published paper, implying that one or both of them was also a primary endpoint. The authors go on to make an unqualified claim of efficacy, even though the drug showed no significant advantage over placebo on the single primary outcome measure. The independent "statistical review," on the other hand, concludes that, "the sponsor did not win on these two pediatric depression studies based on the protocol specified endpoint. The evidence for efficacy based on the pre-specified endpoint is not convincing."[21]

No information is given that provides insight into why the US Food and Drug Administration ultimately approved fluoxetine for childhood depression. Nor is it clear why the UK Committee on Safety of Medicines exempted fluoxetine from its criticisms through accepting the published versions of these studies, when it did not do so in relation to sertraline.[22]

Wagner et al described their work as "two randomised controlled trials," but the methods are identical, and they and we treated them as a single trial.[7] The trials when combined included a large enough number of participants (364) to have adequate statistical power to detect small differences between treatments. Neither trial showed a statistically significant advantage for sertraline over placebo in terms of the primary endpoint, which in this case was change from baseline in the revised children's depression rating scale score.[22] Only when the trials were combined did a statistically significant difference emerge, although this was very small (about 2.7 points on a 113 point scale). Furthermore, we question Wagner et al's inference that because tricyclic antidepressants are no more beneficial than placebo, even a small advantage for newer antidepressants justifies their use. The availability of older interventions that are not beneficial should not lower the threshold for accepting a new intervention, especially given the availability of more effective psychological treatments with no known adverse effects.[23]

Additional educational resources

Medicines and Healthcare Products Regulatory Agency (edicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ssrioverviewclintrialdata_101203.hum)—Selective serotonin reuptake inhibitors: an overview of regulatory status and CSM advice relating to major depressive disorder in children and adolescents

Moncrieff J. *Is psychiatry for sale?* Maudsley discussion paper, 2003 (available as booklet from the Institute of Psychiatry: sarah.smith@iop.kcl.ac.uk)—An examination of the influence of the pharmaceutical industry on academic and practical psychiatry

Social Audit (www.socialaudit.org.uk)—Aims to ensure that organisations of all kinds "properly and adequately serve the interests and needs of the public," and takes a particular interest in antidepressants

Healthy Skepticism (www.healthyskepticism.org)—An international non-profit organisation that aims to improve health by reducing harm from misleading drug promotion

Garland EJ. Facing the evidence: antidepressant treatment in children and adolescents. *CMAJ* 2004;170:489-91—A critique of the way drug companies manage information

Conclusion

The trials consistently found large improvements in placebo groups, with statistically significant additional benefits for active drug on some measures only. These results make a major benefit from newer antidepressants unlikely, but a small benefit remains possible. Randomised controlled trials usually underestimate the serious adverse effects of drugs.[24] The fact that serious adverse effects with newer antidepressants are common enough to be detected in randomised controlled trials raises serious concerns about their potential for harm. The magnitude of benefit is unlikely to be sufficient to justify risking those harms, so confidently recommending these drugs as a treatment option, let alone as first line treatment, would be inappropriate.

We are concerned that biased reporting and overconfident recommendations in treatment guidelines may mislead doctors, patients, and families. Many will undervalue non-drug treatments that are probably both safer and more effective. Accurate trial reports are a foundation of good medical care. It is vital that authors, reviewers, and editors ensure that published interpretations of data are more reasonable and balanced than is the case in the industry dominated literature on childhood antidepressants. This is particularly true in the light of the increasing reliance on online abstracts by doctors who lack the time or the skills for detailed analysis of complete trial reports.

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Lesson of the week

Recurrent hypoglycaemia in a diabetic patient as a result of unexpected renal failure

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Hypoglycaemia is the most frequent complication of diabetes, affecting 10% to 25% of diabetic patients at least once a year and accounting for 3% to 4% of deaths in those treated with insulin.[1] Diabetic renal disease is a common complication and is the most prevalent cause of end stage renal disease in the western world.[2]

The kidney plays an important role in glucose homoeostasis: in addition to metabolising between 30% and 40% of insulin,[3] it provides up to 45% of endogenous glucose through gluconeogenesis during a prolonged fast.[4] In renal failure, it cannot metabolise insulin or generate glucose, thereby increasing the risk of hypoglycaemia. Hypoglycaemia affects 67% of diabetic patients with renal failure, and in almost half (46%) of patients it is often related to the medication they are taking.[5] I present a case where a decline in renal function after treatment with diclofenac resulted in recurrent episodes of hypoglycaemia, highlighting the importance of monitoring renal function in a diabetic patient with new onset hypoglycaemia.

Case report

A 64 year old man with a 15 year history of type 2 diabetes mellitus presented with a third episode of hypoglycaemia in two weeks. His diabetes was well controlled with 35 units of insulin a day, and he had had no hypoglycaemic episodes in the past two years. He had no history of hypertension, retinopathy, or nephropathy. He was compliant with his diet, insulin therapy, and exercise programme. At a regular check up two months previously, his blood pressure had been 116/70 mm Hg and his HbA_1 level 0.07 (normal 0.050 to 0.064), with home blood glucose readings of 5.0-8.0 mmol/l during the previous month. The ratio of urine microalbumin concentration to creatinine concentration was 2.0 (< 2.5), and serum creatinine concentration was 104 μmol/l (44-106 μmol/l).

He had started to experience low back pain a month before presentation with his third episode of hypoglycaemia and saw his family doctor, who prescribed diclofenac 50 mg twice daily; his back pain then improved. Two weeks later, he started to experience headache and irritability with periods of

Remember to check renal function in a diabetic patient with new onset hypoglycaemia

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