

Treating Depressed Children With Antidepressants: More Harm than Benefit?

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Abstract Since the FDA held hearings in February 2004 on the safety of antidepressants in children, there has been a great deal of controversy regarding the use of antidepressants in children, culminating in the well publicized black box warnings about increased risk of suicidal behavior in children and young adults (up to age 25) caused by these medications. Using questions that a parent might ask, the current article attempts to summarize the efficacy and safety data on the use of antidepressants in children so that psychologists, with or without prescription privileges, may be able to inform parents of young patients about the science behind this treatment. This article is based on a presentation at the 2007 American Psychological Association conference by the author in acceptance of the 2006 APAHC Bud Orgel Award for Distinguished Achievement in Research. Much of the information described in this article is drawn from the recent APA Report of the Working Group on Psychoactive Medications for Children and Adolescents. (Brown et al. 2006; available at www.apa.org/pi/cyf/childmeds.pdf) culminating in a book by the same authors (Brown et al., *Childhood mental health disorders: Evidence base and contextual factors for*

psychosocial, psychopharmacological, and combined interventions 2007).

Keywords Depression · Antidepressant · Children

How Effective are Antidepressants in Treating Depressed Children?

Meta-analyses have consistently indicated that tricyclic antidepressants do not produce better a outcome than a placebo in depressed children (Ambrosini, Bianchi, Rabinovich, & Elia, 1993; Dujovne, Barnard, & Rapoff, 1995; Fisher & Fisher, 1996; Hazell, O'Connell, Heathcote, Robertson, & Henry, 1995; Michael & Crowley, 2002; Sommers-Flanagan & Sommers-Flanagan, 1996). Six of the seven published randomized controlled studies of the efficacy of SSRIs in children and adolescents report significant differences on some measures, suggesting SSRIs may work better (Emslie et al., 1997, 2002; Keller et al., 2001; Simeon, Dinicola, Fergusson, & Copping, 1990; TADS, 2004; Wagner et al., 2003; Wagner et al., 2004).

However, methodological issues and publication biases may have inflated the apparent efficacy of SSRIs in the treatment of depressed adolescents and children (Garland, 2004; Lancet, 2004) just as these issues appear to have inflated apparent antidepressant efficacy in adults (Turner et al., 2008; Kirsch et al., 2008). Jureidini et al. (2004) critically reviewed the available published controlled trials of newer antidepressants in children and found that whereas almost half of the clinician-rated measures favored the study drug, none of the patient-rated or parent-rated measures favored the antidepressants over placebo. In addition to questioning the clinical significance of these results, Jureidini et al. (2004) highlighted the

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methodological weaknesses of these trials, including reliance on the last observation carried forward, an emphasis on secondary endpoints, transforming continuous variables into categorical outcomes (e.g., response rates) thereby inflating small differences, and possible unblinding due to side effects from active medication. An independent analysis by the FDA, assisted by researchers at Columbia University, concluded that only 3 out of 15 randomized controlled trials (that included all published and unpublished datasets) of the newer antidepressants showed them to be more effective than placebo on primary outcome measures in depressed children (Laughren, 2004), though several of these trials had positive and significant effects on secondary measures.

What are the Side Effects and Risks of Antidepressants?

The most common side effects of SSRIs in studies of patients with depressive disorders include agitation, sleep disruption, gastrointestinal problems, and sexual problems (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999). Evidence from animal studies indicates that SSRIs may shrink gonadal tissue (USDHHS, 2004), and recent case reports in adults suggest the possibility that sexual side effects can persist even after medication is withdrawn in a small minority of cases (Csoka & Shipko, 2006). These data along with case reports of growth suppression in children linked to SSRIs (Weintrob et al., 2002), raise concerns about the possibility that antidepressants could alter pubertal development in adolescents, though this has not yet been systematically investigated.

Side effects and medical risks increase when SSRIs are combined with other medications (Dalfen & Stewart, 2001), a common practice (Antonuccio et al., 1999). In addition, many patients experience troubling withdrawal symptoms when SSRIs are discontinued (Coupland, Bell, & Potokar, 1996; Fava, 2002; Rosenbaum, Fava, Hood, Ashcroft, & Krebs, 1998). Antidepressant induced mania (e.g., Preda, MacLean, Mazure, & Bowers, 2001) and acts of deliberate self-harm (e.g., Donovan et al., 2000; Healy, 2003) are also reason for concern.

Do Antidepressants Fix a Chemical Imbalance?

There is no evidence that depression is caused by a chemical imbalance, nor is there evidence that antidepressants fix a chemical imbalance (Lacasse & Leo, 2005). The diagnosis of depression is determined by the pattern of symptoms presented by the patient based on criteria from the Diagnostic and Statistical Manual-IV-TR (APA, 2005).

There is no blood test that can determine whether or not a patient is depressed.

How Many Children are Prescribed Antidepressants?

More than 10 million antidepressant prescriptions were written for children and adolescents in the United States during 2002, data that reflected a steep slope upward (Goode, 2004; Rigoni, 2004). Furthermore, in 2002, approximately 6% of outpatient physician visits for U.S. children aged 5 to 17 involved the prescription, ordering, or provision of antidepressant medication (NCHS, 2004). Because of the black box warnings, these numbers may now be trending downward but time will tell.

Despite the Warnings Highlighted in the Media, Could the Use of Antidepressants Actually Decrease Risk for Suicide in Depressed Children?

This is possible. We just do not know. Some population studies have shown a decrease in childhood suicide rates in communities with higher SSRI prescription rates (e.g., Gibbons, Hur, Bhaumik, & Mann, 2006) but this is a correlational result and does not prove a causal relationship. Similarly, reports suggesting that an 18% increase in childhood suicide may be linked to an 18% decrease in antidepressant prescribing (Lineberry et al., 2007), coinciding with the black box warning, represent correlational data and not causal results. Those who might be willing to attribute this increase in suicide to decreased antidepressant prescribing might just as well consider the possibility that it may be due to a large corresponding increase in antipsychotic medication prescriptions for children (Healy, 2006; Moreno et al., 2007). This would be a similar inferential error.

Randomized controlled studies are the only studies that can definitively prove causation. These controlled FDA studies show an increased risk of suicidal behavior relative to placebo. This pattern of results is similar to the pattern found for hormone replacement therapy (HRT) in women, i.e., the population studies suggested HRT was helpful, while the randomized controlled trials (RCTs) found it to be harmful. The RCTs are justifiably given more weight.

It is still possible that there is a decreased risk of suicidal behavior in patients who are prescribed antidepressants relative to doing nothing. RCTs comparing antidepressant treatment with no treatment have not yet been done. Of course, no responsible professional would suggest withholding all treatment from a child who meets criteria for major depression, i.e., nobody is suggesting doing nothing for depressed children given the array of scientifically

supported psychosocial treatment options. If using antidepressants actually does reduce suicidal behavior compared with doing nothing, the available controlled FDA studies (showing increased risk of harm but minimal benefit compared with placebo) would suggest it is quite likely due to the therapeutic alliance with the treating professional or some other related variable and not the chemical in the antidepressant.

What Do We Know About the Risk/Benefit Profile of Antidepressants in Children?

The FDA analysis of the SSRI and SNRI database of antidepressants (24 trials involving a total of 4,400 patients) found suicidal behavior in approximately 4% of those patients randomly assigned to the antidepressant compared with 2% of those randomly assigned to placebo (Hammad et al., 2006). While the risk of increased suicidality appears to be relatively low (i.e., two extra suicidal patients for every 100 treated with an antidepressant compared with a placebo) and no patients actually completed suicide in the FDA database of controlled trials, the stakes are clearly high. A more recent analysis using different statistical methods found 3% suicidality in the medication conditions versus 2% suicidality in the placebo conditions (Bridge et al., 2007). Unfortunately, data concerning potential risk are limited because randomized trials involving antidepressants have typically excluded suicidal patients. The acceptability of the risk/benefit profile with fluoxetine, the only antidepressant to show evidence of some benefit in depressed youth and the only antidepressant approved by the FDA for use with depressed children and adolescents, involves value judgments about the cost of harm-related and psychiatric-related adverse events. A legitimate question is “How many children should benefit from an antidepressant to justify one extra child harmed by an antidepressant?”

Whittington et al. (2004) reviewed all of the available data (published and unpublished) from controlled trials of SSRIs in depressed youth. This meta-analysis concluded that the risk/benefit profile (number needed to treat to benefit one extra patient, NNTB, versus number needed to treat to cause a serious adverse harm event in one extra patient, NNTH) was favorable for fluoxetine, but was unfavorable for paroxetine, sertraline, citalopram, and venlafaxine (see also Kendall, Pilling, & Whittington, 2005).

The Treatment of Adolescent Depression Study (TADS, 2004), conducted more recently than the studies included in the Whittington et al. (2004) review, offers the only data relevant to the short-term relative risks of treating patients

with psychotherapy alone, medication alone, the combination, or a placebo. Despite the fact that suicidality decreased across all four arms of this study, the fluoxetine condition had a significantly higher rate of harm-related adverse events (such as suicidal ideation), physiological side effects (diarrhea, insomnia, and sedation), and psychiatric adverse events (irritability, mania, and fatigue) compared with placebo or CBT alone. Using the global response measure from the TADS study, the NNTB is about three in the combined condition, five for fluoxetine alone, and 12 for CBT alone, all compared to placebo. In terms of harm-related adverse events, the NNTH is approximately 20 in the fluoxetine-containing conditions in comparison to nonmedication conditions. When considering psychiatric-related adverse events, the NNTH is approximately 10 in the fluoxetine alone condition compared with placebo and only about five compared with CBT alone. In other words a practitioner would only have to treat 5 patients with fluoxetine to harm one extra patient compared with treating those same 5 patients with CBT. Adding together the risk for psychiatric, physiological side effects, and harm-related events reduces the NNTH for fluoxetine even further.

Based on the Current Science, What are the Best Choices for Treating a Depressed Child?

Parents and treatment providers are faced with tough choices. It is important for them to understand that many psychosocial interventions, including interpersonal psychotherapy, cognitive-behavior therapy, psychoeducational interventions, and exercise, have at least some scientific support (Brown et al., 2006, 2007). Of all the antidepressants, only fluoxetine has any evidence of efficacy beyond placebo for youth. Considering both safety and efficacy data together further complicates the decision about which treatment to use with a depressed child. Given the fact that children are essentially involuntary patients (i.e., parents make them take prescribed medications), it could be argued that treatment decisions should be guided by evidence that meets the highest possible safety standards, i.e., a “first do no harm” approach. In fact, the report of the APA Working Group on Psychoactive Medications for Children and Adolescents (Brown et al., 2006) concluded “the preponderance of the available evidence indicates that psychosocial treatments are safer than psychoactive medications”.

When considering efficacy, the TADS study, in my view the best comparative study ever done in depressed children, ranks the treatments from best to worst this way: combination treatment (fluoxetine and CBT) followed by fluoxetine followed by CBT followed by placebo. Analysis of longer-term efficacy (Kuehn, 2007; TADS, 2007) shows

Table 1 Potential patient handout about TADS (2004, 2007) study

Who was studied? A total of 439 patients between the ages of 12 and 17 with major depression were treated for 12 weeks with placebo, CBT, fluoxetine, or combination treatment	Children who took placebo		Children given CBT		Children who took fluoxetine		Children given CBT and fluoxetine	
	12 weeks	18 mos FU	12 weeks	18 mos FU	12 weeks	18 mos FU	12 weeks	18 mos FU
% Judged recovered on a global improvement scale	35%	NA	43%	81%	61%	81%	71%	86%
Average degree of improvement on the primary depression measure (CDRS)	32%	NA	29%	53%	38%	54%	44%	56%
% Who withdrew consent, terminated prematurely, or dropped out	21%	NA	22%	50%	17%	50%	14%	36%
<i>Side effects</i>								
% Who experienced psychiatric adverse events (e.g., mania, agitation)	8%	NA	1%	UD	18%	UD	11%	UD
% Who experienced nonpsychiatric adverse events (e.g., headache, sedation, gastrointestinal problems, insomnia)	At least 9%	NA	0%	UD	At least 12%	UD	At least 6%	UD
% Exhibiting self-harm (e.g., suicidal ideation or behaviors)	5.4%	NA	4.5%	6.3%	11.9%	14.7%	8.4%	8.4%

NA = not applicable because placebo condition was terminated after 12 weeks

UD = unable to determine from published article

that CBT alone caught up with fluoxetine alone at 18 week follow-up and CBT caught up with combination treatment at 36 week follow-up (81% response for CBT, 81% response for fluoxetine, 86% response for combination treatment). When considering safety, the treatment rankings from best to worst are entirely different: CBT followed by placebo followed by combination treatment followed by fluoxetine alone. These safety rankings were maintained (suicidal events were 6.3% in CBT, 8.4% in combination treatment, and 14.7% in fluoxetine, not reported for placebo) at follow-up (TADS, 2007), though combination treatment crept closer to CBT.

Using the TADS studies (TADS, 2004; TADS, 2007) as a guide, it is possible to tailor treatment to parent values and preferences (Antonuccio, *in press*). If the parents' highest priority is safety, CBT alone (or, based on the good performance of placebo, another psychosocial intervention) would be a reasonable first choice. If the parents' highest priority is short-term efficacy, the combination of fluoxetine and CBT may offer the best short-term outcome. If a parent is willing to wait 36 weeks, it looks like CBT alone may offer the best option in terms of short-term safety, long-term safety, and efficacy equivalent to combination treatment at long-term follow-up. Table 1 offers a tabular summary of these data that can be used as a patient handout to help parents and adolescents weigh their options.

There are published materials that cover some of the cognitive behavioral skills for preventing and overcoming

depression. Such books may be helpful resources for parents or therapists who want to teach children "depression inoculation" skills. These books include *The Optimistic Child* (Seligman, Reivich, Jaycox, & Gillham, 1995), *Adolescent Coping with Depression Course* (Clarke, Lewinsohn, & Hops, 1990; accessible and downloadable online at no charge at <http://www.ori.org/Research/scientists/scientistPublications/Lewinsohn/LewinsohnCWDpublications.htm>), and *Feeling Good* (Burns, 1999).

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