

## **Antidepressant and Suicidality**

### **Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-Analysis of Randomized Controlled Trials**

Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA.  
JAMA. 2007 Apr 18;297(15):1683-96.

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**CONTEXT:** The US Food and Drug Administration (FDA) has issued warnings that use of antidepressant medications poses a small but significantly increased risk of suicidal ideation/suicide attempt for children and adolescents.

**OBJECTIVE:** To assess the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders.

**DATA SOURCES AND STUDY SELECTION:** PubMed (1988 to July 2006), relevant US and British regulatory agency reports, published abstracts of important scientific meetings (1998-2006), clinical trial registries, and information from authors. Studies were published and unpublished randomized, placebo-controlled, parallel-group trials of second-generation antidepressants (selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine) in participants younger than 19 years with MDD, OCD, or non-OCD anxiety disorders.

**DATA EXTRACTION:** Information was extracted on study characteristics, efficacy outcomes, and spontaneously reported suicidal ideation/suicide attempt.

**DATA SYNTHESIS:** Twenty-seven trials of pediatric MDD (n = 15), OCD (n = 6), and non-OCD anxiety disorders (n = 6) were selected, and risk differences for response and for suicidal ideation/suicide attempt estimated by random-effects methods. Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11.0%; [95% confidence interval {CI}, 7.1% to 14.9%]), OCD (19.8% [95% CI, 13.0% to 26.6%]), and non-OCD anxiety disorders (37.1% [22.5% to 51.7%]), corresponding to a number needed to treat (NNT) of 10 (95% CI, 7 to 15), 6 (4 to 8), and 3 (2 to 5), respectively. While there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs placebo (0.7%; 95% CI, 0.1% to 1.3%) (number needed to harm, 143 [95% CI, 77 to 1000]), the pooled risk differences within each indication were not statistically significant: 0.9% (95% CI, -0.1% to 1.9%) for MDD, 0.5% (-1.2% to 2.2%) for OCD, and 0.7% (-0.4% to 1.8%) for non-OCD anxiety disorders. There were no completed suicides. Age-

stratified analyses showed that for children younger than 12 years with MDD, only fluoxetine showed benefit over placebo. In MDD trials, efficacy was moderated by age, duration of depression, and number of sites in the treatment trial.

**CONCLUSIONS:** Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

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### **Do Antidepressants Cause Suicidality in Children? A Bayesian Meta-Analysis**

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Clin Trials. 2006;3(2):73-90; discussion 91-8.

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**BACKGROUND:** To quantify the risk of suicidal behavior/ideation (suicidality) for children who use antidepressants, the FDA collected randomized placebo-controlled trials of antidepressant efficacy in children. Although none of the 4487 children completed suicide, 1.7% exhibited suicidality. The FDA meta-analyzed these studies and found sufficient evidence of an increased risk to require a black-box warning on antidepressants for children.

**PURPOSE:** The FDA considered different drug formulations and psychiatric diagnoses to be equivalent in their effect on suicidality. If this assumption does not hold, the FDA analysis may have underestimated the variance of the risk estimate. We investigate the consequences of relaxing these assumptions.

**METHODS:** We extend the FDA analysis using a Bayesian hierarchical model that allows for a study-level component of variability and facilitates extensive sensitivity analyses.

**RESULTS:** We found an association between antidepressant use and an increased risk of suicidality in studies where the diagnosis was major depressive disorder (odds ratio 2.3 [1.3, 3.8]), and where the antidepressant was an SSRI (odds ratio 2.2 [1.3, 3.6]). We did not find evidence for such an association in the complement sets of trials. Although the results based on the hierarchical model are insensitive to model perturbations, the robustness of the FDA's meta-analysis to model assumptions is less clear. These data have limited generalizability due to exclusion of patients with baseline risk of suicide and the use of relatively short duration trials.

**CONCLUSIONS:** Because of model specification and interpretation issues raised in this paper, we conclude that the evidence supporting a causal link between antidepressant use and suicidality in children is weak. The use of Bayesian hierarchical models for meta-analysis has facilitated the incorporation of potentially important sources of variability and the use of

sensitivity analysis to assess the consequences of model specifications and their impact on important regulatory decisions.

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### **Generalizing from Clinical Trial Data: A Case Study. The Risk of Suicidality Among Pediatric Antidepressant Users**

Greenhouse JB, Kaizar EE, Kelleher K, Seltman H, Gardner W. Stat Med. 2008 May 20;27(11):1801-13.

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For the results of randomized controlled clinical trials (RCTs) and related meta-analyses to be useful in practice, they must be relevant to a definable group of patients in a particular clinical setting. To the extent this is so, we say that the trial is generalizable or externally valid. Although concern about the generalizability of the results of RCTs is often discussed, there are few examples of methods for assessing the generalizability of clinical trial data. In this paper, we describe and illustrate an approach for making what we call generalizability judgments and illustrate the approach in the context of a case study of the risk of suicidality among pediatric antidepressant users.

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### **Placebo Response in Randomized Controlled Trials of Antidepressants for Pediatric Major Depressive Disorder**

Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA.

Am J Psychiatry. 2009 Jan;166(1):42-9. Epub 2008 Dec 1.

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**OBJECTIVE:** The authors examined characteristics and predictors of response to placebo in all available reports of short-term randomized controlled trials of antidepressants for pediatric major depressive disorder.

**METHOD:** Response, defined as a score  $\leq 2$  on the improvement item of the Clinical Global Impression scale, and potential predictors were extracted from 12 published and unpublished randomized controlled trials of second-generation antidepressants in participants 6-18 years of age with major depression.

**RESULTS:** The single best predictor of the proportion of patients taking placebo who responded to treatment was the number of study sites. Baseline severity of illness also emerged as a significant inverse predictor of placebo response, although the strength of this relationship was diminished when number of sites was controlled for. After one large fluoxetine trial was excluded, younger participants showed a higher placebo response rate than older adolescents. Higher placebo response rates in more recent studies were explained by an increasing trend

toward large multisite trials and by publication delays and failures to publish some negative trials.

**CONCLUSIONS:** The recent shift toward large multisite trials of antidepressant medications for pediatric major depression may be contributing to an increasing incidence of response to placebo. Pharmacotherapy studies of pediatric depression that carefully recruit patients with at least moderately severe depression may be more informative and efficient than many trials conducted to date. Such studies should have sufficient power to determine whether age moderates medication and placebo response.

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### **Suicidality and Its Relationship to Treatment Outcome in Depressed Adolescents**

Barbe RP, Bridge J, Birmaher B, Kolko D, Brent DA. *Suicide Life Threat Behav.* 2004 Spring;34(1):44-55.

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This study investigates the impact of suicidality on treatment outcome in 107 depressed adolescents who participated in a clinical trial, and received either cognitive-behavioral (CBT), systemic-behavioral-family (SBFT), or non-directive-supportive therapy (NST). Suicidal depressed adolescents had a higher dropout rate and were more likely to be depressed at the end of treatment, in large part due to the particularly poor response of suicidal patients to NST. The relationship between suicidality and treatment response was mediated by severity of depression and hopelessness at intake. Hopelessness should be specifically targeted early in treatment. Suicidal depressed adolescents should not receive NST but a specific treatment like CBT.

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### **The Contribution of Pharmacoepidemiology to the Antidepressant-Suicidality Debate in Children and Adolescents**

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*Int Rev Psychiatry.* 2008 Apr;20(2):209-14.

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A number of concerns have recently been raised about whether or not antidepressant medications are associated with suicidal thoughts and behaviour in children and adolescents. These concerns are based largely on results of meta-analyses of randomized, controlled trials (RCTs). Controversy exists about generalizing evidence from short-term RCTs, designed primarily to test efficacy outcomes, to routine practice settings. Pharmacoepidemiological studies complement RCTs by using observational methods to examine safety and effectiveness of medications in the general population. This article reviews the contribution of pharmacoepidemiology to the

controversy surrounding suicide risk in children and adolescents taking antidepressants, noting how variations in study design and adjustment for potential confounding factors influence outcome.

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### **The Risks and Benefits of Antidepressant Treatment for Youth Depression**

Bridge JA, Salary CB, Birmaher B, Asare AG, Brent DA.

Ann Med. 2005;37(6):404-12.

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The U.S. Food and Drug Administration (FDA) has mandated that all antidepressants carry a 'black box' warning label indicating that antidepressants increase the risk of suicidality in youth taking these medications. In the U.K., the Medicine and Healthcare Products Regulatory Agency (MHRA) has determined that the balance of risks and benefits favors only the use of fluoxetine in the treatment of depressive illness in children and adolescents. This article reviews the FDA's analysis linking antidepressant medication use and pediatric suicidality in major depressive disorder, discusses the efficacy of antidepressants in treating depression in children and adolescents, and offers suggestions to aid clinicians, patients, and families in making clinical decisions based on an accurate assessment of the benefits and risks of medication and psychosocial treatments for pediatric depression.

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### **Thinking Outside the (Black) Box: Antidepressants, Auicidality, and Research Synthesis**

Greenhouse JB, Kelleher KJ. Pediatrics. 2005 Jul;116(1):231-3.

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