

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Joel B. Greenhouse and Kelly J. Kelleher

*Pediatrics* 2005;116;231-233

DOI: 10.1542/peds.2005-1041

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/116/1/231>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2005 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Klassen et al<sup>8</sup> found “a prompt and important improvement in children with mild-to-moderate croup who come to the emergency department.” Multiple corroborative studies, performed by Klassen and by others, and subsequent meta-analyses<sup>9,10</sup> established firmly glucocorticoid therapy as the standard of care for croup both in and out of the hospital. A recent, randomized, clinical trial involving children with mild croup (disease so mild that pharmacotherapy was controversial) found that, among those treated with dexamethasone, fewer returned for medical care because of croup and there was more rapid clinical improvement, reduced loss of sleep, and less stress for parents.<sup>11</sup>

There is other evidence in the literature that glucocorticoid therapy reduces hospital admissions because of croup. Geelhoed,<sup>12</sup> in Perth, Australia, documented fewer hospital admissions from an emergency department observation unit after glucocorticoid therapy became mandatory. A 13-fold decrease in admission rates for croup between 1991 and 1996, after the adoption of glucocorticoid therapy, was documented in our institution.<sup>13</sup> For the preparation of this commentary, I asked our health records department to report on the number of croup admissions for the years 1988–2002, the same period studied by Segal et al.<sup>1</sup> There were 191 and 75 admissions in the 3-year periods of 1988–1990 and 2000–2002, respectively, representing a 60% decrease, which is very similar to the 86% decrease reported by Segal et al.<sup>1</sup>

Slides of the pre-PowerPoint era were prepared differently. Characters were typed with a high-resolution typewriter on nonglare paper, the image was photographed, and the photograph was developed. If color was desired to highlight a phrase or title, then we painted it by hand directly on the slide, with translucent enamels of various hues. Although these slides were not chiseled in stone, change, understandably, was not taken lightly. Therefore, data had to be scientifically convincing long before the phrase “evidence-based” had permeated academic medicine. Change is easier with PowerPoint, but it is hoped that the standard of evidence required to support a change of opinion has not diminished. The weight of evidence for glucocorticoids in croup makes this concern irrelevant.

An observation by Jean Martin Charcot (1825–1893) might well apply to the steroid odyssey in croup. “Disease is very old, and nothing about it has changed. It is we who change, as we learn to recognize what was formerly imperceptible.”

MILTON TENENBEIN, MD  
 Departments of Pediatrics, Pharmacology, and  
 Community Health Sciences  
 University of Manitoba  
 Children’s Hospital  
 Winnipeg, Manitoba, R3E 1S1  
 Canada

## REFERENCES

1. Segal AO, Crighton EJ, Moineddin R, Mamdani M, Upshur REG. Croup hospitalizations in Ontario: a 14-year time series analysis. *Pediatrics*. 2005;116:51–55

2. Coffin LA III. Corticosteroids in croup: is there a reply from the ivory tower? *Pediatrics*. 1971;48:493
3. Eden AN, Larkin VD. Corticosteroid treatment of croup. *Pediatrics*. 1964;33:768–769
4. Eden AN, Kaufman MD, Yu R. Corticosteroids and croup: controlled double-blind study. *JAMA*. 1967;200:133–134
5. Leipzig B, Oski FA, Cummings CW, Stockman JA, Swender P. A prospective randomized study to determine the efficacy of steroids in treatment of croup. *J Pediatr*. 1979;94:194–196
6. Cherry JD. The treatment of croup: continued controversy due to failure of recognition of historic, ecologic, etiologic and clinical perspectives. *J Pediatr*. 1979;94:352–354
7. Kairys SW, Olmstead EM, O’Connor GT. Steroid treatment of laryngotracheitis: a meta-analysis of the evidence from randomized trials. *Pediatrics*. 1989;83:683–693
8. Klassen TP, Feldman ME, Watters LK, Sutcliffe T, Rowe PC. Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med*. 1994;331:285–289
9. Ausejo M, Saenz A, Pham B, Kellner JD, Johnson DW, Moher D, Klassen TP. The effectiveness of glucocorticoids in treating croup: meta-analysis. *Br Med J*. 1999;319:595–600
10. Russell K, Weibe N, Saenz A, et al. Glucocorticoids for croup. *Cochrane Database Syst Rev*. 2004;(1):CD001955
11. Bjornson CL, Klassen TP, Williamson J, et al. A randomized trial of a single dose of oral dexamethasone for mild croup. *N Engl J Med*. 2004;351:1306–1313
12. Geelhoed GC. Sixteen years of croup in a Western Australian teaching hospital: effects of routine steroid treatment. *Ann Emerg Med*. 1996;28:621–626
13. Klassen TP. Glucocorticoids in the treatment of croup: barking up the right tree. *Can Med Assoc J*. 1998;159:1121–1122

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

ABBREVIATIONS. FDA, US Food and Drug Administration; RCT, randomized, controlled trial.

In this issue of *Pediatrics*, Leslie and colleagues<sup>1</sup> review the evidence, deliberations, and recommendations of the US Food and Drug Administration scientific advisory committees that led to the black-box warning on the use of antidepressants for children and adolescents. Their article raises a number of critical questions about how we got to this point, including questions about federal drug-regulatory processes and the motivation (or lack thereof) of pharmaceutical companies to design, implement, and report scientifically rigorous trials. However, no question is more compelling than the one faced by many primary care clinicians: How should young patients who are currently on, or potentially in need of, antidepressants be treated?

Although the increased risk of suicidal behavior and ideation for children and adolescents who use

Accepted for publication May 2, 2005.

doi:10.1542/peds.2005-1041

No conflict of interest declared.

Address correspondence to Kelly J. Kelleher, MD, MPH, Office of Clinical Sciences, Columbus Children’s Research Institute, 700 Children’s Dr, J1401, Columbus, OH 43205. E-mail: kellehek@ccri.net

PEDIATRICS (ISSN 0031 4005). Copyright © 2005 by the American Academy of Pediatrics.

antidepressants is statistically significant, unlike Leslie and colleagues, we would not characterize this association as causal for suicidality. In our opinion, the evidence on which the committees based their assertion of a causal link does not yet meet the standards usually required for establishing a cause-and-effect relationship in medicine. Nevertheless, the increase in risk looks real, the black-box warning is in effect, and the critical question that confronts us now is: "Where do we go from here?"

We suggest several areas in which new research is necessary to advance our understanding of the safe and effective use of antidepressants in children and adolescents. First, we need to identify subgroups of children, based on pretreatment risk factors for suicidality, for whom the use of antidepressants might be contraindicated. Second, we need to identify mechanisms of action that explain the relationship between antidepressant use and the increased risk of suicidal behavior and ideation in children. Finally, even without knowledge of the mechanisms by which risk is increased, we need to identify ways to implement close monitoring and careful dose titration of patients, especially in primary care settings to avoid adverse effects and relieve symptoms. In general, not nearly enough research has been done on the delivery of treatments and services for young persons on psychiatric drugs.

Leslie and colleagues identify flaws in the current system of medication testing and approval and suggest regulatory changes that include encouraging larger, longer, and more representative randomized trials. It is not clear to what extent such information would have altered the regulatory review of the efficacy and safety of antidepressants in children, even if all the trials were uniformly well designed. Although the pivotal randomized trials required by the FDA for approval of new drugs are the time-honored gold standard for documenting efficacy, individual randomized trials likely have little value in identifying safety concerns, particularly for rare or delayed-onset events, nor are they efficient in identifying subpopulations at special risk or benefit. Additionally, the generalizability of such trials to routine community practice is a critical issue. The patients that participate in these studies are typically not representative of the general patient population, nor are the research protocols representative of the complex situations seen in routine practice. It seems that answers to the sorts of questions we are asking today are unlikely to come from single trials, even if they are larger.

Where, then, will evidence come that will help us get beyond the current black-box warning? At least part of the answer is likely to be found in the expanded use of methods for research synthesis. It is perhaps self-evident, but significant nonetheless, that the FDA turned to meta-analysis to quantify the risk of suicidality that results from antidepressant use.<sup>2</sup> Research syntheses, such as meta-analysis, play a major role in the formal evaluation of scientific evidence by attempting to integrate empirical research for the purpose of generalizations. Perhaps the single most important strength of research synthesis over

individual studies is the ability to investigate the robustness of a relationship across study-level covariates. Nevertheless, combining information from a number of similar randomized trials, as done in the FDA meta-analysis, often has some of the same limitations as evidence generated from a single randomized trial, such as restrictive study inclusion/exclusion criteria, limitations on generalizability, and narrowly focused questions.<sup>3</sup>

Although meta-analyses have typically focused on combining data from a single study type, such as randomized, controlled trials (RCTs), we believe that evidence that will inform the types of clinical research questions that have been posed here will come from the synthesis of information from multiple data sources including randomized and nonrandomized studies. Examples of the latter include administrative databases (such as claims data), epidemiologic studies, and health-survey data. Such data sets contain tremendous amounts of information on large numbers of patients in much broader settings than found in the typical RCT. Valuck et al,<sup>4</sup> for example, using insurance claims and prescription fills, followed over 24 000 adolescents newly diagnosed with major depressive disorder to investigate the relationship between antidepressant use and the risk of suicide attempt. It is interesting to note that after adjusting for confounders, these investigators found no such association. Experience with combining information from observational studies with results from randomized trials is limited and not without challenge. However, advances in statistical methods, such as the use of Bayesian hierarchical models<sup>5</sup> and methods that capture the diverse strengths of the different study designs while minimizing their weakness by adjusting for selection and confounding effects,<sup>6,7</sup> have begun to address a number of practical problems in the implementation of this more inclusive synthesis paradigm. Still, more methodologic work is needed.

Once again, depressed and anxious youth have limited options for treatment. To get beyond the black-box warning on the use of antidepressants for children and adolescents, we have suggested several open research questions to pursue. These are research questions that won't be answered by RCTs alone. Integrating results from efficacy, effectiveness, practice, and service-system research together means combining data not just from different studies but from different types of studies. Because observational studies are often the only feasible way to collect data on rare events or primary care practices, they are likely to be essential, in combination with RCT data, in answering these questions. This approach promises to elucidate what is safe, what works for whom, and when and where it works. Additionally, combining information from a multitude of data sources holds great promise for better informing policy makers and regulators in their assessments of the efficacy and safety of health interventions. Finally, and at least as important, the use of research syntheses promises to provide the evidence base needed to inform primary care clinicians on how to better manage their patients.

JOEL B. GREENHOUSE, PhD  
Department of Statistics  
Carnegie Mellon University  
Pittsburgh, PA 15213

KELLY J. KELLEHER, MD, MPH  
Office of Clinical Sciences  
Columbus Children's Research Institute  
The Ohio State University  
Columbus, OH 43205

#### ACKNOWLEDGMENTS

This work was supported by National Institute of Mental Health grants MH66960, MH 65430, and MH30915. The order of the author listing was determined alphabetically.

#### REFERENCES

1. Leslie L, Newman TB, Chesney PJ, Perrin JM. The food and drug administration's deliberations on antidepressant use in pediatric patients. *Pediatrics*. 2005;116:195-204
2. Hammand TA. Review and evaluation of clinical data: results of the analysis of suicidality in pediatric trials of newer antidepressants. Presented at: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Pediatric Advisory Committee; September 13-14, 2004; Bethesda, MD. Available at: [www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm)
3. Rothwell R. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365:82-93
4. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS Drugs*. 2004;18:1119-1132
5. Spiegelhalter D, Abrams KR, Myles JP. *Bayesian Approaches To Clinical Trials And Health-Care Evaluation*. Chichester, United Kingdom: John Wiley & Sons; 2004
6. Eddy DM, Hasselblad V, Shachter R. *Meta-analysis by the Confidence Profile Method: The Statistical Synthesis of Evidence*. New York, NY: Academic Press; 1992
7. Droitcour J, Silberman G, Chemlinsky E. Cross-design synthesis: a new form of meta-analysis for combining results from randomized clinical trials and medical-practice databases. *Int J Technol Assess Health Care*. 1993;9:440-449

---

## Pediatricians and Antidepressant Medications: Black Box or Black Hole?

---

ABBREVIATIONS. AAP, American Academy of Pediatrics; FDA, US Food and Drug Administration; AACAP, American Academy of Child and Adolescent Psychiatry.

---

The intent of this commentary on the article by Leslie and colleagues<sup>1</sup> is to describe ongoing efforts by the American Academy of Pediatrics (AAP) and other pediatric professional organizations

Accepted for publication Apr 26, 2005.

doi:10.1542/peds.2005-0928

No conflict of interest declared.

Address correspondence to Lynn Mowbray Wegner, MD, Learning and Development Associates, 3500 Gateway Centre Blvd, Suite 140, Morrisville, NC 27560. E-mail: [lwegner@learningfirst.com](mailto:lwegner@learningfirst.com)

PEDIATRICS (ISSN 0031 4005). Copyright © 2005 by the American Academy of Pediatrics.

to support pediatricians and other pediatric clinicians as they attempt to provide care for their patients who have mental health disorders.

The article by Leslie et al is extremely important to primary pediatric medical providers and provides an important framework for this commentary for several reasons.

- Although there have been periodic short articles published (eg, ref 2), this article responds to requests from pediatricians for a more comprehensive summary of information describing the US Food and Drug Administration (FDA) review of antidepressant use in US children.
- The authors provided the background information of the uneven published evidence of children's responses and observed adverse effects of antidepressants.
- Progressive regulatory steps were described, most of which have occurred in the past 10 years.
- The need for additional research is raised. Kelleher and Greenhouse's commentary<sup>3</sup> expands the discussion. The studies advocated by Kelleher and Greenhouse are essential to the "do-no-harm" dictum guiding the pediatrician's daily work.
- The authors grappled with the thorny issue of "off-label" prescribing of antidepressants and proposed future activities needed to establish the safe and appropriate prescribing patterns pediatricians want to follow.

#### THE PRIMARY CARE PROVIDER ON THE FRONT LINE

The AAP recognizes the critical importance of providing pediatricians with assistance in the pharmacological management of children and adolescents with mental health disorders. The FDA Pediatric Advisory Committee's vote in September 2004 to advise the FDA to require a "black-box warning" sounded an alarm extending from the examination rooms of tertiary child psychiatry clinics in Boston, Massachusetts, to solo primary care providers in the Oklahoma panhandle and rural Montana. Pediatricians were left wondering what to do about their patients already taking antidepressants (for a variety of conditions, as Leslie and her colleagues note). Many of these children had dramatic improvement in the quality of their daily life experiences and showed no evidence of suicidal thinking, let alone self-destructive actions. Would it be more "harmful" to withdraw the medications from their treatment programs than it would be to continue prescribing these black-box medications? What discussions should ensue between the physicians and the parents of these children? Additionally, should these medications be prescribed as part of a newly identified mental health condition? Were there new expectations for informed consent and monitoring? What would be the future implications for other psychotropic medications prescribed for children (eg, the stimulant medications)?

Now, 8 months later, pediatricians grapple with these and additional issues. In an unusual step, the FDA has released suggested practice parameters for

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

Joel B. Greenhouse and Kelly J. Kelleher

*Pediatrics* 2005;116:231-233

DOI: 10.1542/peds.2005-1041

<b>Updated Information &amp; Services</b>	including high-resolution figures, can be found at: <a href="http://www.pediatrics.org/cgi/content/full/116/1/231">http://www.pediatrics.org/cgi/content/full/116/1/231</a>
<b>References</b>	This article cites 4 articles, 1 of which you can access for free at: <a href="http://www.pediatrics.org/cgi/content/full/116/1/231#BIBL">http://www.pediatrics.org/cgi/content/full/116/1/231#BIBL</a>
<b>Citations</b>	This article has been cited by 3 HighWire-hosted articles: <a href="http://www.pediatrics.org/cgi/content/full/116/1/231#otherarticles">http://www.pediatrics.org/cgi/content/full/116/1/231#otherarticles</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Therapeutics &amp; Toxicology</b> <a href="http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology">http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.pediatrics.org/misc/Permissions.shtml">http://www.pediatrics.org/misc/Permissions.shtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.pediatrics.org/misc/reprints.shtml">http://www.pediatrics.org/misc/reprints.shtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

