Commentary by an Academic Child Psychiatrist on the Relationship of the Pharmaceutical Industry, Academia, Psychiatric Practice, and the Food and Drug Administration

Christopher K. Varley, M.D.

THE PAST DECADE'S EXPERIENCE with antidepressant medications will serve as the vehicle for discussion in this commentary on the issues for this special section of the Journal. It was not until 1997 that any psychopharmacologic randomized controlled trial (RCT) of the treatment of major depression in children and adolescents demonstrated efficacy of an antidepressant medication with statistically significant, but modest, differences between fluoxetine and placebo (Emslie et al. 1997). A subsequent industry-sponsored, randomized controlled trial with fluoxetine on a larger scale also demonstrated benefit (Emslie et al. 2002). These two pivotal trials resulted in the securing of a Food and Drug Administration (FDA) indication for fluoxetine for the treatment of major depression in children and adolescents.

The National Institute of Mental Health (NIMH)-funded Treatment of Adolescents with Depression Study (TADS) study was the most comprehensive, rigorous investigation of the treatment of major depression in youth (ages 9–17 years) comparing active drug (fluoxetine) with cognitive behavioral therapy (CBT), combined CBT and fluoxetine, and placebo (TADS 2004). Significant differences were found in terms of response rates with both active drug alone and combined with CBT.

These studies, especially the TADS study, were a major step forward and provided evidence that at least some depressed youth could benefit from antidepressant medication. The story, however, is substantially more complex. Even in the model TADS investigation, differences between all active treatment arms were indistinguishable at 6 months. There is much yet to be learned about the fundamental nature of depression and about the role of antidepressants in the treatment of depression in youth. In the past decade, a number of investigations have been published that reported benefits with serotonin-selective reuptake inhibitor (SSRI) antidepressant medications. For example, there was a statistical difference in a study of paroxetine versus placebo reported as positive (Keller et al. 2001). In subsequent analyses, significant questions have been raised as to whether this was indeed a positive study. Other industry-sponsored RCTs of paroxetine showed no difference between active drug and placebo, but were not submitted for consideration of publication. Considering all the paroxetine trials together, there is essentially no evidence of benefit.

A RCT of sertraline, reported as positive, identified a very modest difference between the rate of response in children and adolescents

with major depression on active drug (69%) versus placebo (59%) (Wagner et al. 2003). Two study groups were combined for an aggregate population of 376 children. It was unclear as to why the two study samples were combined. Considered separately, each study would not have achieved a statistically significant difference between active drug and placebo. In this industry-sponsored study, the decision to combine these two studies permits a conclusion of efficacy based on a design modification.

Following the FDA Modernization Act (FDAMA) initiative, studies were encouraged for industry-sponsored investigations of antidepressant medications in children and adolescents, granting pharmaceutical companies a 6-month extension of patent exclusivity, which had an enormous financial incentive (U.S. Food and Drug Administration 1998). The result was that a number of studies were completed which did not confirm the benefit of SSRIs. Many of the investigations were done by the same groups of investigators, and there were difficulties recruiting enough subjects. The populations of depressed youth may not have uniformly had severe depressions. Ultimately, the results may not have been generalizable.

In the past 3 years, there have been the remarkable actions of regulatory agencies around the world regarding antidepressant medications in youth, beginning with the actions of Medicines and Healthcare products Regulatory Agency (MHRA) Great Britain's counterpart of the FDA, which relied on data collected by the FDA, initially with concerns with the use of paroxetine. Safety concerns were identified with the differences in terms of treatment-emergent mood-related adverse events, including suicide attempts, in 4 per 100 on active drug, versus 2 per 100 on placebo when all classes of antidepressant medications were considered. This modest difference was perceived by regulatory agencies internationally as problematic for a number of reasons, including the fact that the evidence of efficacy was neither strong nor consistent. Regulatory consequences included a black box warning in the United States, a declaration of contraindication for most SSRIs except fluoxetine in Great Britain for children and adolescents, and the relegation of antidepressants as a second-line

intervention in New Zealand (U.S. Food and Drug Administration 2004; Varley 2006). Perhaps most concerning was learning that a number of negative studies that were industry sponsored were not submitted for consideration of publication. The combination of results of published and unpublished studies lent further support to the regulatory actions in Great Britain (Whittington et al. 2004).

In this context, there has been a dramatic change in terms of antidepressant prescribing practices in the United States with a significant increase in the annual rate of increased prescriptions of antidepressant medications as a class for children and adolescents at a rate of approximately 10% per year in the decade prior to the issuance of the black box warning, and a significant drop-off in the annual prescription rate since February, 2004 (Elias 2005).

Where does this leave us? There still are profound questions regarding this specific issue, as to whether antidepressant medications are meaningfully helpful to children with depression, or to a subset of children with severe depression, or not helpful at all. A number of constructive outcomes have resulted from this, and the black box warning is perhaps the least relevant of all of them. Strong support has been voiced for transparency in a number of different ways. The results of unpublished studies are now available, although still difficult to access because they are not published in scientific journals, and not subject to scrutiny by neutral reviewers or by interested consumers. A number of journals have since required investigators who embark upon pharmacologic investigations to register their studies prior to initiation of the trials with <http://www.clinicaltrials.gov>. Currently, this Web site does not include results, but legislation at the state and national levels is being considered to expand the mandate for trial registration and to add results to the data base.

These, however, are not complete solutions to the issue. There is little doubt that the TADS approach is the model for evaluation. However, there are inadequate funds from the National Institute of Mental Health or other federally funded agencies to provide the opportunity to answer questions in the fashion that is required. There are fundamental, and

perhaps irresolvable, conflicts of interest, within the pharmaceutical industry. Clinicians are faced with the reality that there are large numbers of children with severe mental illness/severe depression who are not in receipt of service and need reliable information to move forward. At a minimum, transparency of process and outcome is an absolute obligation. Getting at the truth is difficult. At the present time, it may be that approximations are the best that the field can obtain.

It is not helpful to vilify the pharmaceutical industry. Public skepticism of the timeliness and accuracy of reporting of study results has never been higher. The need is to help children and to advance our understanding of mental illness. There continues to be a need to eliminate publication bias, i.e., the preference for publishing positive findings. Our journals should be publishing adequately powered studies despite negative results.

It is essential that we accurately convey this reality to our residents-in-training. They must be able to understand research findings in context. The process, so strongly promoted recently of evidence-based medicine is doubtless helpful, but it does not necessarily provide full and adequate breadth of understanding of the multiple forces at work in this complex problem. These dimensions must be conveyed to our students as they develop a life-long orientation toward learning and to the interpretation of scientific findings.

DISCLOSURES

The author is on the Speaker Bureau for McNeil and Novartis.

REFERENCES

- Elias M: Fewer children being given antidepressants. Accessed at http://www.usatoday.com/news/health/2005-12-27-children-antidepressants_x.htm/, March 1, 2007.
- Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG: Fluoxetine for acute treatment of depression in children and adolescents: A placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41:1205–1215, 2002.
- Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J: A double blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54:1031–1037, 1997.
- Keller MB, Ryan ND, Stober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP: Efficacy of paroxetine in the treatment of adolescent major depressive disorder: A randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 40:762–772, 2001.
- Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA* 292:807–820, 2004.
- U.S. Food and Drug Administration. Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act. June 1998. Accessed at <http://www.fda.gov/cder/guidance/2414fml.htm/>, March 1, 2007.
- U.S. Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications. FDA Public Health Advisory, October 15, 2004. Accessed at <http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm/>, March 1, 2007.
- Varley CK: Treating depression in children and adolescents: What options now? *CNS Drugs* 20:1–13, 2006.
- Wagner KD, Ambrosini P, Rynn M, Wohlbert C, Yang R, Greenbaum MS, Childress A, Donnelly C, Deas D: Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder; two randomized controlled trials. *JAMA* 290:1033–1041, 2003.
- Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet* 363:1341–1345, 2004.

Address reprint requests to:
Christopher K. Varley, M.D.

Department of Psychiatry and Behavioral
Medicine

Children's Hospital and Regional Medical Center
4800 Sand Point Way, N.E.
Mailstop 359300/W3636
Seattle, Washington 98105

E-mail: cvarley@u.washington.edu