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SSRI Use In Children:

An Industry-Biased Record

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The Use of SSRIs in Children: An Industry-Biased Record

American psychiatrists and other physicians have steadily increased their use of serotonin reuptake inhibitors (SSRIs) to treat children suffering from depression and other psychiatric disorders. One study found that between 1997 and 2000, pediatric use of SSRIs surged 18.8 percent. Another pegged the increase at 50 percent between 1994 and 2000, leading to more than one million children per year receiving one or more prescriptions for fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) and other drugs in the SSRI class. Most of that use has been for depression, which is known as Major Depressive Disorder or MDD in the medical literature.[1]

This explosion in pediatric use has been almost entirely "off-label," that is, without specific regulatory approval. Only one drug in this class – fluoxetine – has been approved by the Food and Drug Administration for use in children and adolescents. That approval didn't arrive until 2003.

The FDA's approval of fluoxetine for children was based on two studies whose outcomes were controversial, even to the FDA reviewers. According to the report issued by the Center for Drug Evaluation and Research at FDA, the treatment effect of fluoxetine compared to placebo was "non-significant" but trended in the direction of favoring the drug in one trial of 96 patients. Even that trend was based on what the reviewer

[1] Martin A, Leslie D., "Trends in psychotropic medication costs for children and adolescents, 1997-2000," Arch Pediatr. Adolesc. Med. 2003 Oct.; 157(10):997-1004; Interview with Julie Zito, Ph.D., associate professor of pharmacy and psychiatry at the University of Maryland, January 28, 2004.

considered a low threshold for measuring relief from the symptoms of depression. A second trial involving 210 youths "did not win on the protocol specified endpoint." However, other measures of psychic wellbeing indicated that about 70 percent of patients improved compared to 60 percent on placebo. "The sponsor appeared to achieve nominal significance on other secondary endpoints," the reviewer noted.[2]

If the studies behind fluoxetine's approval for use in children show the drug to be marginally useful at best, the evidence for the rest of the class is all but non-existent. In order to secure a six-month patent extension for their drugs under the pediatric testing provisions of the 1997 amendments to the Food and Drug Act, SSRI manufacturers have submitted a number of pediatric clinical trial results to the FDA. Many of these tests have not appeared in the academic literature.

Dr. Thomas Laughren, an FDA reviewer, recently surveyed these trials for the February 2, 2004 FDA Advisory Committee meeting concerning SSRIs use in children and suicidality. His review included 15 placebo-controlled clinical trials that evaluated SSRIs for treating MDD in children and adolescents. Only three, including the two for fluoxetine, generated positive results. The other 12 revealed drugs that proved to be no better than placebo. "These are sobering findings and certainly raise a question about the benefits of these drugs in pediatric depression," Dr. Laughren wrote in his review.

[2] "Statistical Reviews, Application Number 18-936/SE5-064," Center for Drug Evaluation and Research, Food and Drug Administration, pg. 25.

"Ultimately, this is a risk benefit assessment, so it is important to know where we stand on the benefit side of the issue."[3]

Shortly after the FDA reviewer's presentation was posted on the World Wide Web, the American College of Neuropsychopharmacology, which is the leading professional association for physicians who routinely prescribe anti-depressants, offered its own interpretation of much of the same data reviewed by the FDA. The group concluded there was no link between suicide and use of SSRIs. However, the task force, whose 10-member roster included nine members with financial ties to the pharmaceutical industry, went on to claim "there is sufficient evidence to conclude that, overall, SSRIs are effective in treating depression in children and adolescents."[4]

How could the FDA and the prestigious college of neuropsychopharmacologists come to opposite conclusions using much of the same data? Laughren's limited analysis of the academic literature found one paper involving paroxetine (Paxil) failed on its primary endpoint, but was reported in the academic literature as positive on most secondary endpoints. Another study of sertraline (Zoloft), reported as positive in the academic literature, was in fact a pooling of two separate studies that, when looked at individually, failed. "The published literature gives a somewhat different perspective," he noted.[5]

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[3] Laughren, Thomas P., "Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee," Food and Drug Administration Center for Drug Evaluation and Research, January 5, 2004, p 5.
[4] American College of Neuropsychopharmacology, "Preliminary Report of the Task Force on SSRIs and Suicidal Behavior in Youth, January 21, 2004, p 4.
[5] Laughren, p 5.

Given the marked difference in evaluations offered by the FDA and by industry-backed scientists, the Center for Science in the Public Interest thought it would be useful to analyze the academic literature to see if studies funded by industry differ markedly in their results from those offered by clinicians who studied without industry support the pediatric use of this class of drugs.

The Academic Record

The academic literature was surveyed using the PubMed database of the Institute of Medicine. The first thing that jumps out is the skimpiness of the published record on the efficacy of SSRIs in children, which does not include the handful of unpublished sponsor studies submitted to the FDA. While there are close to 2,000 studies involving the use of this class of medicines in adults (there are nearly 1,000 for Prozac alone), CSPI could identify only 61 published studies reporting efficacy results of pediatric clinical trials for the eight drugs in the SSRI class.

This spotty record has not slowed their rapid adoption by physician and psychiatrist prescribers. In part, the aggressive use of this class of anti-depressants in American youths can be attributed to the overwhelming support these medications have found in the academic literature. The CSPI survey showed nearly 4 out of every 5 studies

that made it into the literature indicated a positive outcome from the use of these drugs for treating mental health problems in children.

Therefore, it is not surprising that published clinical practice guidelines (CPG) based on reviews of this literature have overwhelmingly supported the use of SSRIs in children for various psychiatric disorders, even though many reviewers have had to admit that the evidence is sparse.[6] While this report does not include a review of the reviews or their funding sources, it should be pointed out that one study of CPGs in the medical literature has shown that "most CPG authors have interactions with pharmaceutical companies and that a significant proportion work as employees/consultants for drug manufacturers." The authors of that study called for full disclosure of financial conflicts of interest for CPG writers and exclusion of authors "with significant conflicts of interest."[7]

To determine if the published scientific record on SSRI use in children and adolescents suffers from a similar bias, the Center for Science in the Public Interest undertook a systematic review of the published academic literature. Using the Institute of Medicine's PubMed database, CSPI entered common search terms for the eight FDA approved drugs in the SSRI class (drug name AND children AND clinical trial; drug name AND adolescents AND clinical trial). After screening out duplicate studies and trial

[6] See, for instance, McClellan JM, Werry JS, "Evidence-based treatments in child and adolescent psychiatry: an inventory," Journal of the American Academy of Child and Adolescent Psychiatry, December 2003, 42(12) 1388-400; Milin R, et al, "Major depressive disorder in adolescence: a brief review of recent treatment literature," Canadian Journal of Psychiatry, October 2003, 48(9) 600-6.
[7] Choudhry, NK, et al, "Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry," Journal of the American Medical Association, February 6, 2002 287(5) 612-617.

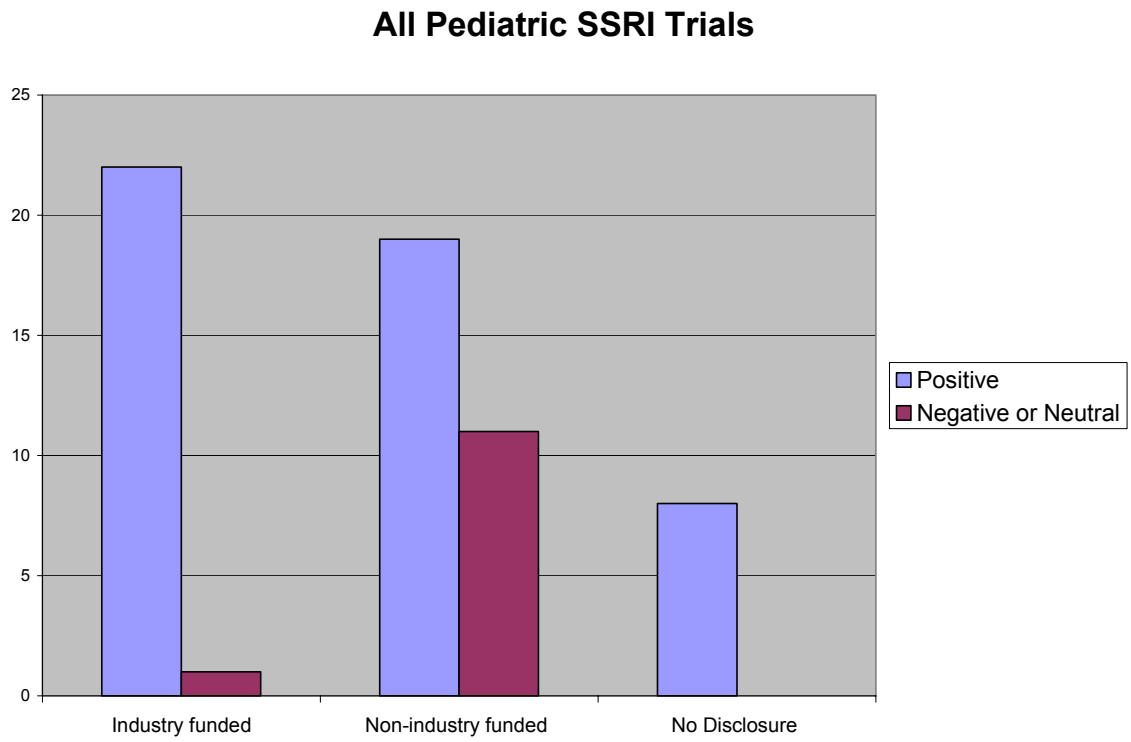
results that did not involve some measure of efficacy, we identified 61 studies since 1989 that involved pediatric testing of SSRIs. Most of the studies involved youths with depression, obsessive compulsive disorder or general anxiety, but the group included a handful of studies on children with autism, mutism, Tourette's syndrome, and other less common disorders.

The studies were then grouped by their outcomes. By reading abstracts and in some cases the full study, the studies were classified as either positive (the authors of the study believed the drug was at least somewhat useful in ameliorating the condition); negative (the drug had no effect or was harmful); or neutral (the authors either could not determine if the drug was useful or had no effect even if there was a tendency in one direction or the other; that usually occurred in safety trials where the author commented, in passing, on efficacy; safety trials that contained no comments on efficacy were eliminated from this study).

The studies were then further divided into those that were open label, where a group of children or adolescents were given the drug without a control group; and placebo-controlled, where the children and adolescents in the study were divided into groups either given the drug as part of their therapy or were told they were given the drug even though the pill was inert. Only in a small handful of trials were the two arms of the placebo-controlled studies double-blinded, that is, the attending physician or psychiatrist did not know which group of patients was receiving drug or placebo.

Printed copies of the studies were then surveyed to determine the funding source of the studies. Since many academic journals voluntarily publish funding disclosure, this information could be readily obtained for a majority of the studies. A substantial fraction, however, contained no disclosure. The authors were followed up with emails and telephone calls (when obtainable), which elicited further information. The studies were then coded as "industry-funded," "non-industry funded" (either government or institutional discretionary funds), or "no disclosure."

The results are shown below:

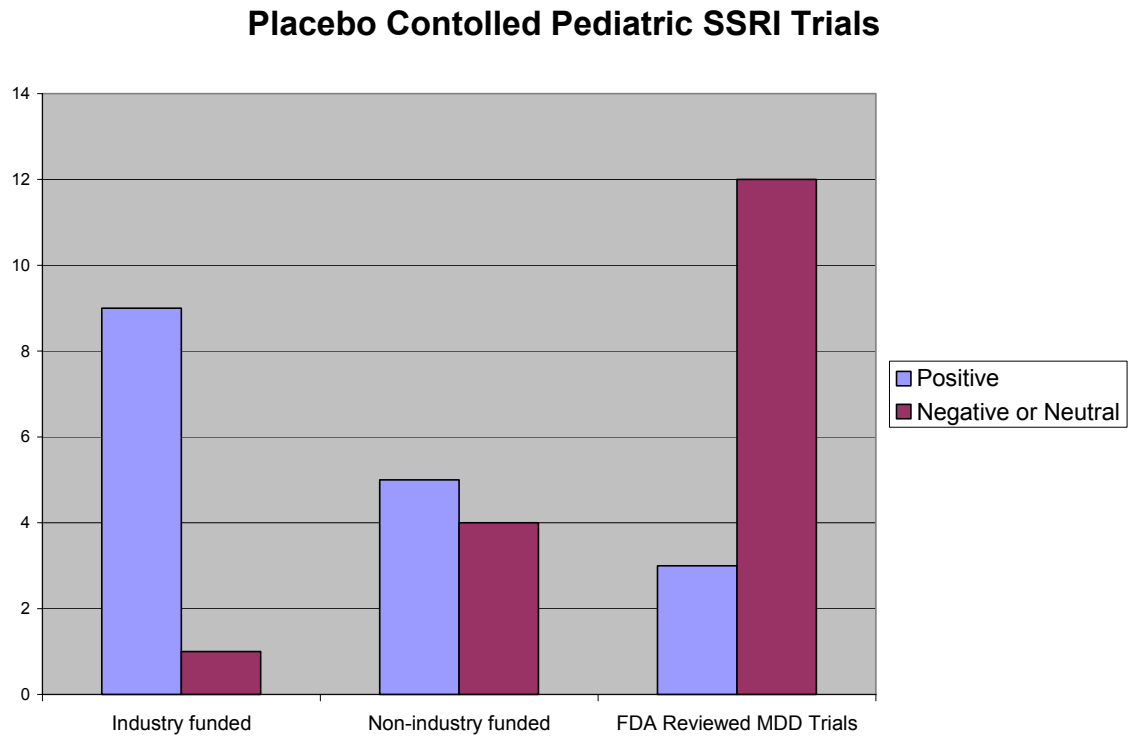


The vast majority of industry-funded studies (including placebo-controlled trials) – 22 of 23 or 95.7 percent – generated positive reports in the academic literature. If one

includes the non-disclosed studies in this group, the results are even more overwhelmingly positive since all eight studies whose funding sources could not be determined reported positive outcomes.

However, the picture is quite different for non-industry funded studies. In this group of 30 studies, 19 or 63.3 percent of the published papers based on those studies reported positive outcomes. The marked difference in outcomes suggests clear evidence of bias in the conduct and reporting of clinical trials based on funding source. Studies funded by industry are more than 50 percent more likely to report positive outcomes than studies supported by independent sources like government or academic institutions.

The evidence of industry-bias in the outcome of trials is even starker when looking at just placebo-controlled trials. Industry-funded placebo-controlled, clinical trials published in the academic literature are 61.9 percent more likely to contain positive results than government or academic-funded, placebo-controlled clinical trials.



The above chart shows that 9 of 10 or 90 percent of industry-funded, placebo-controlled trials reported positive results from the use of SSRIs in children. However, just five of nine, or 55.6 percent, of non-industry funded trials reported positive outcomes.

By including in the chart the FDA analysis of pediatric SSRI trials submitted by manufacturers to obtain patent extensions (12 of 15 either negative or neutral, many of which have not been published), a full portrait of the limited evidence for these drugs' efficacy in children emerges. There is a clear bias in the academic literature that results from industry funding of clinical trials involving the use of SSRIs in children and adolescents.

These results are consistent with previous studies of industry-funded clinical research, some as far back as the mid-1980s when industry domination of clinical trial research emerged as a major issue for academic clinicians. (Industry's share of total biomedical research jumped from 32 percent in 1980 to 62 percent in 2000.[8]) In January 2003, the Journal of the American Medical Association published a systematic review of 1,140 clinical trial studies in the academic literature that concluded "industry-sponsored studies were significantly more likely to reach conclusions that were favorable to the sponsor than were non-industry studies," and "strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions."[9]

How has industry been able to flood the literature with studies suggesting the widespread use of SSRIs in children is warranted? There is, of course, the documented publication- bias effect. Positive studies are more likely to get published than negative studies. That makes the fact that nearly half of non-industry funded, placebo-controlled studies in the literature proved either negative or neutral even more troubling regarding the efficacy of these drugs.

The overwhelmingly positive response contained in industry-funded studies may also result from the possibility that industry has placed restrictions on publication of

[8] Bekelman JE et al, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," Journal of the American Medical Association, January 22, 2003 289(4), p 454.
[9] Op cit, Bekelman JE et al, p 454-465.

negative results, or delayed their publication.[10] Several studies of industry-funded studies have pointed out that clinical-trial design can affect the trial's outcome. A recent JAMA study found four studies that "empirically demonstrated that industry preferentially supports trial designs that favor positive results."[11]

Whatever the cause, there can be no doubt that the pharmaceutical industry's domination of this field of research has biased the published record regarding the efficacy of SSRIs in children and adolescents. That fact should be taken into account when evaluating the alleged benefits of these drugs versus their potential risks.

Industry influence on the published research also highlights the importance of having independent evaluators (people who have not conducted clinical trials in this class of drugs) serving on the FDA advisory committees that will be reviewing any aspect of these drugs performance.

[10] Bodenhimer T, "Uneasy Alliance: Clinical investigators and the pharmaceutical industry," New England Journal of Medicine, May 18, 2000, 342(20): 1539-44.
[11] Bekelman et al, p 463.