

AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

**Joint Statement for the Record
from the**

**American Academy of Child and Adolescent Psychiatry
and
American Psychiatric Association**

**For the
Publication and Disclosure Issues in Pediatric Antidepressant Clinical Trials
Hearing
Before the**

**Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
2123 Rayburn
U. S. House of Representatives
11:00 a.m., September 9, 2004**

Introduction

The American Academy of Child and Adolescent Psychiatry (AACAP) and the American Psychiatric Association (APA) appreciate the opportunity to submit this statement for the record regarding the publication and disclosure issues in pediatric antidepressant clinical trials. Research is key to understanding the cause of depression, especially in children and adolescents, and access to negative and positive research findings will help clinicians develop the most effective treatment plans.

Members of the Subcommittee on Oversight and Investigations, and members of Congress, are to be thanked for increasing the level of appropriations for research into the causes and treatment of mental illnesses. The prevalence numbers for children and adolescents with these illnesses are estimated to be as high as twenty percent of the population, with only one in five receiving treatment; depression alone is responsible for over one-half million suicide attempts each year. The statistics for adolescent suicide attempts and suicidal ideation have declined over the last ten years, but more research is required to understand that decline, the treatment options available and what new options should be explored. Access to all data must be available to clinicians, patients and families.

The AACAP is a medical membership association established by child and adolescent psychiatrists in 1953. Now over 7,000 members, the AACAP is the leading national medical association dedicated to treating and improving the quality of life for the estimated 7 - 12 million American youth under 18 years of age who are affected by

emotional, behavioral, developmental and mental disorders. The AACAP supports research, continuing medical education and access to quality care. Child and adolescent psychiatrists are the only medical specialists specially trained in the treatment of mental illnesses in children and adolescents.

APA is a national medical specialty society, founded in 1844, whose 38,000 members specialize in the diagnosis, treatment and prevention of mental illnesses including substance abuse disorders.

The AACAP and APA would like to thank the chair of the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce for holding this hearing and for his interest in determining the patterns and policies related to the publication and disclosure of research findings for the clinical trials on pediatric antidepressant medications.

In 2002, the AACAP and APA members raised the issue of publication and disclosure of research findings and expressed concern about the balance of research findings published in professional journals. In particular, we were concerned that physicians and parents were not seeing the results of the full range of trials that were conducted. Members also felt strongly that this was an issue not limited to psychiatry, but rather a problem affecting all of medicine. As a result, the AACAP and APA brought our concerns to the American Medical Association's policy-making House of Delegates (HOD) and asked the AMA's Council on Scientific Affairs to investigate this issue.

The Subcommittee's examination of the publication and disclosure issues in the pediatric antidepressant clinical trials is timely. The recent report by the AMA questioning the validity of some clinical trials and the withholding of trial data in others raises concerns by all physicians. General psychiatrists and child and adolescent psychiatrists, who often include the antidepressants in their treatment plans, are especially concerned.

Pediatric Depression and Treatment

Through research and reports that examine the treatment and services most effective in reducing the symptoms, the federal government has encouraged a range of programs and projects designed to help understand the mental illnesses of childhood and adolescence. Four recent Surgeon General's reports and calls for action looked specifically at children's mental health, or indirectly at mental health needs related to youth violence or suicide. Research projects, such as the Treatment for Adolescents with Depression Study (TADS), assessed the value of treating adolescent depression.

The 1999 Surgeon General's report on the nation's mental health determined that "Population studies show that at any one time between 10 and 15 percent of the child and adolescent population has some symptoms of depression. The prevalence of the full-fledged diagnosis of major depression among all children ages 9 to 17 has been estimated at 5 percent. Estimates of 1-year prevalence in children range from 0.4 and 2.5 percent and in adolescents, considerably higher (in some studies, as high as 8.3 percent)." Struggles with depression cause over 500,000 young people to attempt suicide each year,

with approximately 2,000 deaths. These numbers have declined in recent years, but the need for increased screening and treatment to save and improve lives is pressing.

Approximately half of all young people with major depressive disorder have other psychiatric disorders, with at least 20 to 50 percent having two or more comorbid diagnoses. Comorbid substance abuse, conduct disorder, social phobia and general anxiety disorder are more common in adolescents, while separation anxiety disorder is more common in children. Studies in adults and one study in youth have suggested that each successive generation since 1940 is at greater risk for developing depressive disorders, and that these disorders are being recognized at a younger age.

Pediatric depression is a real illness, and treatment intervention is effective, especially when started early. A child or adolescent with signs and symptoms of depression should have a comprehensive evaluation in order to have an accurate diagnosis, which is essential to the development of an appropriate and effective treatment plan.

Medication, specifically antidepressants, can be helpful and even lifesaving for some children, but medication alone is rarely a sufficient treatment approach for complex child psychiatric disorders such as depression. All children and adolescents who are taking antidepressant medication should be monitored closely by a physician, especially early in the course of treatment or when medications are being changed or dosages adjusted. Studies, such as the TADS, demonstrate that individualized treatment plans using a combination of medication and therapy are more effective than either option used alone, but the treatment plan should fit the needs of the child and family. Both individual therapy and family therapy can be part of the plan, and work with the school is part of treating children and adolescents. All treatments have potential risks and benefits, and parents need and deserve access to as much information as possible in order to make fully informed decisions regarding treatment options.

Background

The 1997 Food and Drug Administration Modernization Act recognized the need for increasing the number of clinical trials for medication use in children and adolescents. Few clinical trials for new medications involved children or adolescents, and medications were prescribed “off label,” or without specific FDA approval; however, physicians recognized then and now that children are not just little adults when it comes to medication. Dosages, response rates and side effects can and do vary considerably. There is agreement that large-scale clinical trials are needed to provide physicians and parents with even more information about both efficacy and safety, especially for psychotropic medications, but the clinical trials must be valid and reliable for the findings to be trusted.

Before the FDA issued its June 2003 warning about possible safety concerns with a specific antidepressant, the AACAP and APA members had become concerned enough to take separate action. We reacted to scientific journal articles that indicated the funding sources for research projects might be creating subtle bias in the research and in the decision whether to publish the findings. The seriousness of the bias or the non-

publication of negative findings was difficult to assess, but it is imperative that parents and physicians, especially those treating children and adolescents, have access to all available information. While general psychiatrists and child and adolescent psychiatrists are trained to combine therapy with psychotropic medications in a treatment plan, non-psychiatrists write the majority of prescriptions for depression. Parents, who must be involved in treatment decisions, and who are advocates for their children's treatment and services, must be assured that the research data available to them and their organizations is not biased and that the medications are safe and effective.

Questions about lack of access to research information, possible research bias, and the element of not having dosages set for young patients led the AACAP and APA to ask the AMA to "study the impact of funding sources on the outcome, validity and reliability of pharmaceutical research, and to develop guidelines to assist physician-researchers in evaluating and preserving the scientific integrity, validity and reliability of pharmaceutical research, regardless of funding source."

Shortly before the AACAP/APA requests for the study and the guidelines were considered at the AMA's Annual Meeting of the House of Delegates, the second, stronger FDA advisory was distributed. It warned that a specific antidepressant should not be used in children and adolescents because of possible increased risk of suicidal thinking and suicide attempts. The AACAP and APA members' reactions were equally strong in demanding access to the research and the clinical trials data that led to the warning.

The second FDA advisory and resultant publicity and concern coincided with consideration of the AACAP and APA resolution at the June 2003 AMA HOD annual meeting. At that meeting, delegates from state and specialty societies approved the request for an AMA review of the publication and disclosure issues that influenced research in their specialties.

At the June 2004 HOD meeting, the Council on Scientific Affairs issued its report on the "Influence of Funding Source on Outcome, Validity, and Reliability of Pharmaceutical Research." It reviewed the sources of possible publication bias: investigators and authors, journal editors and reviewers, clinical trial agreements and outcome bias. It found that, together, the sources of bias warranted an expression of growing concern about the "influence that industry sponsorship exerts on clinical trial design and outcome, academic freedom, transparency in the research process, and ultimately, the public good."

The report specifically addressed the funding source influence by stating, "With regard to the extent of financial relationships, at least \$1.5 billion flows from industry to academia annually, so a significant percentage (at least 25%) of academic investigators receive industry funding for their biomedical research, and at least one-third have personal financial ties with industry sponsors."

The study documented "that industry-sponsored research tends to yield pro-industry conclusions. Even among comparison trials, the sponsor's drug is almost always deemed

equivalent to the comparator.” This response to the AACAP and APA’s questions about research bias was also accompanied by specific recommendations.

The boldest of the recommendations is for the establishment of a national registry of clinical trials to assure that physicians, parents, journal editors and researchers would have appropriate access to clinical trials that had been conducted. The HOD delegates discussed the seriousness of the report’s findings and approved the Council’s recommendations. Delegates agreed that the practice of medicine depends on access to accurate, valid and complete information about research findings that include both positive and negative results.

To address the issues of bias and influence in research, the Council’s report noted steps that were already underway, such as the scientific journal editors adopting the revised Consolidated Standards for Reporting of Trials Group (CONSORT) statement, and via revision of the “Uniform Requirements” by the International Committee of Medical Journal Editors (ICMJE).” The major recommendation surrounds the establishment of a clinical registry, which prompted the national and international interest in research bias and the establishment of a clinical registry. The AACAP and APA strongly endorse the recommendation for a clinical registry.

The AACAP and APA realize there are many issues to be resolved regarding the details to be entered into the registry, and we look forward to participating in the discussions and decisions. Both organizations have been active participants in the discussion about the use of antidepressants and the treatment of childhood depression. At the February 2004 FDA advisory panel meeting, representatives testified in support of the antidepressant clinical trials data with respect to safety and efficacy issues. We understand that the increased access to unpublished data that has occurred because of this discussion has been a positive development in terms of providing physician and parents with more information and in helping researchers design future studies. Already there has been positive outcome with public debate because it has provided more information for physicians and parents.

It is now clearer than ever: depression is a serious illness. Children and adolescents with depression who are not identified and treated are likely to have ongoing problems in school, at home and with their friends. Children without treatment for depression are often linked to substance abuse, and research indicates that over 40 percent will attempt suicide, with 2.5 percent of the attempts ending in death. With treatment, including monitoring when medications are prescribed, parents and their children who are depressed can be reassured that there are effective treatments available and that they should seek treatment as soon as possible.

Issues and Recommendations

As part of the discussion surrounding the public and medical communities’ access to clinical data, the issues of treatment needs and barriers is relevant. Access has become a key word in assessing the health care system’s barriers to treatment and services, especially for individuals with mental illnesses. The research that can generate life-

changing medications must be available to all stakeholders. Along with that openness and access, the system will only be fair when the treatment is provided with parity for physical illnesses, both in coverage and reimbursement, or when there are enough practitioners, such as psychiatrists and child and adolescent psychiatrists, trained to diagnose and treat mental illnesses in children.

The AACAP and APA support the AMA Council on Scientific Affairs' recommendations regarding the means to remove funding influence and publication and disclosure bias. Specifically, we support the following recommendations from the AMA and regarding pediatric depression:

- The Department of Health and Human Services should establish a comprehensive registry for all clinical trials conducted in the United States, with every clinical trial assigned a unique identifier. All results from registered clinical trials should be made publicly available through either publication or an electronic data-repository;
- Institutional Review Boards should consider registration of clinical trials to an existing registry as a condition of approval; and
- The FDA should review and then standardize better methods in eliciting adverse effects to deal with biases in reporting adverse events in children and adolescents.

We add that consideration should be given to the impact a U.S. clinical trials registry may have on incentives for conducting trials in the United States versus abroad.

Conclusion

The AACAP and APA appreciate this opportunity to submit a statement for the record on publication and disclosure issues in antidepressant pediatric clinical trials. Both organizations are eager to work with Members of Congress to address the issues related to research into childhood mental illnesses and the training, treatment and services needed to assure that those who should have treatment receive the most effective care.

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Attachment:

Research Advisory Background: SSRI's and Children/Adolescents

**Prepared by
Division of Research
American Psychiatric Association
September 2, 2004**

In the past few weeks, three significant events have occurred that have provided clinicians, parents, and patients important new evidence about the effectiveness of treatments for depression among children and adolescents.

- On August 18, the NIMH-supported Treatment of Adolescents with Depression Study (TADS)¹ was released. This multi-site clinical effectiveness trial compared the use of fluoxetine, cognitive behavior therapy (CBT), a combination of the two, and placebo in the treatment of adolescents ages 12-17 years with moderate to severe major depressive disorder.
- On August 20, the Food and Drug Administration released background information² that will be presented at the September 13-14 joint meeting of the Psychopharmacologic Drugs Advisory Committee and Pediatric Advisory Committee to review clinical trials data about risks of suicidality in association with antidepressant treatment.
- On August 26, New York State Attorney General Elliot Spitzer announced the settlement of a lawsuit against GlaxoSmithKline (GSK) following the company's agreement to make available data on effectiveness and adverse side effects obtained from all GSK-sponsored clinical trials -- published as well as unpublished -- including those for the antidepressant Paxil.

A number of key points can be drawn from these sources of information:

- In the TADS study, 29% of adolescents with moderate to severe depression experienced clinically significant suicidal ideation prior to treatment. Over the course of the study, 71% of the patients responded positively to the combination treatment therapy (i.e., fluoxetine + CBT) -- a rate double the 35% response rate for patients on placebo. The response rate for study participants who were prescribed fluoxetine alone was 60.9%, and among those who received only cognitive-behavioral

¹ March J et al: Fluoxetine, Cognitive Behavioral Therapy, and Their Combination for Adolescents With Depression: Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial. JAMA 292(7), August 18, 2004, pp 807-820

² Available at: <http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm>

therapy, the response rate was 43.2%. Response to treatment was rated by independent evaluators at the beginning of the study, at the 6-week mark, and at 12 weeks, using standardized clinical rating instruments. Rates of clinically significant suicidal thinking declined to 10% after 12 weeks of treatment. Suicidal ideation declined most for those on both fluoxetine and CBT, while the decline for the fluoxetine alone and CBT alone were not significantly different from placebo. Although there were no completed suicides in this study, it will be important to examine the 5.5% of subjects who had suicide-related events sometime during the course of the study. Such events and their timing need to be related in future analyses to exposure to medications as well as to other medical conditions that could increase impulsivity, such as ADHD, and significant factors such as substance abuse and adverse life events.

- The FDA now has in hand the results of two meta-analyses of clinical trials data on antidepressants in adolescents. Averaging all clinical trials conducted with eight different antidepressants, these analyses identified a risk ratio for serious suicidal events ranging from 1.78 to 1.89 associated with active medication in comparison to placebo; that is, active medication was associated with approximately a doubling of the risk of suicidal events in youth taking the medications. Within this group of medications, fluoxetine had a risk ratio ranging from 0.88 to 0.92, implying reduced risk in comparison with placebo, although the reduction is not statistically significant. Statistically significant elevations of risk for medication over placebo in individual clinical trials were found for only two medications -- venlafaxine and paroxetine. In the upcoming weeks, the agency will carefully examine these data to assess the relative risk of suicidal behaviors with an active drug in comparison to a placebo.
 - While the data appear to suggest the presence of some increased risk for suicidal behavior with the medications examined, it is important to understand this risk in the context of the low rates at which such behavior was observed with both placebo and active medication. In almost 4,555 adolescents in all of the trials, 33 subjects (0.72%) engaged in suicidal behavior and 45 additional subjects experienced suicidal ideation, bringing the total affected to 1.7%; there were no completed suicides. Similarly, in the TADS study, which involved 439 moderately to severely ill patients, there were no

completed suicides; only 7 suicide attempts (1.5% of the sample); and 24 "suicide-related events" (5.5% of the sample). Of the latter group, fifteen patients (6.9%) were on an SSRI and nine (4%) were receiving CBT or placebo, but no medication. Again, these differences are not statistically significant.

- Placing the risk of suicidal ideation and attempts into an overall population perspective is important to understand these 12-week clinical trial data. One source of such data is Madelyn Gould and colleagues' report of the NIMH-sponsored Methods for the Epidemiology of Child and Adolescent Mental disorders (MECA) study of community samples of about 1300 youths age 9-17 years.³, wherein 7.5% of all respondents reported suicide ideation in the past 6 months, 3.3% reported a suicide attempt in their lifetime, and 1.6% reported a suicide attempt in the past 6 months. For those with Major Depressive Disorder, most of whom were untreated, 23% had significant suicidal ideation in the prior six-months and 37.5% stated that at some point in their lives, they did something to try to commit suicide and had not just talked about it. Hence, pre-treatment findings of suicidal ideation for 29% in the TADS study, and suicide attempt rates over 12 weeks of 1.5% in TADS and 1.7% in the FDA combined analysis of major depressive disorder, are well under those found in community population studies.
- It is noteworthy in this context that suicide rates in the 10-19 year age group have declined significantly over a recent 10-year period. In 1992, suicide occurred in this age group at a rate of 6.2/100,000 (equal to .006% of this population); by 2001, the rate had declined to 4.6/100,000. This 25% reduction in adolescent suicide rates occurred during a period when the use of antidepressant medications in this population has expanded markedly. Because completed suicides are such rare events, very large studies are needed to assess causal relationships between factors that contribute to suicide and the reduction of population rates.
- Overall, rates of suicidal behavior/ideation among subjects on active medication were approximately double the rates in the placebo groups. In the TADS study of moderate to severely ill

³ Gould MS, King R, Greenwald S, et al: Psychopathology Associated with Suicidal Ideation and Attempts Among Children and Adolescents. *J Am Acad Child Adolescent Psychiatry*, 1998, 37(9):915-923.

patients, suicide related events were found in 4% who were not receiving medication and in 7% who were on an SSRI. It is critical, however, to view this “doubling” in perspective; that is, in contrast to a risk of suicide related events in 4-7% of the patients, 71% of those receiving fluoxetine+CBT, and 60.9% of those receiving fluoxetine only responded positively to treatment. Thus, a striking 25- to 35% more of the patients had a positive treatment response than was experience by subjects on placebo.

- A critical issue addressed by the GSK announcement and one that will be the subject of a Congressional hearing on September 9 is the need to make all clinical trial data available from positive as well as negative clinical effect studies. This information is necessary not only to understand the effect size for all active treatments but also to understand the rate and relative risk of adverse side effects associated with these treatments. The APA has led an initiative in the AMA to request that all clinical trial data be made available in a publicly accessible registry. GSK's announcement and announcements from other industry leaders indicates a growing consensus that such information should be made available. Upcoming congressional hearings will address the most effective means of combining voluntary industry reporting and federal government reporting through a registry such as the NIH-administered clinicaltrials.gov.
- As heretofore undisclosed information on relative risks of treatments has become available, the need for careful monitoring of suicidal ideation and other potential adverse side-effects such as agitation and activation of bipolar disorder must be emphasized. The need to document the benefits of both pharmacological and psychotherapy treatments to reduce the severe disability associated with these conditions is no less important than monitoring adverse events in this severely ill population of patients. The TADS study – a trial that required \$17 million to complete – is an excellent example of the type of research design that is required for a definitive evaluation of these treatments.
- Regardless of the efficacy that was demonstrated in even the most effective combination of medication and psychotherapy in the TADS study, 30% of patients did not improve on the best combination of fluoxetine and CBT treatments. These patients

underscore the need for a range of medications and psychotherapeutic interventions that are responsive to the unique characteristics of individual patients. Although first-line treatments should be guided by definitive clinical trials of efficacy and effectiveness, further research is needed to address treatment resistant depression--including examinations of the unique genetic risk and metabolic characteristics of adolescents with subtypes of major depressive disorder. In clinical practice, carefully monitored "off-label" use of other antidepressant medications that have proven effectiveness in adults have also shown effectiveness in otherwise treatment-resistant adolescents.

Thursday, September 02, 2004