AHRP: Published NIMH Funded Prozac Trial Report Concealed Suicide Attempts by Teens

Recent revelations indicate that pharmaceutical companies have selectively reported partial (favorable) clinical trial results from pediatric antidepressant trials and concealed evidence of harm from physicians, other health care professionals, and the public. It is universally agreed in the literature that failure to disclose all trial results compromises physicians' ability to provide professional care - thereby increasing the likelihood of causing preventable harm. More generally, failure to disclose trial results in scientific publications taints the scientific literature (by rendering it not credible) and, as New York State Attorney General Elliot Spitzer charged recently, constitutes plain and simple fraud.

To: Thomas Insel MD; Tommy Thompson

Re: Published NIMH Prozac Trial Report Concealed Suicide Attempts by Teens

ALLIANCE FOR HUMAN RESEARCH PROTECTION

(AHRP)

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Related Link:

NIMH Response to AHRP Letter

Meryl Nass, MD

Sally Rogow, Ed.D.

June 22, 2004

Thomas Insel, MD

Director

National Institute of Mental Health

Re: Published NIMH Prozac Trial Report Concealed Suicide Attempts by Teens

Recent revelations indicate that pharmaceutical companies have selectively reported partial (favorable) clinical trial results from pediatric antidepressant trials and concealed evidence of harm from physicians, other health care professionals, and the public. It is universally agreed in the literature that failure to disclose all trial results compromises physicians' ability to provide professional care - thereby increasing the likelihood of causing preventable harm. More generally, failure to disclose trial results in scientific publications taints the scientific literature (by rendering it not credible) and, as New York State Attorney General Elliot Spitzer charged recently, constitutes plain and simple fraud.

The Alliance for Human Research Protection (AHRP), a non-profit, tax-exempt educational organization that promotes openness and full disclosure in research, is concerned that clinical trial data about the potential hazards of Prozac (fluoxetine) for children and adolescents may have been concealed from physicians, other health care professionals, and the public. We are writing to you on this matter because we are concerned that taxpayer funds to the National Institute of Mental Health (NIMH) may have been used to conceal some of this data.

As you know, one of two clinical trials submitted by Eli Lilly to gain Food and Drug Administration (FDA) approval for Prozac to treat depression in children was funded by the NIMH. A report of this trial was published in 1997 in Archives of General Psychiatry (Emslie et al., 1997). Data from this same NIMH-funded trial was used by Eli Lilly to gain an additional 6-month patent exclusivity for Prozac (FDA, 2001). The second clinical trial was funded entirely by Eli Lilly, and a report from this trial was published in 2002 (Emslie et al., 2002). The principal investigator and lead author in both trials was Dr. Graham Emslie.

According to FDA documents posted on the FDA website on September 25, 2003, at least 2 of 48 children treated with Prozac in the NIMH-sponsored trial attempted suicide:

Two subjects who attempted suicide may have had their blinded treatment revealed to a non-study physician who was not an investigator (Fluoxetine patients 2051 and 2163). (FDA, 2001a, p. 19, italics added)

In the single published report of this trial, however, there is no mention of any children attempting suicide. Instead, the published report states:

Side effects, as a reason for discontinuation, were minimal, affecting only 4 patients who were receiving fluoxetine. (Emslie et al., 1997, p. 1033)

Furthermore, on April 23, 2004, the NIMH posted an announcement on its website, entitled "Antidepressant Medications for Children: Information for Parents and Caregivers." This announcement discusses both Emslie trials specifically, indicates that one was funded by the NIMH, but makes no mention of suicide attempts among Prozac-treated children. Instead, parents were merely told: "The studies found that [Prozac] reduced depression for many children better than a placebo (a fake pill) and it did not increase suicide or suicidal thinking."

As part of their evaluation of Eli Lilly's submission for approval of Prozac for the treatment of depression in children, FDA reviewers examined Lilly's integrated safety data summaries (ISS) from 3 pooled Prozac pediatric trials: the NIMH-funded trial (Emslie, 1997), the Lilly-funded trial with depressed children (Emslie, 2002), and a trial with children diagnosed with obsessive-compulsive disorder (Geller, 2001) The ISS includes only solicited reports of adverse drug reactions (ADRs) on 228 children treated with Prozac and 190 given a placebo in these 3 clinical trials.

According to the FDA medical review, the ISS summaries indicate that 22 children dropped out because of ADRs in the Prozac-treated group compared to 5 in the placebo groups. The FDA review also states that there were 3 suicide attempts among the Prozac-treated group versus one such attempt among the placebo group. FDA's review refers to additional children being hospitalized for suicidal events: "In addition, one fluoxetine patient was hospitalized because of suicidality" (p. 26). This leads one to wonder how many children required hospitalization for suicidal ideation?

Furthermore, the ISS summaries indicate that 6 of the Prozac-treated children, but none on placebo, developed mania or hypomania. FDA's medical reviewer noted: "Mania and hypomania appear to be much more common with fluoxetine treatment in these trials than has been the case in adult clinical studies." (FDA, 2001a, p. 27).

The FDA review also reveals that an additional, though unreported study exists (the identity of which is blanked out in the FDA documents), it involved 42 depressed adolescents, 21 of whom were treated with Prozac. This study included a 6-week double blind, placebo-controlled phase, to be continued for 52 weeks as an open label study. This study, however, was terminated "due to slow patient recruitment." The ADR data from the terminated study were not included in Lilly's ISS summaries. However, according to the FDA's review, there were 5 serious ADRs in the terminated trial, including 2 cases of "overdose" and 2 adolescents hospitalized for "suicidality."

When asked by a New York Times reporter about the issue of concealment

of negative findings in pediatric trials of antidepressant drugs, Dr. Emslie declined to disclose what he knew, invoking secrecy contracts with pharmaceutical companies (Harris, 2003).

According to Lilly's Clintrace Safety Database for post-marketing, spontaneously reported ADRs, by August, 2001 - before FDA's approval of Prozac for children--there were 3,815 ADR reports for 6 to 17 year-old youths. The following represent more than 1% of reported ADRs and are more common among this age group than others: dermatitis, overdose, agitation, aggression, suicide attempts, convulsions, vomiting, and 6 reports of QT interval prolongation, 1 report of QTc prolongation, 3 reports of cardiac arrest, one sudden unexplained death. (FDA, 2002, p. 4-5)

In light of the above information, AHRP kindly requests that the NIMH answer the following questions underlying our concerns:

1. How many children receiving Prozac in the NIMH-sponsored study attempted suicide?

2. Was the NIMH informed about suicide attempts and other adverse events in the NIMH-sponsored study?

3. How does the NIMH explain that suicide attempts by children treated with a psychotropic drug in an NIMH-sponsored study were not duly reported in a publication resulting from that study?

4. How do NIMH officials explain that in the announcement posted by the NIMH on its website on April 23, 2004, specifically addressing parental concern about the possible link between antidepressants and suicidality, suicide attempts by children treated with Prozac in an NIMH-sponsored study are not disclosed?

AHRP is also concerned about the NIMH's role in funding a study with taxpayer money that was subsequently used by Eli Lilly to extend its Prozac patent exclusivity and to obtain FDA approval for treating depression in children - while apparently failing to ensure that all relevant data from that study be fully disclosed. AHRP is also concerned that conflicts of interest may undermine the credibility of taxpayer funded research findings and support. The following is the basis for our concerns.

In the FDA review of Eli Lilly's submission for the approval of Prozac for pediatric depression, Dr. Russell Katz, Director of Neuropsychopharmacological Drug Products, refers to "Study X-658" as "the Emslie study," noting:

Eli Lilly was not involved with the conduct of this study, but obtained the primary data and performed their own analysis. (FDA, 2001b)

Dr. Andrew Mosholder, FDA expert reviewer, notes:

Lilly arranged to acquire the data from Dr. Emslie and colleagues

in 1997, as part of their pediatric development program for fluoxetineŠ (FDA, 2001a, p. 16)

In light of the above information, AHRP kindly requests that the NIMH answer the following questions:

5. How much did NIMH pay for this study?

6. If the study was "part of [Eli Lilly's] pediatric development program for fluoxetine," did Eli Lilly pay for the data, and did Lilly reimburse the NIMH for the funds disbursed to Dr. Emslie, his colleagues, and their institution to conduct the study?

7. How much did the investigators receive in total from Eli Lilly in the past 10 years?

In sum, you will recognize that our concerns raise important questions about preventable harm to children who are prescribed antidepressants without their physician's knowledge about the risks.

Indeed, they also raise questions about the credibility of the most recent announced findings of an NIMH-funded Prozac trial in adolescents. New positive findings from this trial were announced on June 2, 2004, by the NIMH and by the principal investigators, Drs. Emslie and John March. Though the announcement was reported on the front page of the New York Times and in numerous other media outlets, no data were released for independent review, nor was any publication date announced.

We anxiously await your answers to this letter and to our previous letter of April 30.

Sincerely,

Vera Hassner Sharav, President

David Cohen, Ph.D. Secretary

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The Alliance for Human Research Protection, AHRP

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cc: Tommy Thompson, Secretary, Department of Health & Human Services

Senator Charles Grassley

Senator Max Baucus

Congressman James Greenwood

Congressman Joe Barton

Congressman Peter Deutch

Related link: NIMH Response
to AHRP Letter, dated Aug 5, 2004

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