In Response to the November 21, 2004 New York Times Magazine article: "The Antidepressant Dilemma," by Jonathan Mahler

Properly researched, this article would have been entitled "The Antidepressant Fraud: No Better Than Placebo." However, the November 21, 2004 New York Times Magazine cover was the first clue that the article inside was inadequately researched. The cover stated: "Warning: Antidepressants increase the risk of suicidal thinking and behavior in children and adolescents with major depressive and psychiatric disorder. Caution: The very same antidepressants are helping thousands of kids who might think of killing themselves - and now doctors are nervous about writing prescriptions."

In fact, only 3 out of 15 trials examined by UK regulators and the FDA, which led to suicide warnings, demonstrated any efficacy in children and adolescents. UK regulators were clear that their summer 2003 ban of the antidepressants for use in children and adolescents was due in part (in addition to the suicide risk) to the fact that the drugs had not been shown to be effective. FDA itself has stated that "effectiveness has not been demonstrated." Notwithstanding, the article quotes Graham Emslie, one of the authors of the "TADs" (Treatment for Adolescents With Depression Study) Prozac study as stating: "This study should put to rest doubt about whether these drugs work in teenagers with severe depression." On the other hand, one of the FDA advisory committee experts evaluating the antidepressant suicide connection more recently pointed out:

I think we have to come back to the issue of efficacy. We have I think very strong evidence of harm and really not very good evidence of efficacy, and although I know many practitioners are convinced that these drugs work, if you look very closely at the [Prozac] trial, just as an example, at the Childhood Depression Rating Scale, the improvement with placebo was 19 points, and the improvement with the drug was 23.4 points. You bring people in, you start a medication, and you see an improvement, you are very, very likely to believe that the drug is effective, and the reason why we do randomized, double-blind trials is because personal experience, however compelling, is not a reliable way to tell whether drugs work. In the study where they worked, in the [Prozac study], the improvement over placebo was really very, very small, and I would say not detectable by a clinician treating individual patients. ...

The chairman of the FDA advisory panel seconded these views, stating "there is a dearth of data on efficacy." The advisory panelist's point was further articulated when he wrote: "It is easy to see why the personal experience of clinicians and patients would lead them to believe the drug to be effective, since they would have no way of knowing that more than 85 percent of the benefit they observed would also have occurred with placebo." In fact, the lack of proof of effectiveness was a consistent theme throughout both FDA advisory panel meetings, in February and September 2004, and the Congressional hearings that took place in September 2004 concerning the FDA's handling of the antidepressant suicide issue.

Any perception that the drugs work is likely reinforced by the pharmaceutical influenced medical literature. A good illustration of this point is a September 1, 2003 published study conducted by Dr. Karen Dineen Wagner, et al., which proclaimed that "Zoloft appears to work for children, with no major side effects." The study was highly publicized; however, its conclusions received considerable criticism through letters to the

journal editor. One doctor wrote: "The relative benefit increase of sertraline [Zoloft] over placebo . . . suggests that there might in fact be no benefit from sertraline for these patients." Another doctor stated: "[Zoloft] barely achieved a statistically significant improvement over placebo . . . I would appreciate more information about the degree of influence the sponsor [Pfizer] had over the presentation of the data and interpretation of the results. . . . Given the safety and efficacy precautions recently raised about [Paxil], another selective serotonin reuptake inhibitor with a similar mechanism of action (at least in adults), I believe that more convincing data are needed before [Zoloft] can be recommended as first-line treatment for major depression in children and adolescents." Another doctor complained that Dr. Wagner's claims about the study "reach[] well beyond the trial's results" and concluded "this trial suggests that [Zoloft] shows little to no perceptible benefit compared with placebo in the treatment of depressed youths." It was recently learned that the Wagner study was, in fact, ghostwritten by a Pfizer employee.

The issue of "lack of efficacy" should come as no surprise. In fact, the FDA expressed internal concern over the lack of efficacy, related to adults, as early as 1991. According to an internal FDA memo dated August 26, 1991, Dr. Paul Leber, formerly of the FDA, stated: "In recommending [approval], I have considered the fact that the evidence marshaled to support [Zoloft's] efficacy as an antidepressant is not as consistent or robust as one might prefer it to be."

A later FDA memo, dated December 24, 1991, also from Dr. Paul Leber states: "[S]everal foreign national drug regulatory authorities … presumably provided with the same body of information [as the FDA], have not yet been willing to allow [Zoloft's] marketing in their respective countries … [because of] what may be considered the 'lack of robustness' of the clinical evidence supporting efficacy in the treatment of depression." Dr. Leber concluded: "Approval [of Zoloft] may … for the reasons enumerated above, come under attack by constituencies that do not believe the agency is as demanding as it ought to be in regard to its standards for establishing the efficacy of antidepressant drug products."

Pfizer's difficulty in proving efficacy to foreign regulators is further demonstrated through documents obtained in litigation. These documents show, for instance, that Pfizer was surprised in 1991 that the FDA had not questioned it about the lack of efficacy. The memo states: "I find it odd that FDA did not at all questioning [sic] efficacy and there are significant questions raised by several European companies." Another memo states "we have serious concerns regarding the approval of sertaline in key European countries."

Yet another 1991 memo states that Zoloft had "received an unfavorable review in a number of countries. The common key issue is that regulators are not convinced of sertraline efficacy versus placebo." In response, Pfizer withdrew the applications in those countries and planned studies that would be sure to succeed. The memo goes on to state that the "lack of approval [in Germany and France] will have devastating consequences on the commercial potential of sertraline internationally." What Pfizer needed was a "strongly positive, placebo controlled study … to ensure regulatory success." The Pfizer memo concludes: "To enhance the probability of success in a timely manner, we recommend that the study: … be designed to enhance the probability of success. …"

In fact, according to "The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration," which analyzed the efficacy data submitted to the FDA for approval of 6 of the most widely prescribed antidepressants approved between 1987 and 1999, 75 percent of the response to antidepressants is duplicated by placebo. FDA approval of these medications implies that the data were strong enough and reliable enough to warrant approval. However, the authors point out: "These data were the basis on which the medications were approved by the FDA. If [the data] are suspect, then perhaps the decision to approve the medications should be reconsidered." The authors later wrote: "The small difference between the drug response and the placebo response has been a 'dirty little secret' [Hollon, DeRubeis, Shelton & Weiss, 2002), known to researchers who conduct clinical trials, FDA reviewers, and a small group of critics who analyzed the published data and reached conclusions similar to ours (e.g. Greenberg & Fisher, 1989). It was not known to the general public, depressed patients, or even their physicians. [Footnote omitted.] We are pleased that our effort facilitates dissemination of this information." Antidepressants and Placebos: Secrets, Revelations, and Unanswered Questions by Kirsch, Moore, et al., Prevention & Treatment, Volume 5, Article 33, posted July 15, 2002.

Not addressed in "The Antidepressant Dilemma" is the degree to which the drug companies influence what doctors and the public think about these drugs. As a case in point, the editors of The Lancet wrote a scathing editorial in their April 2004 edition pointing out that: "The story of research into selective reuptake inhibitor (SSRI) use in childhood depression is one of confusion, manipulation, and institutional failure." The editors concluded that "these failings are a disaster" and suggested that "[c]hanges are required at every level of the global health-care infrastructure." The underlying study that sparked this strongly-worded editorial, also published in the April 2004 edition of The Lancet, found that, after a systematic review of published versus unpublished antidepressant clinical trial data involving children and adolescents, the published data alone show a favorable profile, while hidden and unpublished data show the risk/benefit profile as unfavorable.

Another article, also published in April 2004, in the British Medical Journal, similarly concluded: "[Clinical] investigators' conclusions on the efficacy of newer antidepressants in childhood depression have exaggerated their benefits"; "Adverse effects have been downplayed"; "Antidepressant drugs cannot confidently be recommended as a treatment option for childhood depression," and; "A more critical approach to ensuring the validity of published data is needed."

There ought not be fear of frightening parents whose children could benefit from Zoloft and similar drugs since there is scant evidence of benefit to begin with. Nor is there proof that the drugs prevent suicide. In fact, in a study of clinical trial data for drugs approved by the FDA between 1985 and 2000, all the selective serotonin reuptake inhibitors were examined. The Psychiatric Times reported: "One striking finding was the elevated rate of completed suicides for patients during these trials. Compared with the rate of 11/100,000 persons per year for the population at large, the rates of completed suicide were ... 718 in antidepressant trials." According to the author of the study: "This was particularly surprising in light of the attempt, in most clinical trials, to exclude patients who are actively suicidal. ... In the case of trials for depression and anxiety disorders, suicide rates were in fact higher among those who received the investigational drug than placebo." Another recent study by Herman Van Praag published in "World

Journal of Biological Psychiatry" titled "A Stubborn Behaviour: the Failure of Antidepressants to Reduce Suicide Rates,"points out that despite the increased use of antidepressants "completed suicide has remained quite stable" and "suicide attempts even seem[] to have increased." A study published in the July 2004 British Medical Journal similarly concluded: "There is no strong evidence that increases in antidepressant prescribing lie behind recent reductions in population suicides."

With respect to the evidence concerning the suicide risk in children and adolescents, one of the FDA experts on the advisory panel, Dr. Thomas Newman stated that the FDA's review of the clinical trials was "striking" and "such a dramatic result would be expected to occur by chance only 1 time in 20,000." Dr. Newman observed that "some FDA staff and committee members expressed reservations about the data used for this analysis. For example, there was a relatively small number of events, the trials had not been designed to evaluate suicidality, and the methods of ascertainment and classification of the events in the various trials were not uniform." Dr. Newman pointed out that "these concerns only made the results more compelling." He explained that "[i]nadequate sample size and misclassification of outcomes make it more - not less - difficult to detect differences between groups in randomized, blinded trials. The fact that an association emerged from the meta-analysis ... for an outcome that the sponsors of the trials were not looking for, and presumably did not wish to find, was quite convincing."

Given the above, coming to the conclusion that there have been "comparatively few failures" in those taking the drugs and that "lives have been saved" by these drugs is insupportable. The bases for making such statements appear to be the "anecdotal" stories claiming that "a number of teenagers (and their parents) lives have been saved by antidepressants," provided to the New York Times by the heavily pharmaceutical company-funded front organization, NAMI

Finally, the article failed to disclose the fact that Dr. John Mann, who is quoted as stating: "It would be ludicrous to think that antidepressants could actually contribute to suicide in the United States in any kind of significant way" has been a handsomely paid litigation expert witness for at least three antidepressant manufacturers (Lilly, Pfizer, and GSK, all makers of the antidepressants under question). The article also makes no mention of Dr. Mann's testimony in the Tobin v. SmithKline Beecham trial, which resulted in a 6 million dollar verdict for the plaintiff: "I still think that akathisia has the potential when it is severe of contributing to suicidality and aggression." (The common mechanism through which much of the violent and suicidal behavior stems is a drug-induced neurological phenomenon called akathisia. The manifestations are extreme internal restlessness, agitation and inner turmoil. The outward signs can be an inability to sit still and pacing. Dr. Robert Temple of the FDA told reporters following the February 2, 2004 advisory committee meeting: "There isn't any doubt that these drugs cause akathisia. That's not in doubt.")

The article laments that "[n]ot prescribing these drugs may very well pose a greater threat than prescribing them." With the increased risk of suicidal behavior, the lack of demonstrated efficacy, and no evidence that they prevent suicide, how can one justify prescribing the drugs except in the most extreme cases? This is not to mention the impact these drugs have on the developing brain of a child or adolescent into young adulthood when the brain is believed to end its development. In fact, according to a recent study out of Columbia University, antidepressants may change "crucial phases of brain development that might, paradoxically, predispose [children] to depression and

anxiety disorders later in life." One of the study's researchers warned that the widespread use of SSRIs is a "large scale experiment with our nation's youth. I think that we don't really know necessarily what the long-term effects are."

The FDA's requested black box warning is an appropriate step in ensuring public safety. How anyone can argue with providing information that accurately reflects the benefits versus risks of these drugs is a mystery to me. Frankly, when we heard that New York Times Magazine was soliciting antidepressant success stories from NAMI, coupled with the large two-page Zoloft advertisement placed in the magazine by Pfizer just weeks before this article, we were rightfully concerned about the slant the article would take. The New York Times has published some well-researched and important articles on the antidepressant suicide issue as well as other related topics. Perhaps, in this instance, the author was misguided by sources with close ties to the pharmaceutical industry.

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Karen Barth Menzies is a partner in the national law firm , Baum Hedlun located in Los Angeles, which has been involved in pharmaceutical litigation since the mid 1980s. She represents dozens of families including those whose children have committed suicide or attempted suicide on one of the SSRI antidepressants and is lead counsel of the Plaintiffs' Steering Committee in charge of the multi-district litigation re Paxil Products Liability Litigation and represents thousands of people who have suffered from Paxil withdrawal/dependence. Ms. Barth Menzies testified twice this year before the FDA's Psychopharmacologic Drugs and Pediatric Advisory Committee and before the California State Senate regarding the risk of suicide in children and adolescents taking antidepressants.