Ethical Human Psychology and Psychiatry, Volume 7, Number 3, Fall/Winter 2005

FEATURE ARTICLES

Contra Pfizer

David Healy, MD
North Wales Department of Psychological Medicine
Wales, UK

Against a background of longstanding concerns that antidepressants may trigger suicidality, the Food and Drug Administration (FDA) in 2004 convened two committees to review the issues. Prior to the second meeting Pfizer posted an extensive ad hominem attack on me on FDA's website. There was no opportunity to post a response. This article covers the points made in response and sheds some light on pharmaceutical company handling of debates about adverse events.

Keywords: sertraline; suicide; warnings; FDA

In July 2004, Pfizer posted an ad hominem attack on me on the Food and Drug Administration's (FDA) Web site under the heading of documents relevant to a then forthcoming Psychopharmacologic Drugs Advisory Committee (PDAC) hearing on the use of antidepressants in children (Ryder, 2004). FDA refused to post my response to the issues raised in the Pfizer document. This response has been adapted for a freestanding publication, and may be timely in light of the fact that the FDA has scheduled a further hearing on treatment-induced suicidality in adults for the fall of 2005. In completing this piece, I remain heavily constrained by confidentiality orders, and it can be noted that Pfizer has attempted to enforce such orders vigorously by means of court action.

Pfizer's letter starts with a commitment to open debate. The letter then seeks to attack my credibility in an ad hominem way rather than to address the scientific issues. This attack comes despite the fact that I have been previously invited by Pfizer to chair symposia for them, to author articles for journal supplements for them, to give international guest lectures for them, and to adjudicate on studies submitted for Pfizer research awards for them. Clearly, at one point Pfizer thought me a credible scientist in the area of psychopharmacology.

More recently, however, when scientists from Pfizer have sought to have me come and speak at forums, they have been told by their superiors that this is not appropriate. Of even greater interest is that the senior Pfizer physician representing sertraline at the September hearings, Dr. C. Kremer, when working for another company had been a key person supportive of my involvement as an expert witness in court actions involving fluoxetine.

It has in fact been very difficult to get issues of suicidality and psychotropic drugs debated in academic forums. In one of the few such forums, at an Irish College of Psychiatrists meeting in 2003, my understanding is that many clinicians and academics in the

audience were briefed by individuals linked to Pfizer and GlaxoSmithKline on issues to raise with Healy. Many of these issues are reproduced in this letter from Pfizer.

At other scientific meetings to which I have been invited to contribute on these issues, such as the International Society of Pharmacoepidemiology annual meeting, distinguished academics with links to some of the major companies producing selective serotonin reuptake inhibitors (SSRIs), who have never heard me present the data, it would appear, apparently sought to have me removed from the scientific program. Yet, when later given the chance to challenge the points I make, they have failed to ask me any questions in public.

I believe this effort to close down debate has little to do with the scientific issues, in that my work on these points has been extensively peer-reviewed and published in six different journals. I have taken the unusual step of presenting many of these reviews, especially the negative ones, on the Internet to make it clear where others differ in their interpretations of the data (Healy, 2004). I believe the issue has much more to do with my temerity in being prepared to testify as an expert for plaintiffs. Since my involvement as an expert witness, I have received documents from at least one public relations company working for one of the relevant SSRI companies that have listed me as a problem to be managed, and I think what we are witnessing here is part of the management strategy.

Before proceeding, it is worth putting the issue of expert witnessing in context. In over 90% of the SSRI cases on which I have been approached, I have given the view that the injuries in question have not been caused by the SSRI. I have charged nothing for the great majority of these reports, or nothing for any reports I have offered to coroners' courts for the purposes of inquests.

Moreover, regarding actions by plaintiffs in general, far from being plaintiff friendly, I have been used as an expert by the National Health Service in the United Kingdom, and in that capacity have offered reports favoring the defense rather than plaintiffs in, again, over 90% of cases.

It should also be noted that I have no interests in any competing treatments. I use antidepressants, including SSRIs, to treat both adults and children, and, as a former secretary of the British Association for Psychopharmacology, convened a consensus conference and authored the ensuing guidelines on the issue of treating children with psychotropic drugs (BAP, 1997). These guidelines endorsed the cautious use of such drugs, a position I maintain to this day.

SPECIFIC RESPONSES TO PFIZER

In its July 2004 letter to the FDA, Pfizer made 12 points to which I will respond.

First

First, the company claims its depression program has shown no evidence of suicidality. In fact, Pfizer's depression program has a roughly 50% failure to demonstrate efficacy in clinical trials, and many of the trials undertaken with Zoloft remain unpublished. So poor were the results from the early trials that they raised concerns that this drug might not get approved, as publicly available memoranda from Dr. P. Leber to Dr. R. Temple indicate (Leber, 1991a, 1991b).

Zoloft, however, on the back of a selected set of published-only studies, has been sold by Pfizer as an SSRI with unparalleled evidence of efficacy. Arguably, there is a comparable discrepancy between the claims made by Pfizer and the evidence base for those claims, and the claims made for the use of Paxil for minors and the evidence base for that use. The claims in the latter instance were characterized in June 2004 by the attorney general from New York, Elliot Spitzer, as close to fraudulent. Regarding the evidence for suicidality from the Zoloft studies, in over 20 cases investigators have concluded that Zoloft has caused suicidality/suicidal acts, and in more than 20 further cases, Pfizer monitors overrode the judgments of the clinical investigators who had not linked Zoloft to suicidality. These Pfizer personnel attributed causality to Zoloft in the cases of these suicidality/suicidal events. Given this, it is something of a mystery as to how Pfizer can claim there is no evidence their drug causes suicide.

When data from the studies undertaken and submitted to FDA are analyzed statistically, the point estimate for the odds ratio of suicidal acts on Zoloft compared to placebo is greater than 1.0, which is indicative of a risk, and probably greater than 2.0. Pfizer has sought to manage this problem by a variety of methods, detailed below.

The question of what a point estimate greater than 1.0 means in the context of SSRIs and suicide raises issues of interpretation that epidemiologists and others interested in safety issues have to deal with. Many reputable figures in these areas, including some working in the FDA, would argue that the correct interpretation of a point estimate greater than 1.0 is that given that this hazard is a potentially lethal one, it deserves appropriate warnings and monitoring.

Second and Fourth

Pfizer claims that its studies of 800 healthy volunteers reveal no problem with Zoloft-induced suicidality. It should be noted that 75% of Pfizer's healthy volunteer data remains unpublished. Were these data published in their entirety, some of the reasons for the issue of suicidality being less visible in these studies than it might otherwise have been would be more apparent. One of these reasons is that the lead investigators in these studies were, for the most part, either nonclinicians or clinicians with a primary training in fields such as otorhinolaryngology, for instance. These clinicians had no directions to look out for suicidality and no expertise in pursuing indications of suicidality, had they noticed such problems. Despite this, there are clear indications of probable suicidality from studies on Zoloft in healthy volunteers, even in published studies. Volunteers became agitated and apprehensive on Zoloft, as the Saletu article cited by Pfizer makes clear (Saletu, Grunberger, & Linzmayer, 1986).

A healthy volunteer study conducted by Ian Hindmarch in 1983 cited by Pfizer also makes this clear. In fact, the question of Zoloft and suicidality could probably be settled close to definitely if Pfizer made the full data from this study available, along with the reports from Pfizer clinicians responsible for the study. In this study, 12 volunteers were randomized to either placebo or Zoloft and all, bar one of those who took Zoloft dropped out within days, suffering from severe agitation. Volunteers offered comments such as "I was running like a machine inside" and "I have never felt as bad as this in my life" (Doogan, 1983).

Making these reports available would also undercut claims made by Pfizer, which contends that Ian Hindmarch settled issues to do with this study in court. There, Hindmarch primarily claimed that what had happened was that one of his volunteers had effectively

induced a collective hysteria in other volunteers and this explained the profile of adverse effects that the British regulator has described as serious and concerning—on the basis of a four-page summary of the study. This was not explored further by the court in *Miller v. Pfizer*. Even currently available reports of this study from Pfizer monitors, however, make it clear that this was not the way the company then regarded the events that led to a premature termination of this study. "I consider this to be reliable information from these volunteers and also the symptoms to be drug related. There was no question of the volunteers conferring on the nature of their side effects . . . These side effects have been noted previously with Sertraline and other serotonin-specific antidepressants" (Doogan, 1983).

Third

Pfizer argued that my approach to the scientific issues was rejected in a Daubert hearing by the court in *Miller v. Pfizer*. The first point to make clear is that the court in *Miller v. Pfizer* characterized Pfizer's position as "extreme, incredible and self-serving" (Vratil, 2001).

The second point is that my approach to issues in this area has been reviewed by American courts in five other Daubert or Frye hearings that have taken place both before and after Miller, and in all of those cases the court found my opinions legitimate.

The Daubert hearing in *Miller v. Pfizer* was a unique event triggered by a proposal from Andy Vickery, counsel for the plaintiffs, to have an independent expert assist the court in determining the validity of my expert testimony. This proposal was unusual and stemmed from the real and ongoing difficulties courts and others have in sifting the relevant evidence that can be brought to bear on cases.

Several experts were approached who declined or were rejected by Pfizer. Finally, John Davis was put forward by the plaintiffs. Dr. Davis had sat on the Zoloft Psychopharmacologic Drugs Advisory Committee meeting in 1991 that somewhat controversially approved Zoloft. This on the face of it was not someone who might have been expected to be sympathetic to the plaintiff's claim. Pfizer then altered the initial proposal and put forward Dr. John Concato from Yale as a further expert. The plaintiffs had no background on Dr. Concato.

In brief, the instructions to the experts were to look at aspects of my methodological approach toward the issues rather than the content of my opinions. The attempt to distinguish comments on content from comments on methodological approach typically causes considerable confusion on both medical and legal sides of Frye and Daubert hearings.

In this case, the transcript from the open hearings suggests that the hearings generated an unprecedented amount of confusion, perhaps because of the unprecedented procedural format. This confusion came to a focus in a series of exchanges regarding the replicability of some of my figures that are cited verbatim below.

The independent experts indicated that they had not been able to reproduce a key figure where I had indicated that my analysis of Zoloft trials made available to me indicated that the relative risk of suicidal acts on Zoloft was 2.19 times greater than on placebo. In the course of attempting to establish why the experts might have been unable to replicate this figure, a series of exchanges took place in which Dr. Davis put forward the view that the precise methodological approach taken to generating the figures had not been made available in my initial expert causation report and therefore, unlike, for instance, attempting to replicate the results of a scientific study, the experts were unable to replicate what had happened.

Judge Vratil was clearly unhappy that anything presented to the court might apparently fall short of the standards of a scientific paper and this appears to have heavily colored the court's interpretation of the proceedings and their findings (see transcript below). However, my assessment of the relative risk had arisen in response to challenges put forward by Pfizer after my expert report had been filed—the report the experts were asked to assess—but the court refused plaintiff's permission to bring any new evidence into play after the initial reports had been filed.

This created a situation where the independent experts were left commenting on a figure of 2.19, but it was not possible for the defense to demonstrate just how this figure was obtained. Reading the transcript of the hearings makes it clear that there was considerable scope for confusion. For example, there was scope for the independent experts to believe that requests of them to assess my methodological approach could not be responded to, for instance, in the absence of a sheet of detailed calculations that would have laid out how a particular figure (the relative risk of 2.19 for suicidal acts on Zoloft over placebo) had been generated.

On issues like this, it would presumably have been possible for the experts to approach me through the court in the 18 months during which they pondered the issues, indicating difficulties in seeing how particular figures had been generated and requesting a breakdown on the steps taken to arrive at a particular figure. No such approaches to me were made. No allowance was made by the court for me to explain just where these figures came from.

Such steps could have been included in the original report but had not been included for the simple reason that detail of this sort is not ordinarily and perhaps has rarely, if ever, been presented as part of a plaintiff's expert report. When attempts were made in court to indicate that the independent experts should not take Pfizer's figures at face value as the company had inappropriately added suicidal acts to the placebo column that should not have been added, the court ruled this point inadmissible.

This point goes to the confusion at the heart of this issue, which hinges on the word "methodology." In the ordinary course of events in Frye and Daubert hearings, the word "methodology" refers to the general approach taken by experts. For example, do experts take into account randomized controlled trial evidence and epidemiological evidence or are they basing their views on some unproven theory or on statements based on the authority of others rather than on scientific procedures?

In common scientific parlance, however, methodology can also refer to mundane aspects of an approach taken, such as precise calculations. One could therefore have an appropriate scientific methodology and yet have no calculations present in a paper, or have an expert report full of calculations but yet not have an appropriate methodological approach to the issues at stake.

To put it in other terms, the term methodology in general refers in chemistry experiments, for instance, to whether the experimenters are adopting a set of procedures such as distillation, condensation, fractionation, etc., but it can also include a specification of the precise amount of chemicals A and B that will need to be added to the mix. Daubert and Frye hearings refer in general to determining whether valid chemical procedures such as condensation, distillation, and so forth, are being used rather than to a specification of precise chemical ingredients. This is for the rather obvious reason that an expert could precisely specify the chemical ingredients but could then simply toss those chemicals to the wind and such an approach would be no more scientific than attempting to divine the future from the entrails of a goat. The Miller-Daubert hearing effectively focused on the question of whether the precise chemical ingredients had been outlined in the expert report.

A further point worth noting here was that the notion of an independent expert was proposed a long time after the expert report on causation had been first generated. The precise form that the expert report on causation took did not take into account the possibility of a review by independent experts in the context of a Daubert procedure, and in particular did not take into account the need to construct an expert report that would be fireproof against the many confusions that Daubert procedures can generate.

The situation arguably would have been a lot more fair if having agreed to the Daubert approach the court had indicated to me and the experts that a report on expert causation would be assessed in this way, that the focus of the independent expert scrutiny would be under specific headings, and that a report that would achieve maximum clarity on these points should be submitted to the court on a specified date, thus facilitating the work of the independent experts.

Such an approach would have meant at the very least that, in the actual hearing that took place, both counsel for the plaintiffs and counsel for the defense as well as the judge and the experts, both for the plaintiffs and the defense, and the independent experts would have been in a position to examine and cross-examine in a meaningful way. This clearly did not happen, as any scrutiny of the transcript will reveal.

Finally, at the time this hearing took place, I had a series of articles under peer review. Two of these were accepted, one wasn't. The reviews of all three are available and one of the published articles comes with a detailed published commentary by a distinguished scientist taking the opposite point of view. None of them, even the most hostile, claim that I used invalid methodological procedures in the sense that such methodologies are usually scrutinized in Frye and Daubert hearings. All these reviews, including the hostile ones, have been made publicly available at healyprozac.com.

Transcript from *Miller v. Pfizer* November 20, afternoon:

DR. DAVIS: And it may be an evolving field and that, so there is a matter of judgment. I'm reminded of a short story, one of the Sherlock Holmes stories where I think the title was "On the Matter of the Dog That Did Not Bark." And the night of the murder, the dog didn't bark. It was a very irritable dog that had barked at strangers very vigorously. The clue was that the murderer was a friend or the master.

And what I anticipated when I came today that Dr. Healy might present his calculations or there might be a lot of discussions of the techniques of the calculations. And the normal scientific process, you present your method in some detail, you present your data, you do your statistics,

390

and you describe exactly how you do it. And then in the discussion you might speculate. And as I—and we commented in our report that we couldn't replicate the relative risk of two point whatever it was. And I would have anticipated that Dr. Healy would have calculated it or there would have been more said about it.

And the numbers here on this last page of—is the unadjusted incidence is .28 for Zoloft, and .31 for placebo so that Zoloft would have a trivial protective factor. The unadjusted incidence for people going in blinded trials for

Zoloft is .26 and for placebo is .29. So it's about the same.

But there's been—Dr. Healy in his testimony has given a lot of relative risk, and I've never been sure how they were calculated. One of them was 2,000 to 1. One of them is you assume that the average patients getting SSRIs are less sick than the profoundly depressed patients, so forth and so on, the relative risk is 10. In other cases he said the relative risk was 4. In all these cases, I am—there's no methodology, there's no way of calculating it. And there's just—and I don't know where these numbers come from, what their methodology is. And it's also sprung on me at the last moment. And I have a feeling that numbers have come up in the court before and there's no methodology. And I don't feel that that conforms with scientific methodology.

391

Now, it's quite possible that this was sprung on Dr. Healy at the last moment because I think I heard him say that it's something he only recently got into, and it may not be fair to ask him before.

THE COURT: Maybe I can shed some light on this, especially in regard to your comment that you may be expected to hear some more full explanation of where the 2.19 figure was derived. This is part of where the intersection of law and science is maybe not clear to somebody coming in from the outside.

But under our federal rules which govern pretrial proceedings, each side obviously has a chance to call their own experts who will testify, and there's a time set as part of the discovery process where each expert is required to produce a written report that states all of the opinions that that expert will offer at the trial, and also the basis for the opinions. That has to be done by a certain time prior to trial. Both sides then have a chance to take the depositions of the experts or, as Dr. Healy says, I love this, the depositions. And both sides have a chance to file objections to that testimony so that we then determine whether it's sufficient under Daubert, sufficiently scientifically reliable that that information should be allowed to be presented before a jury.

And what I've told the parties is that to the

392

extent that Dr. Healy had information and could have made calculations by that deadline, he was required to do that if that was part of what he relied upon in developing his theories and opinions in the case, and he can't go back now and retread that information. So that if he had this figure of 2.19 and he didn't do the figures and explain it to the other side earlier on in the case, it's not fair for him to sit back and come back at this time and spring it on them at this particular hearing.

So that's why, that's what my ruling was earlier, and that's why you haven't heard the Power Point presentation that was alluded to earlier. Now, I'm with you in that some of these figures that I've heard today I've never heard before and I don't know where they're coming from. So—

DR. DAVIS: And I feel that of course, I'm biased. I'm a statistically oriented psychiatrist, but I feel that it's important to say your method, to say how you got your numbers, and the statistical parts are really not as complicated if you lay it on the line beforehand because it's really four numbers. It's the number who suicided on drug, and the number who got the drug, and the number who suicided on placebo, and the number who didn't, and put it in a percentage. After that, you can go to statistical significance and beyond. And I want to comment on that. And there is a common-sense test looking at the raw numbers and knowing where they came from. Then you have something to work from.

Where Pfizer refers to the independent experts' differing assessments of the medical evidence, a scrutiny of the report of Drs. Concato and Davis will reveal that in their minds articles like the Beasley et al. (1991) paper in the *British Medical Journal* remained the gold standard in the field. With the benefit of some further years and a great deal more information on the Beasley meta-analysis and related meta-analyses such as that by Dr. Stuart Montgomery—see below—such a position would now be impossible to sustain.

Just as it was posting this letter, in fact, Pfizer was also submitting data to the British regulator, reporting 4 suicides and 20 suicidal acts in 7,169 patients randomized to Zoloft and 0 suicides and 8 suicidal acts in 5,108 patients randomized to placebo. These figures give an infinitely greater risk of suicide on Zoloft compared to placebo and a relative risk of either a lethal or nonlethal suicidal act on Zoloft compared to placebo of 2.14, with a 95% CI of 0.96 to 4.75 (see Figure 1).

There must be some doubt that there were in fact as many as eight suicidal acts on placebo in Zoloft trials. Pfizer's submissions to FDA in 1991 indicated there were five suicidal acts from 786 patients, when in fact they have since conceded that only one of these happened in the randomized phase of these trials. In addition, some of the suicidal acts on placebo claimed by Pfizer appear to me to be doubtfully categorized as suicidal acts.

This figure for relative risk of 2.14 is almost exactly the same as the figure found in a recent analysis of all pediatric trials submitted to FDA, which was 2.19 (95% CI. 1.50 - 3.19; $p = .00005$) (Newman, 2004). This risk has formed the basis of warnings in this age group. More generally, in clinical trials for adults submitted for regulatory approval of all new antidepressants, I have published in peer-reviewed publications a comparable risk ratio for suicidal acts compared to placebo of 2.17 (95% CI 1.39, 3.39; $p = .0004$) (Healy & Whitaker, 2003). And, of course, these figures all map closely on to the figure I offered in the Miller case.

Fifth

I am happy to stand by my interpretation that the Saletu et al. article, reporting the results of a healthy volunteer study with Zoloft, demonstrates a dose-dependent agitation on Zoloft. Anyone wishing to pursue this further should note that two different versions of this article were published (Saletu et al., 1986; Saletu & Grunberger, 1988).

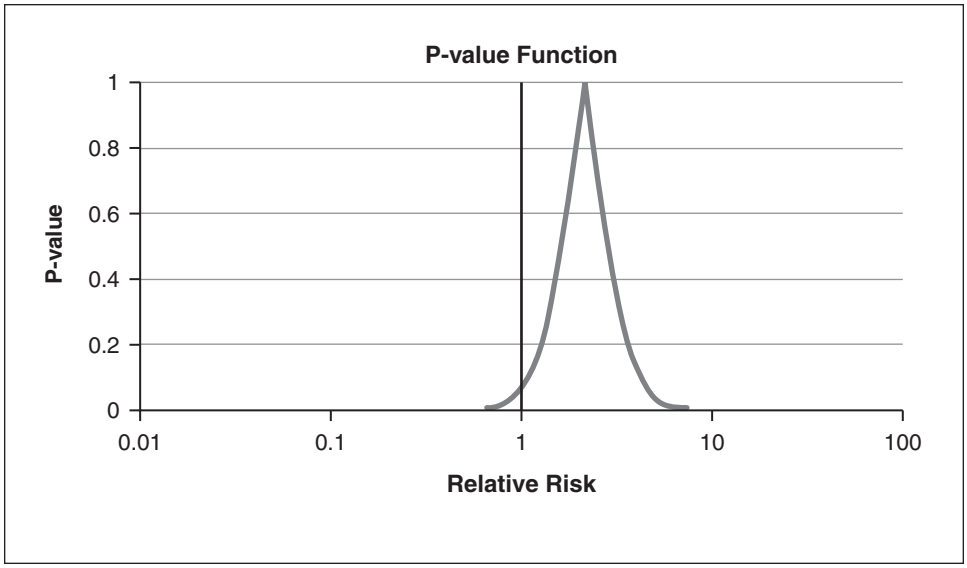

Figure 1. All confidence intervals for Zoloft adult placebo-controlled trials for suicides and suicidal acts; relative risk = 2.14.

Sixth

In early 2000 and subsequently I published details of a blind, randomized, healthy volunteer study comparing Zoloft and reboxetine, in which two volunteers taking Zoloft became suicidal (Healy, 2000; Tranter, Healy, Cattell, & Healy, 2002). Since April 2000, I have gotten used to Pfizer mischaracterizing aspects of this study. The claims made have in many instances been quite extraordinary. They have suggested that: One of the volunteers who became suicidal had an alcohol problem (untrue); all or most of the volunteers were my employees (untrue—only 1 of 20 could be regarded as an employee). They have implied that suicidality appeared in one volunteer with a prior history of depression that had been missed. One volunteer had a prior history of depression that had been missed but this was not a volunteer who became suicidal—this volunteer, in fact, responded well to Zoloft. Pfizer has no evidence that any of these volunteers were unblinded. This study, in fact, was less likely to suffer from unblinding than Pfizer's own healthy volunteer studies in that it is self-evidently going to be more difficult to distinguish Zoloft from reboxetine than it is to distinguish Zoloft from placebo.

Perhaps the most telling point, though, is that Pfizer has been invited to depose the two volunteers who became suicidal on Zoloft, but have declined to do so.

Seventh and Eighth

Pfizer asserts that the FDA was fully aware of how the data it submitted to the agency were coded as regards suicidality and chose not to criticize how this had been done. Having made it clear that: "Pfizer's 1990 report to FDA plainly shows . . . that 3 placebo attempts as having occurred during single blind placebo phases," it adds "FDA has neither criticized these data or the report as inappropriate, nor required additional analyses" (Ryder, 2004). What Pfizer and other companies did is laid out in Figures 2 and 3.

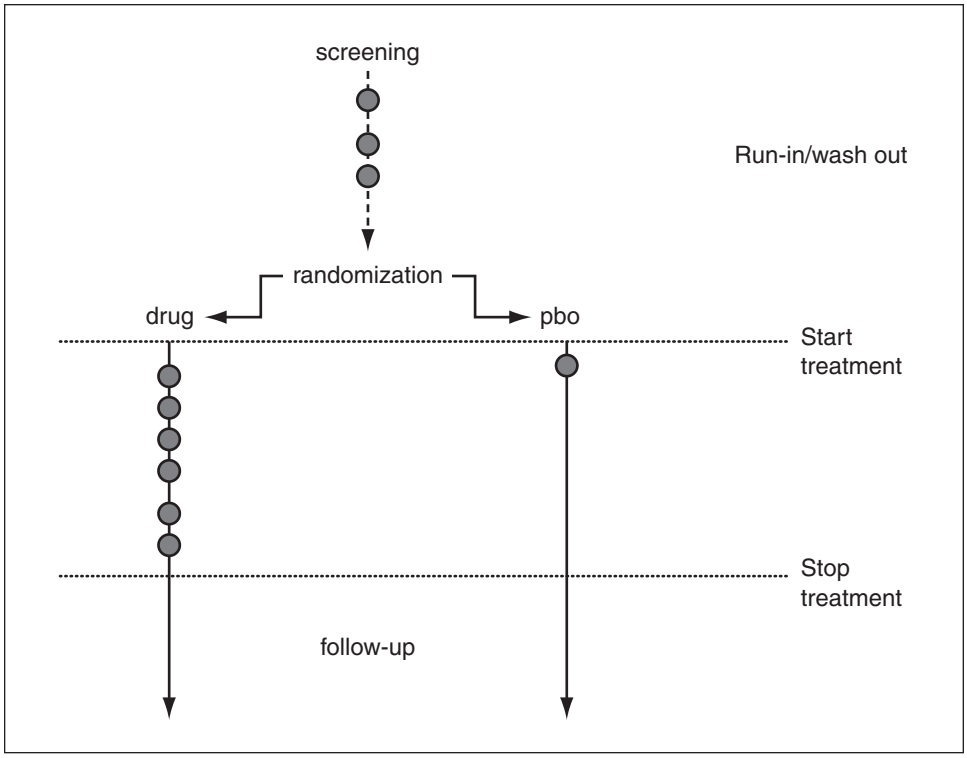

Figure 2. Fluoxetine paroxetine sertraline adult trials. Occurrence of suicidal acts.

The statistical review of the data carried out by FDA does note an inclusion of placebo run-in suicidal acts under the placebo heading, which FDA regulations and any text on clinical trial methodology would regard as inappropriate (Lee, 1991).

Why FDA might choose not to further criticize this report is perhaps a key point at the heart of these hearings. At the same time, Martin Brecher, who was handling the Paxil submission for FDA, had contacted SmithKline and asked it to resubmit its data. As reported by SmithKline personnel, he indicated that FDA's view of the issue of suicidality on SSRIs was that this was a public relations issue, and that it would help if SmithKline resubmitted its data (Brecher, personal communication, October 3, 1990).

SmithKline did so. In the process, an eightfold excess of suicidal acts on Paxil over placebo was transformed into a parity of suicidal acts between Paxil and placebo. SmithKline achieved this by resorting to some of the inappropriate methods used by Pfizer, namely recoding, under the heading of placebo, suicidal acts that had occurred during the run-in phase of the trial, without in any other way adjusting the denominators for placebo, and so forth. GlaxoSmithKline's view on this recoding as reported by R. Waters in the *San Francisco Chronicle* on January 4, 2004, is:

> There were unfortunately some inconsistencies in how the data on suicide attempts were presented to FDA. . . . When we became aware of this, we went back and looked at the clinical trial data again. GSK did not intentionally submit any erroneous or misleading

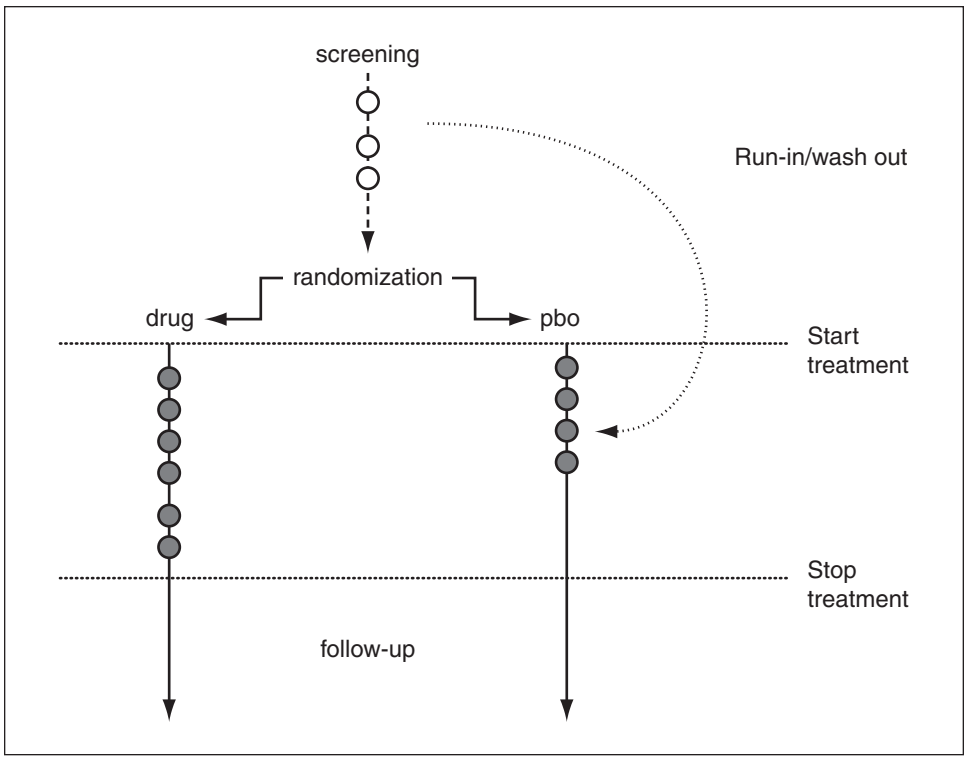

Figure 3. Fluoxetine paroxetine sertraline adult trials. Reporting of suicidal acts.

information to FDA. The suicide data submitted to FDA explicitly identified when events occurred during the placebo run-in period. FDA had all this information right from the beginning.

Four years after submission of its revised figures, Stuart Montgomery, along with a company coauthor, supposedly meta-analyzed SmithKline's database in an article that cites the distorted SmithKline figures (Montgomery, Dunner, & Dunbar, 1995). This article appears in a journal of which Dr. Montgomery was the editor. Its second author, Dr. Dunner, has since said he did not see the raw data. The third author, Dr. Dunbar, was an employee of SmithKline. The resulting article has been at the heart of GlaxoSmithKline's defense in legal actions involving Paxil.

In this case Dr. Montgomery claimed that Paxil was five times less likely to be linked to suicide than placebo. This dramatic manipulation was achieved by introducing another inappropriate step that Pfizer has also availed itself of, and continues to avail itself of, namely adjusting the figures to take into account exposure to the drug. This maneuver introduces a "space shuttle" fallacy into the debate; according to this fallacy, space shuttle travel is proven to be safer than walking around a resort town on the Virginia coast by virtue of there being fewer deaths per million miles traveled. However, as anyone at the PDAC hearings could explain to Pfizer, GlaxoSmithKline, or Lilly, the hazard in shuttle travel lies in entries to and exits from orbit/treatment, and factoring in the millions of miles safely traveled is inappropriate.

Dr. Montgomery was also the leading psychiatry expert to the United Kingdom's Committee on the Safety of Medicines, which was responsible for licensing Paxil and Zoloft in the U.K. Dr. Montgomery was, in fact, consulted extensively by Pfizer in connection with its submission regarding Zoloft, but did not declare this interest at British regulatory hearings.

Dr. Montgomery was also a panelist at the 1991 PDAC hearings on Prozac, where he spoke against the position that Prozac could cause suicidality, although as a consultant to Lilly at this time he would appear to have authored a report indicating that it was no surprise that the issue of suicidality on Prozac had surfaced (Healy, 2004).

This was doubly interesting to me, in that I made efforts to get a hearing at the February 2004 hearings only to be told that the committee does not have experts from outside the United States.

Ninth

Pfizer argues that I have misrepresented the data in the Alderman paper—a study in which some of the pediatric patients were depressed and some had obsessive-compulsive disorder (OCD) (Alderman, Wolkow, Chung, & Johnston, 1998). In this, the authors report no data on suicidality in children, even though 4 of 44 depressed minors demonstrated suicidality on Zoloft—a 9% rate. Interestingly, the final article only reports on side effects happening at a 10% rate or more.

I think the key issue here is the fact that ghostwriting has eviscerated the scientific literature in psychiatry. It's difficult to know whether any articles on therapeutics are any more dependable than Olympic gold medals these days. This is a state of affairs for which Pfizer would appear to shoulder a considerable responsibility. Its view regarding the purposes of undertaking studies appears to be that these exercises produce data that can support off-label use of their drugs, or can be used to counter claims made by other companies. They pick academics to be authors on these studies insofar as these individuals will become champions of Pfizer products and select journals for the marketing advantage such journals offer.

This is a matter on which I have peer-reviewed published work specifically relating to Zoloft that covers the Alderman article noted above (Healy & Cattell, 2003). What readers should know is that *The British Journal of Psychiatry* had six reviewers of the article rather than its usual two. It was then subsequently re-reviewed before being sent to lawyers for review and then copy-edited within an inch of its life.

The major journals in the field are clearly scared of companies like Pfizer. This includes *The New England Journal of Medicine*, which accepted a review of *Let Them Eat Prozac* before reneging on its commitment to publish, and *The Journal of the American Medical Association* (JAMA), which was not prepared to take this article on ghost-writing. Company efforts to intimidate academia are one of the gravest crises to face science in its history.

Tenth

When challenged on the issue of why FDA failed to think that a sevenfold increase in suicidal acts on Zoloft in the Zoloft pediatric OCD studies was not a matter warranting warnings, Pfizer has simply fallen back on the fact that FDA did not see fit to warn. This is an issue for the academic community in general to ponder as well as an issue for the media.

There is another interesting point to these pediatric OCD studies in that Pfizer consistently portrays this study as having had one suicidal event on placebo when no such event was reported to FDA and there was no dropout for suicidality in the placebo group (March,

Biederman, Wolkow, Safferman, & Mardekian, et al., 1998). This would appear to be a case of Pfizer creating suicidal events.

Eleventh

Pfizer objects to the model that generates estimates of the likely numbers of deaths on SSRIs since the launch of these drugs, on the basis of which I have argued there have been more deaths on SSRIs than following any other drug disaster. If the risks demonstrated in clinical trials are, in fact, greater on SSRIs than on placebo as it appears these risks are, then no matter how conservatively the figures are handled given the numbers of people exposed to these drugs, it is a reasonable estimate that there must have been more deaths and injuries on SSRIs than on thalidomide, fen-phen, or even the Cox-2 inhibitors, for instance. The model I have been using has now been published (Healy & Aldred, 2005). It has been reviewed by the British regulator, the Medical and Healthcare Products Regulatory Agency (MHRA), which has not to date pointed to any failure of logic in the model as it applies to antidepressants.

Twelfth

Later, in its more detailed argument, Pfizer claims that there are inconsistencies in the statements I have made before and after my involvement as an expert witness. I dispute that there are any inconsistencies. The points raised by Pfizer are ones that are handled in my book, *Let Them Eat Prozac* (Healy, 2004). As mentioned above, it is interesting that Pfizer made this claim when one of its senior personnel played a big part in involving me in these cases in the first instance.

Overarching Issues

The current crisis with SSRI agents has profound philosophical and methodological underpinnings that deserve better than ad hominem attacks. Current procedures to manage the entry of drugs onto the market favor the detection of drug effects and are biased against the detection of adverse effects. For instance, in order for a drug to be licensed it has to show superiority to placebo in two controlled trials. Companies, however, can run ten or more trials in carefully selected samples using instruments carefully designed to pick up any effect in order to demonstrate this, and even if the results show the drug failing to beat placebo in the clear majority of trials, this is not held against them. These other trials are commonly termed failed trials rather than drug failures. This was a live issue in the licensing of Zoloft as the Leber memoranda outlined above make clear.

In contrast, the demonstration of a safety issue is not handled in this way. In the case of safety, regulators only act if the overwhelming preponderance of the data show a hazard. These differences in approach have at their heart unresolved philosophical issues about the nature of statistics. Safety data are typically presented in terms of confidence intervals, so that, for instance, in recent antidepressant studies, the rate of suicides on drugs compared to placebo is typically of the order of two times greater but what is termed the confidence interval surrounding this figure of 2.0 might be anything from .9 to 4.4.

There are two ways to interpret such a finding. First, according to a school of thought stemming from R. A. Fisher, is the view that nothing has, in fact, been shown unless the confidence interval does not include 1.0—for instance, only a confidence interval that shows a range from 1.1 to 4.4 for instance would be significant. Pfizer is relying heavily on just this point to claim that it has not been proven that Zoloft causes suicidal acts.

However, the Neymann-Pearson school of thought, and, in fact, the whole point behind confidence intervals, argues that the best estimate of the effect is 2.0, in this case, and that with a confidence interval of .9 to 4.4, while the data may be consistent with no effect, the scientific data are also consistent with a 4.4-times increase in risk. The 2.0 figure is the one regarding which we can be most confident and is the one that should dictate whether, for instance, warnings are placed on a treatment.

In practice, regulators adopt Fisher's approach. This is outdated and cannot be viewed as a rigorous approach to safety. On the other hand, epidemiologists (including, in all probability, most epidemiologists within FDA), would argue that in this example the figure of 4.4 is the one that we should be concerned with. In other words, the data on the hazard in question points to the fact that this hazard may, in fact, happen up to 4.4 times more often on the drug than on placebo or nontreatment. If the hazard is serious, it follows that there is a considerable onus on regulators to warn patients and doctors about this possibility, but FDA has not been inclined to do so.

If a "sauce for the goose is sauce for the gander" approach were taken to the issue of whether the drugs, in fact, do work, and a company's trials were all analyzed together, in the case of Pfizer's Zoloft there is every chance that it would result in a figure of less than 1.0 for a risk of getting better on treatment. In other words, the evidence that Zoloft works is in many respects less strong than the evidence it causes suicidal behaviors. When it comes to efficacy, however, the regulators are prepared to accept a signal that Zoloft might work in order to let it on the market, but not prepared to accept a signal that Zoloft might pose hazards as a basis for warnings.

The bottom line is that the public needs to know that at this point the science shows nothing without a choice by regulators or companies to adopt one or another approach. And at present, the regulators find common interest with pharmaceutical companies rather than consumers and adopt an approach that facilitates drug entry to the marketplace and minimizes the likelihood that a company will have to warn about hazards.

CONFLICT OF INTEREST STATEMENT

David Healy has been a consultant for, clinical trialist for, speaker for, chairman of symposia for, or engaged in other capacities for Astra-Zeneca, Eli Lilly, Pfizer, SmithKline Beecham, Sanofi-Synthelabo, Janssen-Cilag, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, and Roche. He has also been an expert witness for plaintiffs in a series of SSR-related suicide, homicide, and physical dependence cases, and for defense in a series of LSD-therapy cases.

REFERENCES

Alderman, J., Wolkow, R., Chung, M., & Johnston, H. F. (1998). Sertraline treatment of children and adolescents with OCD or depression: Pharmacokinetics, tolerability, and efficacy. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*, 386–394.

British Association for Psychopharmacology. (1997). Consensus statement on childhood and learning disabilities psychopharmacology. *Journal of Psychopharmacology, 11*, 291–294.

Doogan, D. (1983). *Comments on study 50/70.1. March 25, 1983*. Available from author.

Healy, D. (2000). Antidepressant induced suicidality. *Primary Care Psychiatry*, 6, 23–28.

Healy, D. (2004). *Let them eat Prozac*. New York: New York University Press. Supporting documentation available on www.healyprozac.com

Healy, D., & Aldred, G. (2005). Antidepressant drug use and the risk of suicide. *International Review of Psychiatry, 17*, 163–172.

Healy, D., & Cattell, D. (2003). The interface between authorship, industry and science in the domain of therapeutics. *British Journal of Psychiatry, 182*, 22–27.

Healy, D., & Whitaker, C. (2003). Antidepressants and suicide; Risk-benefit conundrums. *Journal of Psychiatry & Neuroscience, 28*, 331–339.

Leber, P. (1991a). *Zoloft NDA approvable action recommendation. Memorandum to R. Temple. August 26, 1991.* Available from the author.

Leber, P. (1991b). *Recommendation to approve NDA 19-839 (Zoloft, Sertraline). Memorandum to R. Temple. December 1991.* Available from the author.

Lee, H. (1991). *Statistical reviews on sertraline for FDA.* August 14, 1990, and January 31, 1991.

March, J. S., Biederman, J., Wolkow, R., Safferman, A., Mardekian, J., Cook, E. H., et al. (1998). Sertraline in children and adolescents with OCD: A multicenter randomised controlled trial. *JAMA, 280*, 1752–1758.

Montgomery, S. A., Dunner, D. L., & Dunbar, G. (1995). Reduction of suicidal thoughts with paroxetine in comparison to reference antidepressants and placebo. *European Neuropsychopharmacology, 5*, 5–13.

Newman, T. B. (2004). A black-box warning for antidepressants in children? *The New England Journal of Medicine, 351*, 1595–1598.

Ryder, S. (2004). *Letter to Robert J. Temple, Director, Office of Drug Evaluation, July 26, 2004.* Posted on FDA Web site, pp. 24–25. Retrieved August 20, 2004, from www.FDA.gov/ohms/dockets/ac/04/briefing/2004-406561-31-pfizer-letter.pdf

Saletu, B., Grunberger, J., & Linzmayer, L. (1986). On central effects of serotonin reuptake inhibitors: Quantitative EEG and psychometric studies with Zoloft and zimelidine. *Journal of Neural Transmission, 67*, 241–266.

Saletu, B., & Grunberger, J. (1988). Drug profiling by computed electro-encephalography and brain maps with special consideration of sertraline and its psychometric effects. *The Journal of Clinical Psychiatry, 49*(Suppl.), 59–71.

Tranter, R., Healy, H., Cattell, D., & Healy, D. (2002). Functional variations in agents differentially selective to monoaminergic systems. *Psychological Medicine, 32*, 517–524.

Vratil, K. H. Order to show cause. August 18. In *Miller v. Pfizer* (2000).

Offprints. Requests for offprints should be directed to David Healy, MD, North Wales Department of Psychological Medicine, Bangor, Wales LL57 2PW, United Kingdom. E-mail: healy_hergest@compuserve.com