

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF KANSAS

MARK MILLER AND CHERYL	§	
MILLER, INDIVIDUALLY AND	§	
MARK MILLER AS	§	
ADMINISTRATOR OF THE	§	
ESTATE OF MATTHEW MILLER,	§	
DECEASED,	§	
Plaintiffs	§	
v.	§	CAUSE NUMBER 99-2326 KHV
	§	
PFIZER, INC. (Roerig Division)	§	
Defendant	§	

DECLARATION OF JONATHAN COLE, M.D.

My name is Jonathan Cole and I am providing this sworn declaration to counsel for the Miller family in this case who have previously retained my services as a consulting expert. A copy of my CV is attached to this Declaration. It is my understanding that this Declaration will be filed in conjunction with something called a “Daubert” motion. If the Court decides to conduct a formal hearing, and if my health permits, I have agreed to testify at that hearing.

Plaintiffs retained me to provide my opinions concerning the scientific reliability of the arguments made by Dr. Healy in his memorandum entitled “Zoloft and Suicide: Causal Mechanisms” as well as to respond to the contention by Pfizer that the only path to scientific truth is by means of randomized clinical trials (RCT’s).

By way of background, as my CV indicates, I am a psychiatrist and psychopharmacologist. I have been a member of the ACNP for many years and am well acquainted with Pfizer's experts Drs. Casey and Mann. I am also acquainted with Plaintiffs' expert, Dr. David Healy, whom I consider to be one of the bright young minds in the field of neuro-psychopharmacology and one of the three most eminent academic clinical psychiatrists in the U.K. Dr. Healy's book, *The Antidepressant Era*, reflects a broad understanding of the history, the science, and the medicine involved in antidepressant medications. I also know that he has published and lectured widely on various issues related to the matters in dispute. He is certainly a reputable expert concerning the serotonin system and the drugs which impact it.

The Millers' counsel has provided me with a copy of Dr. Healy's memorandum, "Zoloft and Suicide: Causal Mechanisms" as well as a number of other items which are reflected on the attached list. I have also discussed directly with Dr. Healy his thinking and approach to the scientific/medical issues involved in this case.

In 1990 I co-authored an article with my colleague Martin Teicher about treatment emergent suicidal ideation among some of our patients who were taking the SSRI drug Prozac. Our purpose in writing this article was to alert the profession to an alarming, probable drug side effect which we had observed. There

was a very clear association, not merely temporal, between the ingestion of Prozac and the patients' suicidality. In my judgment, this association merited further scrutiny, research, and testing. Pending the outcome of such testing, it also warranted careful warnings to prescribing physicians, particularly in view of the large percentage of prescriptions for SSRI antidepressants that are written by non-psychiatrists.

The SSRI drugs, as a class, clearly have the potential to cause, and in reasonable medical probability or certainty do cause, akathisia in some patients. As Dr. Healy indicates, they may also cause emotional blunting or dysregulation. Either of these conditions could, and probably do, trigger or contribute to violent or suicidal behavior. In other words, they are "biologically plausible" explanations of how the SSRI drugs cause suicidality. Although in 1997 practicing physicians undoubtedly varied in their level of sophistication and knowledge about the phenomenon, the potential to cause akathisia and its potential, in turn, to trigger suicidal behavior, was well known and "generally accepted" among psychopharmacologists before Matt Miller's death in July 1997.

To say that it was "generally accepted" does not mean, of course, that anyone had established an incidence rate or relative risk. As a practical matter, this is normally done by means of controlled randomized clinical trials (RCT's) or large scale epidemiological studies. Although the manufacturers of SSRI drugs

could and should have done these studies, to my knowledge no manufacturer of an SSRI drug has ever done a study where the primary outcome of interest was to measure treatment emergent suicidality.

They have done pooled, after-the-fact, retrospective “meta-analyses” of their clinical trial data. However, these trials themselves were not designed to detect or measure treatment emergent suicidality. Therefore, the meta-analysis methodology is a poor and inadequate way to detect or measure the phenomenon. Moreover, the HAM-D, item 3 scale used retroactively to “measure” increased or decreased suicidality is an extremely inaccurate, insensitive, and unsuitable rating instrument for this purpose.

Psychopharmacologists have arrived at conclusions about drug side effects based on clinical judgments and observations, particularly with the benefit of challenge, dechallenge and rechallenge, for many years without the benefit of clinical trials or epidemiological studies to quantify the degree of risk or “strength of association.” For example, a class of psychoactive drugs called neuroleptics cause a condition known as tardive dyskinesia. Tardive dyskinesia, like akathisia, is commonly referred to as an extrapyramidal symptom. Both Dr. Casey and I have been extremely active in the investigation, prevention and treatment of tardive dyskinesia. I have discussed tardive dyskinesia with him on a number of occasions. Both Dr. Casey and I concluded, long before any large scale epidemiological study

was ever done to attempt to quantify the degree of risk, that this class of drugs does cause tardive dyskinesia in some patients. And the large scale study required a large federal grant.

The reasoning and methodology that Dr. Healy has brought to bear on the question of SSRI induced suicidality is scientifically reliable. That is not to say that other psychiatrists or pharmacologists would necessarily agree with his conclusion. Many of them, particularly those who have some affiliation with pharmaceutical companies or whose research is funded by those companies, would prefer to see data from RCT's establishing the strength of the association. However, the methodology and reasoning is scientifically reliable. Moreover, I expect that, if the Court were to ask several independent experts who have no financial ties to the pharmaceutical industry, the Healy methodology would be "generally accepted" and, indeed, a significant percentage would agree with Dr. Healy's conclusions and agree that bad drug reactions rarely get well studied.

The problem with the detailed extensive controlled study of suicidal ideation and suicide itself being elicited by SSRI's is not unique in clinical psychopharmacology. For some reason, no drug company is ever eager to study the potential or real and relatively uncommon adverse effects of its drugs. In the U.S. and the U.K. there has been no use of public grant money to study this problem. Even the FDA committee convened to consider the suicidal ideation described in

the Teicher paper never came to grips with the reality or non-reality of the phenomenon. Instead, the last third of the meeting considered only the possible adverse public health effects of placing a warning in the Lilly labeling on fluoxetine (Prozac) and decided that a warning might cause suicide by causing a depressed patient to stop taking Prozac for their depression and thus slip back into suicidal depression. My clinical judgment and evaluation of David Healy's data is that we both judge SSRI's to be capable of eliciting suicidal thoughts and behavior, particularly early in treatment. Neither of us would contend that current SSRI's, including Prozac and Zoloft are ineffective in depression or that they may avert suicide by relieving depression in many patients. Unfortunately, as with many effective drugs, they also can cause disturbing and sometimes lethal side-effects. I have access to only a portion of the material Dr. Healy presents, but I have talked with him at length, and I have also seen patients and reviewed cases where an SSRI unmistakably precipitated a driven preoccupation with suicide.

In my judgment, the best U.S. data is from Seymour Fisher's group in Galveston, Texas. They did extensive prescription surveys, first of fluoxetine versus trazodone (1993) and second of fluoxetine versus sertraline (1995). Both are published in respectable journals. In both studies, fluoxetine patients called 800 numbers to report "unusual" drug effects at about the same rate as is shown in the package insert except that about 1 in 200 patients reported new suicidal ideas on

fluoxetine while none did so on trazodone, an older antidepressant. Sertraline and fluoxetine were found to have the same rates of side effects of a psychiatric nature including suicidal ideas. (I called Dr. Fisher to make sure of this). The rate of new or increased ideation of 0.5% sounds about right to me B rare enough to make most physicians not notice the effect but common enough to cause serious adverse effects such as death by suicide in a few patients.

Rothchild and Locke (1991) at McLean gave an SSRI (fluoxetine) to three patients who had survived suicidal leaps while on the same drug. All three developed the same symptoms again in the hospital. The study is published. I have been told that Dr. Rothchild has now disavowed the obvious interpretation of the study, saying now that the design he used was not perfect (no placebo). No money has been provided to attempt to replicate the study with a placebo control. Dr. Jick (1995), referred to by Dr. Healy for his British study, which again appears to show a higher suicide rate with an SSRI, has also now apparently disavowed his study. It is certainly interesting in this day of high grant monies and some dependence on drug company support that so many distinguished experts avoid testifying for plaintiffs in suits like the Miller case and even disavow their own studies. One cannot prove undue influence but I have to admit that I thought three times about entering this Daubert hearing against a company for whom I have done work and from whom I might wish to receive funds in the future.

The other problem with bad drug side effects (agranulocytosis on clozapine, tardive dyskinesia on antipsychotic drugs, convulsion on bupropion, priapism on trazodone, hypertensive crises on MAO inhibitors, cardiac deaths on neuroleptics) is that it is almost impossible to get support for any extensive or definitive study unless the FDA holds up approving a drug pending such a study or a rash of bad events occurring in a cluster gets major news attention. As an example, I have used mono-amine oxidase inhibitors for depression for years. A registry of foods and drugs which have caused severe reactions in people on MAOIs would be very helpful to patients and doctors alike. I have been unable to get funding for such a registry from any of the three companies involved over the years.

The conclusion is that serious side effects are always discovered first by clinicians and reported as case reports or letters to the editor. Such reports are good evidence if the event is unusual, striking and well reported. To go beyond this requires either grant funding the drug company whose drug may have the problem (unlikely without regulatory pressure), or small occasional studies which were designed for other purposes but turn out to be scientifically sound (double blind) and show adverse events more clearly than anyone could have foreseen B Dr. Healy's two healthy volunteers who developed suicidal impulses on sertraline without ever having been depressed.

One can wish for clearer, stronger, more definitive data one way or the other but it is unrealistic to expect it in the real world. Bad drug effects can and will occur sporadically and causation has to be addressed by clinical judgment and knowledge of psychopharmacology until more definitive studies are designed and run and analyzed properly.

Even then a bad effect (striking new suicidal urges) occurring once in 200 patients and real suicidal attempts and successful suicides (at much lower frequencies, perhaps 1 in 1,000) would take a huge study and many years. Data from countries or HMO's with huge data bases might be easier. But the studies would require careful scrutiny of patient information to discriminate between the kinds of suicidal drives Dr. Healy and I have seen in SSRI's from the occasional suicides occurring in the course of an unsuccessfully treated depression. In passing, it is to be noted that the randomized double-blind controlled studies used to establish efficacy are not the place to look for this phenomenon. Their rating instruments are insensitive and the patients are too carefully monitored. Additionally, I am aware of reports of company data being rearranged or selectively provided.

The real world is not perfect. Drugs can and do cause adverse effects which can resemble the manifestations of the illness and arguments about the causes and nature of these adverse events, including suicides, must rest on case reports and

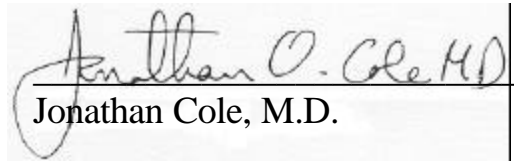
data collected in small studies for other purposes. The real suicidal drive caused by an SSRI often stands out from the patient's long standing depression like B pneumonia in a patient with a long history of dust allergies. If some cases stand out strikingly, there are logically others where the adverse effect is more subtle.

With respect to Pfizer's apparent position that RCT's are the only way to prove what side effects are caused by psychoactive drugs, it is my firm belief that this is ridiculous. I have been practicing psychiatry and pharmacology for over fifty years and was involved with the design and implementation of RCT's to test psychoactive drugs in this country from the inception of their use. RCT's are valuable tools to show efficacy which is important for FDA regulatory approval. That is their principal use in this country. To suggest that they are the only valid way to demonstrate drug side effects is, however, extremely misleading.

It is equally misleading to suggest that a relative risk of 2.0 or greater is some kind of magic, scientific "bright line." A relative risk is an important measure of the strength of an association across a group of patients. But it is not the only or even a firm scientific determinant of causation. A side effect that occurs in a relatively small percentage of patients, such as the treatment emergent suicidality which Dr. Teicher, Nurse Glod and I reported on in 1990, is not likely to be detectable in a standard RCT or measured by a relative risk calculation. That does

not mean, however, that the side effect is not real, not dangerous, and not caused by the drug.

Executed under penalties of perjury this 28th day of April, 2000.



Jonathan Cole, M.D.