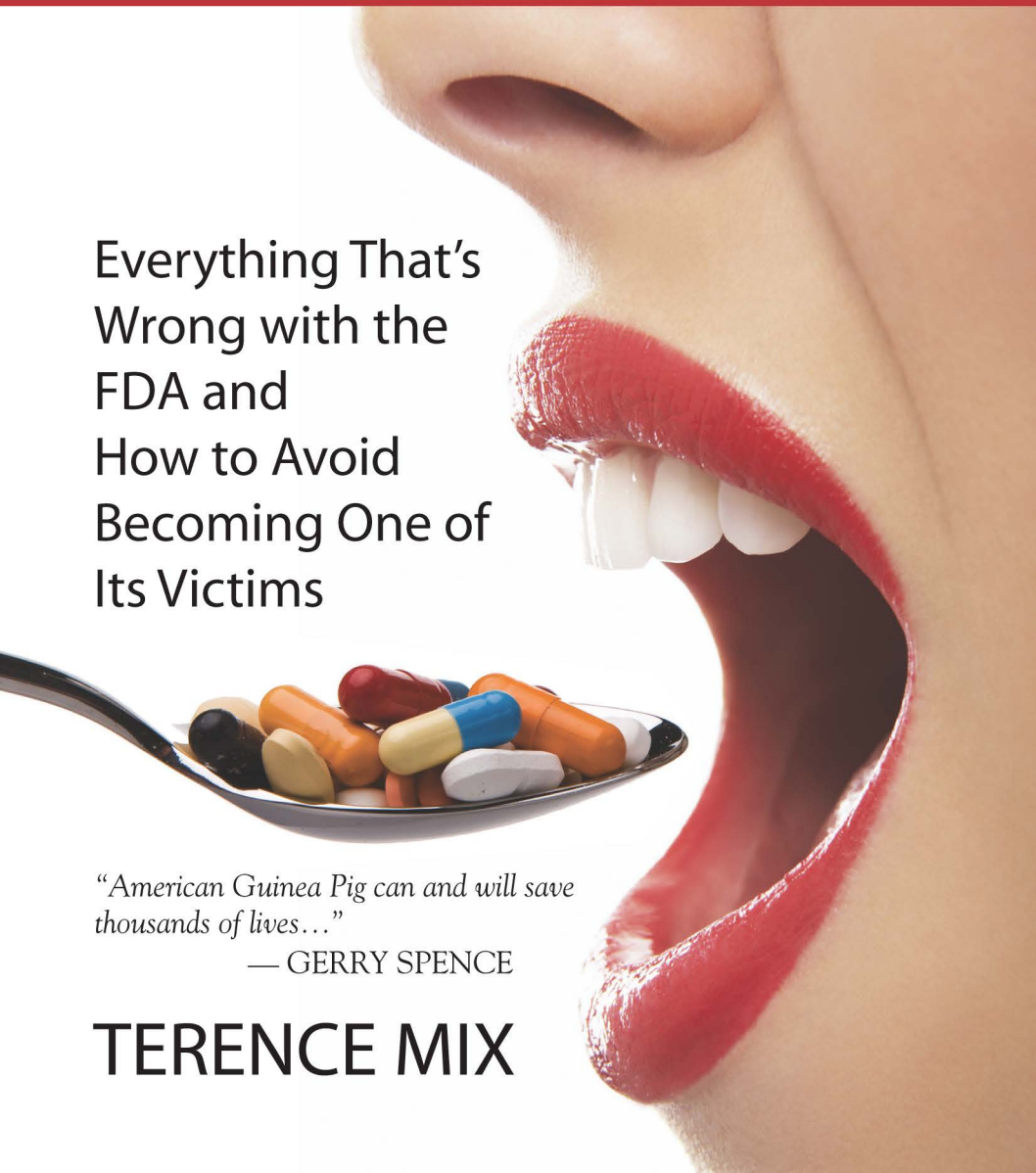
AMERICAN GUINEA PIG



Everything That's Wrong with the FDA and How to Avoid Becoming One of Its Victims

"American Guinea Pig can and will save thousands of lives…"

— GERRY SPENCE

TERENCE MIX

AMERICAN GUINEA PIG

Everything That's Wrong with the FDA
and How to Avoid Becoming One of Its Victims

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AMERICAN GUINEA PIG

Everything That's Wrong with the FDA and How to Avoid Becoming One of Its Victims

By Terence Mix

Foreword by Gerry Spence

Gerry Spence is a nationally known trial attorney who gained fame in the Karen Silkwood case and others. He is the author of over 16 books including Gunning for Justice *and* With Justice for None.

American Guinea Pig can and will save thousands of lives, and, if Congress hears its message, that number could be in the hundreds of thousands. It is an absolute must read, as it may help you avoid a trip to the hospital or to the morgue. It explains why you cannot rely upon the FDA to protect you and your loved ones. It sets out in clear and convincing terms not only how "big brother" is looking out more for the interests of the drug industry than the consumers of drug products but why it is happening. It is eye-opening, especially when one considers the magnitude of the problem and the level of risks to the general public.

This book is truly unique and stands head and shoulders above anything else on the market. When it comes to equipping you with everything you need to know to minimize the risk of becoming another drug industry casualty, it is literally a life-saver.

For anyone desiring to be an activist for change—to be proactive in bringing about changes to our archaic system of testing and monitoring of drugs—*American Guinea Pig* provides a wealth of information and statistics for Congress to consider.

But more important than anything else, it should be a handbook for everyone using prescription drugs, especially those 55 years of age or older. From practical advice, such as avoiding new drugs for their first three years on the market, to how to access the latest studies and other information about a drug that the FDA is sitting on, this book offers it all.

Terence Mix

It is a wake-up call about the marriage between the FDA and the drug industry and the impact it is having on all of us.

Gerry Spence
Jackson, Wyoming
2011

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INTRODUCTION

What did Michael Jackson, Heath Ledger and Anna Nicole Smith have in common?

They all died as a result of an adverse reaction to a combination of prescription drugs—a drug cocktail, you might say. But these were the ones who got attention. There were actually many more—hundreds of thousands more—who lacked celebrity, but experienced a similar fate.

Every year about 230,000 Americans die as a result of an adverse reaction to one or more prescription and nonprescription drugs.[1] You read that right—*230,000 Americans die every single year as a consequence of the use of legally purchased drugs,* the vast majority either prescribed or recommended by the victim's treating physician. In five years they kill in excess of *one million Americans*. It is the third leading cause of death in the United States, behind only heart disease and cancer. To put this in perspective, it would be comparable to every man, woman and child in the city of Orlando dying within a 12-month period—leaving a ghost town right next to Disney World.

And here's the scary part. Of that number, almost half—105,000—are taking the drug exactly as specified by the pharmaceutical company that manufactured the drug.[2] Bottom line: *prescription and over-the-counter drugs can kill you*—even when everything is done right.

The other 125,000 deaths occur as a result of a *mistake*. Either the prescribing doctor did not follow the directions specified by the drug company, or a nurse did not properly administer the drug, or the patient did not follow the instructions given by the physician and/or the pharmacy, or the pharmacy filled the prescription improperly. And yes, doctors and other medical care providers do make mistakes. According to the Institute of Medicine, there are approximately

1,500,000 *preventable* medication errors every year, most of which are caused by physicians and nurses.[3] Indeed, the majority of medication errors leading to deaths or a serious adverse drug reaction (ADR) occur in a hospital setting, where the patient has little opportunity to make a mistake with ordered medications. No less than 770,000 of these ADRs are serious enough to actually extend the hospital stay.[4]

Thus, pharmaceutical products do more than kill us—they also put us in the hospital. Every year 1,500,000 Americans are hospitalized as a result of a serious ADR.[5] Combined with in-hospital events, this equates to 2,270,000 annual victims spending time in the hospital as a direct consequence of using one or more prescription and/or nonprescription drugs. Although we never quite make it into a hospital, over 4,000,000 more of us seek medical care at physician offices and hospital outpatient departments and emergency rooms.[6]

Unfortunately, these tragedies are not limited to prescription drugs. Over-the-counter (OTC) drugs also take their toll. For example, according to statistics recently released by the FDA, 56,000 patients annually seek emergency room treatment as a result of liver failure caused by the use of acetaminophen, with most of the cases involving inadvertent overdosing.[7]

Acetaminophen overdoses are the leading cause of acute liver failure in the United States, Great Britain and most of Europe; and of the 56,000 related emergency room visits in the U.S., 2,600 of these patients are hospitalized and nearly 500 die annually.[8] But even keeping your use at recommended doses may not afford protection. Researchers have also found that taking acetaminophen at regular doses can cause liver damage.[9] For those of you who rarely read the labeling on OTCs, one brand of acetaminophen is *Tylenol*.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of pharmaceuticals that also wreak havoc on this country. And although the most dangerous NSAIDs are prescription drugs, others such as ibuprofen (i.e., *Advil* and *Motrin*) also take their toll. Even taken at recommended doses (up to 1200 mgs/day), ibuprofen has been known to cause hospitalization and death, especially when used with aspirin. Since ibuprofen has anti-inflammatory benefits, it is often taken by patients with arthritis. However, if combined with aspirin, it can be deadly. It has been reported that patients taking both aspirin and ibuprofen have a 73 percent increased risk of death from heart disease.[10]

This national crisis goes beyond the tragedy of hundreds of thousands of preventable deaths and the avoidable suffering of millions. It also has an impact on our pocketbooks. It has been calculated that the total annual health care costs as a consequence of adverse drug reactions equals $177.4 billion.[11] And that was in 2000 prices. The current number *easily exceeds a staggering $200 billion.* That is one trillion dollars over five years. It is thus a major contributor to the health care calamity that is consuming this country and holding us hostage in the results of a recession that will be felt for years to come.

Those are the numbers and they are as frightening as they are shocking.

They have also driven me to write this book. As a trial attorney who spent a major part of his career litigating against pharmaceutical companies, I had an intimate knowledge of what went on behind the scenes in the drug industry and its unhealthy relationship with the Federal Food and Drug Administration (FDA) that purportedly was its regulatory overseer. I thus was quite familiar with the multitude of problems in the system and why so many of my clients were suffering severe side effects from drugs that were never the subject of a

warning, either by their doctor or the pharmaceutical company. What I lacked was an appreciation of the *scope* of the problem.

Since 1975, I have had numerous exchanges and dealings with the FDA, ranging from requests for records under the Freedom of Information Act, to multiple pieces of correspondence and e-mails, to testifying in front of an FDA advisory committee,[12] to the filing of a formal citizen petition demanding that the agency order studies and warnings on fertility drugs. I have seen confidential corporate memoranda prepared by drug companies containing the content of discussions with FDA personnel at meetings and during telephone conversations. I have read numerous papers and books written by members of both the medical and legal professions, dissecting all of the problems associated with the testing and monitoring of drugs in the United States. I have literally reviewed over 1,000 peer-reviewed published studies assessing the effectiveness and risks associated with the use of pharmaceuticals. I have examined and cross-examined medical experts in the fields of pharmacology and toxicology, epidemiology, pathology and the standards of care for drug companies, including a former commissioner of the FDA. In the recent past, I spent no less than three and a half years researching and writing a nonfiction book[13] which followed the 48-year history of the fertility drug, Clomid, exposing all of the concealment, deception and failures not only of its manufacturer but also the manufacturer's counterpart in Rockville, Maryland.

You might say that my education has not only been extensive but historical. I have had the benefit of seeing how the FDA has dealt with adverse reaction issues in the 1970s, 1980s, 1990s and currently. Over those decades, of course, there have been changes, both procedural and substantive. Some have represented an improvement. But in my opinion the most significant ones have been enacted to

accommodate the interests of the drug industry, all to the detriment of the American consumer of drug products.

This view is shared not only by many members of the medical profession but even some holding important positions with the FDA itself. When Dr. David Graham testified before the Senate Finance Committee on November 18, 2004, he really opened some eyes. Not only did he recite the tragic history of Vioxx,[14] he also painted a graphic picture of inefficiency that then existed at the FDA. At the time of his testimony, Dr. Graham had worked for the agency for 20 years and was the associate director for science and medicine of the Office of Drug Safety (ODS).[15] As an insider, he spoke from a position of knowledge and experience. His words had the conviction of a concerned scientist who wanted to right the ship. What was portrayed to Senator Grassley (R-Iowa) and his committee was not pretty.

> The problem you are confronting today is immense in scope. Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless. It is important that this Committee and the American people understand that what has happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, FDA and its Center for Drug Evaluation and Research[16] are broken. . . . The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division [Office of New Drugs] approves a new drug, it is also saying the drug is 'safe and effective.' When a serious safety issue arises post-marketing, their immediate reaction is

> almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. *The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest.* At the same time, The Office of Drug Safety [ODS] has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs. (Emphasis added.)

Dr. Graham's views seem to be shared by Dr. Janet Woodcock, Deputy Commissioner of Operations for the FDA and the director of the Center for Drug Evaluation and Research (CDER)—at least back in 2005. When Dr. Woodcock appeared before a medical advisory panel to the Institute of Medicine on June 8, 2005, her comments seemed to echo the views of her FDA colleague.[17] The FDA's drug safety program had "pretty much broken down," she reported. And when it came to discovering the dangers of drugs already on the market, there was room for a "lot of improvement."

Some might argue that those problems were fixed when Congress passed the Food and Drug Administration Amendments Act of 2007 in the fall of that year, which certainly granted post market powers to the FDA that it lacked prior to its enactment. But, as will be explained later, until such time that the FDA demonstrates a willingness to efficiently *use* those powers, this might be another example of the horse unwilling to drink the water. For as currently structured, it is the

partnership between industry and regulator that has a stranglehold on the rank and file of the FDA, many of whom are committed to public safety. That legislation, unfortunately, addressed neither the conflict referred to by Dr. Graham nor the two major *premarket* problems that, in my view, are largely responsible for using the general public to discover most of the serious ADRs that are killing and sending us to hospitals—that have effectively made us unwitting guinea pigs for the pharmaceutical industry.

More than 50 percent of approved drugs have serious adverse reactions not detected prior to approval—they are discovered only *after* they are marketed.[18] What makes this statistic particularly terrifying is that the study upon which it is based used statistics compiled from 1976 to 1985, prior to the enactment of the Prescription Drug User Fee Act (PDUFA) in 1992. As is explained in Chapter 2, the PDUFA and its renewals every five years have created an environment at the FDA in which drugs are literally rushed to market. This percentage is thus unquestionably higher, as corroborated by a study published in 2007[19] in which they found a 2.6-fold increase in serious ADRs reported to the FDA between 1998 and 2005, 87.6 percent of which were new and serious drug reactions *not included in the product labeling*.

If an adverse reaction occurs only once in 100,000 users—or even once in every 10,000—then this might be understandable. But when the incidence is less than 1/1000, this is not only unacceptable, it is inexcusable. When evidence of a serious and fatal drug reaction surfaces only *three months* after the drug was introduced on the market—as it did with the cholesterol-reducing drug, Baycol—something is horribly wrong with our premarket testing system. The Baycol story will be discussed, along with a number of other drug debacles, and the multiple reasons why they occurred and continue to occur at an alarming rate.

To solve any problem, it is necessary to recognize that it does in fact exist and look at why it is occurring. Part I of this book will explore in depth what is and has been occurring, with special emphasis on the past decade. The use of example is a great educational tool; and you will read about several different drugs, some of which have received considerable notoriety and others you may not have heard about. All will demonstrate the problems with the current system of testing and monitoring of drugs.

Part 2 will propose important solutions to those problems, which can only come about by an act of Congress. In fact, as you will learn, Congress played a major role in establishing laws which virtually mandate pushing new drugs onto the market without an adequate opportunity to assess their safety. This first occurred in 1992, when agency and industry approached members of Congress and encouraged them to enact the Prescription Drug User Fee Act—which they renewed with minor revisions in 1997, 2002 and 2007.

The current system by which the FDA evaluates the safety and effectiveness of drugs is inefficient and responsible for a large proportion of our country's annual health care costs. Not only does the FDA lack accountability and transparency, the *premarket* testing of drugs is archaic—in need of a major overhaul—and the FDA's *postmarket* monitoring system lacks any reasonable measure of urgency to promptly respond to established dangers arising out of the general public's use of prescription and nonprescription drugs. Addressing and fixing these problems could result in an annual savings of at least $100 billion in health care costs—a savings of one trillion dollars over ten years. Part 2 of this book proposes ways to do just that—and so save 100,000 lives a year and immeasurable suffering in the process.

All drugs have side effects, including those which you can purchase at your local pharmacy or supermarket without a prescription. However, to reach the marketplace, they must go through an assessment by the FDA to determine whether their *benefits outweigh their risks.* This is a process referred to at the FDA as *risk evaluation and mitigation strategies*. If a drug cannot meet this minimum standard, it is either not approved for marketing or removed from circulation if it has already been sanctioned for sale. Thus, if a drug has only negligible or minimal effectiveness, the presence of even mild to moderate adverse reactions will likely keep it off the market—at least in theory. But if it has been shown to be effective at treating a serious or potentially fatal disease or condition, even severe side effects will not preclude its use. In such instances, it is dealt with by requiring *adequate warnings* of those risks. The strongest cautions about a serious ADR are contained within a *black box warning*.

Warnings serve two primary purposes. First, they allow the user of the drug to make an *informed choice* on whether or not to use the drug. What are the odds of developing a serious side effect? Can it be permanent or fatal? Is it worse than the condition I am trying to treat? Is there an alternative form of treatment available, including another drug with less severe adverse reactions? This is the ideal analysis a patient should make before agreeing to take a drug or, for that matter, even before it is purchased.

Second, they provide patients with an *early detection system* to educate them about what to be on the lookout for before the drug reaction becomes so severe and advanced that it is beyond any form of effective treatment. What are the initial warning signs? How quickly do they develop? Are they too far advanced by the time the clinical symptoms are manifested? If so, are there laboratory studies available that can monitor your vital organs and expose the ADR

when it is still subclinical? This is the desired education every patient should seek before ingesting the pill or receiving the injection.

But what do you do when the ADR is never mentioned by the prescribing doctor or listed in the product labeling that accompanies the drug or is handed out by the pharmacy? How can you protect yourself when neither the doctor nor the pharmacy is aware of the ADR? Part 3 of this book arms you with the tools needed to protect yourself and your family as a last line of defense—to access available information about the dangers of the drug that has yet to be distributed to the medical profession at large. Much too often, the FDA has received incriminating evidence that it is sitting on, *sometimes for months and years*, before acting to mandate warnings or to order removal of the drug from the market. Part 3 will educate you on –methods and means available to discover and understand the results of cutting edge studies about the potential risks of drugs currently on the market. It will become your handbook for each step to take before using *any* drug in the future.

We can never know with certainty that all true *rare* ADRs have been discovered until a drug has been on the market for years and consumed by millions. With proper use if this book, however, and implementation by Congress of its many proposals, there will no longer be a reason for each of us to be viewed by the drug industry and the FDA as an *American Guinea Pig*.

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[1] Smith, *American Pharmacy* NS29 (1) February 1989; Lazarou et al., JAMA 279 (15) April 1998: 1200–05.

[2] Lazarou et al., JAMA 279 (15) April 1998: 1200–05.

[3] "Preventing Medication Errors," Institute of Medicine Report Brief, July 2006.

[4] Classen et al., JAMA 277 (4) 1997: 301–06; Cullen et al., *Critical Care Medicine* 25 (8) 1997: 1289–97; Cullen et al., *Journal of Quality Improvement*, 21 (10) 1995: 541–48.

[5] Moore et al., JAMA 279 (15) April 1998: 1571–73.

[6] Zhan et al., *Jt Comm J Qual Patient Saf* 31 (7) July 2005: 372–78.

[7] Matthew Perrone, Associated Press article, June 30, 2009.

[8] Lee, *Hepatology Research* 38 (Suppl.1) 2008: S3–S8.

[9] Watkins et al., JAMA 296 (1) July 2006: 87–93.

[10] MacDonald and Wei, *The Lancet* 361 (9357) 2003: *cet*, 361, 573–74.

[11] Ernst et al., *J. Am. Pharm. Assoc*. 41 (2) March–April 2001: 192.

[12] The FDA currently has at its disposal 16 different advisory committees comprised of independent experts who provide the agency with the benefit of their opinions on a multitude of issues, including the necessity of warnings or whether a drug should be withdrawn from the market. The FDA, however, is not bound by the decision.

[13] *THE PRICE OF OVULATION: The Truth about Fertility Drugs and Birth Defects—and a Solution to the Problem* (Aurora, Colorado: Tendril Press, 2009).

[14] For the full story on Vioxx, see Chapter 8.

[15] The Office of Drug Safety is now the *Office of Surveillance and Epidemiology*, which is responsible for the monitoring of drugs after they are on the market.

[16] The Center for Drug Evaluation and Research (CDER) is the division of the FDA responsible for evaluating and monitoring the safety and effectiveness of drugs.

[17] "Drug Safety Problem's Broken, a Top FDA Official Says," *New York Times*, June 9, 2005.

[18] *FDA Drug Review: Postapproval Risks, 1976–1985* (Washington DC: US Government Accountability Office, April 26, 1990), GAO/PEMD-90-15.

[19] Moore et al., *Archives of Internal Medicine* 167 (16) September 10, 2007: 1752–59.

CHAPTER 12:

THE PAXIL STORY

PAXIL (paroxetine hydrochloride) is one of a class of drugs called Selective Serotonin Reuptake Inhibitors (SSRIs) and is manufactured by GlaxoSmithKline (GSK). Yeah, them again. The FDA cleared it for market on December 29, 1992, for the treatment of depression. The controversies involving Paxil include no less than three different adverse reactions; namely, (1) its capacity to addict patients to its use; (2) its potential to induce suicidal thoughts; and (3) its ability to increase the risk of birth defects.

The patent rights to Paxil were originally purchased from a Danish company (Ferrosan) in 1980, which had conducted animal studies with the drug on pregnant rats and rabbits. One of the purposes of conducting the studies was to determine whether or not the drug could cause birth defects. During one of the studies, different pregnant rats were exposed to Paxil throughout pregnancy at doses of 5 mg, 15 mg and 50 mg/day and then examined after birth. What they found was that of the offspring exposed to 5 mg, 65 percent of the litter was dead; of those exposed to 15 mg, 92 percent were dead; and at 50 mg, 100 percent were dead. In comparison to pups from pregnant mothers not exposed to Paxil, only 12 percent were dead after delivery. Significantly, *no autopsies were performed* on the dead pups to determine whether they died as a result of birth defects.

In 1980, an expert consultant for SmithKline Beecham (SKB), which ultimately became GSK, reviewed the studies and forwarded a March 20, 1980, memo to the company. Among other things, his memo noted that the study demonstrated the possibility that at non-toxic doses to the mothers, Paxil could potentially be lethal to an embryo and might "contraindicate the use of [Paxil] in pregnancy."

He also added, “There remains the possibility of this compound could be teratogenic [cause birth defects] at higher dose levels.” The underlying message was that more studies were needed to verify the potential toxicity of the drug to the fetus and the possible risk of birth defects. *However, Glaxo chose not to conduct such studies.*

Postmarket History

- 1993: During the first year that Paxil is on the market, Glaxo destroys the raw data (i.e., laboratory notebooks, slides, photos, etc.) from the 1980 animal studies of the drug, leaving only the reports for review. As a consequence, no one can verify whether or not there were in fact birth defects charted in the lab notes. The notes of the laboratory—where the studies had been performed in 1980—contained a statement that “this material will be stored” and the “material will not be discarded or released from these laboratories without the [drug company’s] consent.” The implication being that Glaxo had authorized the destruction.

- February 9, 1994: One of the executives at Glaxo prepares a memo related to seeking approval to sell Paxil in Japan. Of concern is how Japan will react to the 1980 rat studies. What are they going to do if Japan requires them to do studies to determine why the rat pups died? It is not a big market and adverse animal studies could have a consequence in the United States where the market is huge. A change in the pregnancy category from B to C is a possibility (see below). The memo states in part: "A positive finding [in one of their required studies] would be more of a problem since in this case it is undoubtedly exposure during early pregnancy that is of concern for women." Additionally, "a strengthening of the labeling might be likely, e.g., women of childbearing potential should not take the drug unless they know

they are not pregnant and are taking adequate contraceptive precautions." He also warned, "Worst case, but just possible, *contraindication of women of childbearing potential*." (Emphasis added.) Later in the memo, they state: "Obviously, conducting no more studies and arguing the case with [Japan] would have no regulatory implications elsewhere unless our arguments fail and [Japan] requests us to do the type of study we wish to avoid." This memo clearly reflects intent to avoid learning of the *true risk* to the embryo and how to manipulate the system to avoid conducting potentially incriminating studies. Sales of Paxil debuted in Japan in 1999 without a problem.

- 1997: The possibility of being ordered to conduct animal teratology studies becomes a matter of discussion among the top execs at Glaxo. One of them, Bonnie Rossello, has the answer to the problem that she expresses in a memo: "If neg, results can bury." Now there's an easy answer. If they are done and turn out bad, just bury them.

- 1998: By now, Glaxo has received reports on numerous miscarriages, intrauterine deaths and birth defects associated with the maternal exposure to Paxil, and in an internal review by its own scientists they describe the volume of cases as an "alarmingly high number." This report, however, is never submitted to the FDA and the "alarming" language deleted from the review entirely. A number of the adverse reaction reports fail to find their way to the FDA, as required under Federal law.

- Through the end of the calendar year 2000, there are at least *36 articles* appearing in medical journals documenting individual case reports or studies validating the presence of *withdrawal*

symptoms in patients attempting to discontinue use of Paxil.[1] These papers date back at least as early as 1994.

- 2001: A woman writes to Glaxo about having a child with a heart defect after taking Paxil during pregnancy. A Glaxo exec notes in an internal memo they are "almost certain" that Paxil had caused the birth defect, but do not tell the woman or the FDA.

- April 2002: A study is published in *CNS Drugs* comparing the withdrawal symptoms between Paxil (paroxetine) and Prozac (fluoxetine).[2] Each group was treated for a minimum of eight weeks. They find that 42 percent (22/52) of the Paxil patients had symptoms of withdrawal compared to only 9 percent (4/45) of the Prozac patients.

- August 19, 2002: A federal court judge in Los Angeles orders GSK to pull all of its Paxil commercials off the air, targeting its claim that the drug was not habit-forming. She finds that *in other countries*, labels on the drug warn of adverse reactions when use of the drug is discontinued, and that the commercials in the U.S. were "misleading and created inaccurate expectations about the ease of withdrawal from the drug." The ruling comes about a year after a class-action lawsuit was filed on behalf of 35 patients who claimed they suffered withdrawal symptoms while attempting to discontinue the drug. GSK immediately contacts the FDA concerning the ruling, after which the agency notifies the judge that approval of commercials and other advertisements is within the exclusive jurisdiction of that regulatory body. The FDA had previously *reviewed and approved of the commercial*. Two months later, the judge reverses her ruling.

- December 31, 2002: Total Paxil worldwide sales for the year equal $2.67 billion, representing nearly 10 percent of Glaxo's annual gross income.

- December 10, 2003: The United Kingdom announces that all SSRI antidepressants (except Prozac) would be contraindicated for use in children and adolescents under 18 due to their lack of efficacy and their association with suicidal thoughts and actions. Another occasion when Great Britain beats us to the punch.

- February 2004: A joint meeting of the FDA Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-infective Drugs Advisory Committee takes place from February 2–4, concerning the risk of suicide in children and adolescents taking antidepressants. The day before the meeting (February 1, 2004) a story breaks in the *San Francisco Chronicle* that one of the FDA's own experts from the Office of Drug Safety, Dr. Andrew Mosholder, was being denied by senior FDA officials the opportunity to present his findings and conclusions at the hearing. Dr. Mosholder, a child psychiatrist and expert on the subject, had previously been assigned the task by the FDA to do a study and analysis on unpublished company data. He was now prepared to testify to his conclusion that the drugs—including Paxil—*doubled the risk of suicide.* Although Dr. Mosholder testifies at the hearing, it is an abbreviated presentation and he offers no opinion about the increased risk. One of the speakers at the hearing, Vera Hassner Sharav, advises the committee members of the suppression, who also hear testimony from more than 50 families whose children had suffered from the drugs. The committee recommends that, until the issue could be studied further, there should be an interim warning that antidepressants might be linked to suicidal thinking

and other violent behavior in children and adolescents. Watered-down warnings from the FDA follow the next month and its officials immediately *launch a criminal investigation* into who leaked the results and suppression of Mosholder's report to the press.

Controversy follows the hearing. The FDA retains a group of experts out of Columbia University to do an additional study on the question, including a review of the records relied upon by Dr. Mosholder. At first it would seem to be a stacked deck. The chairman of the group, Dr. John Mann, has significant financial ties to the companies whose drugs are under scrutiny. He has also been a defense expert witness for Pfizer and GSK in litigation related to SSRIs on this very issue.

- September 2004: To everyone's surprise—including, I am sure, those within the FDA—Columbia concludes that the available data from clinical trials of SSRIs and other new generation antidepressant medications indicate a small increase in the risk of adverse event reports of suicidal thinking or suicide attempts in youth (2 percent vs. 4 percent on average). It seems that Dr. Mosholder was right all along.

- September 13–14, 2004: A follow-up hearing of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Drugs Advisory Committee is held. The committee members review the study results from Columbia and hear further testimony, after which they vote 15–8 to require a black box warning for children and adolescents taking antidepressants.

- October 15, 2004: The FDA announces that it will be requiring a black box warning on all antidepressants regarding their use in children and adolescents. Based on its analysis of the data, the

FDA concludes that there is a medication-induced risk of increased suicidal thinking or behavior in children below the age of 18.

- December 8, 2005: Following the preliminary results of two unpublished studies, the FDA sends out an advisory that exposure to Paxil in the first trimester of pregnancy could increase the risk for congenital malformations, particularly cardiac malformations. The advisory states in part: "The early results of two studies showed that women who took Paxil during the first three months of pregnancy were about one and a half to two times as likely to have a baby with a heart defect as women who received other antidepressants or women in the general population." It also announces that it has ordered GSK to change the pregnancy category from C to D (studies in pregnant women have demonstrated a risk to the fetus, but that the benefits of therapy may outweigh those potential risks). Following the advisory, a GSK spokeswoman states that GlaxoSmithKline "had not concluded that there was a definite, causal link between the drug and the increased incidence of birth defects."[3] This public position would seem to be in direct conflict with the company's internal memo of 2001.

- February 9, 2006: A study that appears in the *New England Journal of Medicine*[4] reports that the use of Paxil and other SSRIs during late pregnancy (after 20 weeks of gestation) is associated with a six-fold increase in persistent pulmonary hypertension in newborns. Infants born with the disorder often require mechanical assistance to breathe and between 10 and 20 percent die soon after birth. Those infants who do survive often experience developmental delays, hearing loss and brain abnormalities. The

study was drawn on data from four metropolitan areas in the United States between 1998 and 2003.

- May 2006: GSK posts a letter to healthcare professionals on its website and through the mail, also including a package insert on Paxil with a new warning. The purpose is to reveal the results of a new meta-analysis it had conducted on earlier placebo-controlled clinical trials. The result? The data demonstrated that young adults (18–24) were at an increased risk of suicidal thoughts or behavior when using Paxil for the treatment of various psychiatric disorders, including Major Depressive Disorder (MDD). The trials included 8,958 patients on Paxil and 5,953 on a placebo. When looking only at MDD, suicidal behavior occurred in Paxil patients at an incidence of 11/3455 compared to 1/1978 on a placebo. When they broke it down into age groups, they found the suicidal behavior overwhelmingly with young adults.

  When I initially saw this report I was absolutely stunned. GSK had actually conducted a study of its own earlier clinical data, determined that its drug posed an increased risk of suicide and then dutifully reported it to the FDA and medical profession. Wow! I was truly impressed—and surprised . . . until I read the follow-up story. As it turns out, there was a much darker motive to GSK's sudden development of a conscience. And that twist did not come to light until January 18, 2008, when a federal court judge in Sacramento, California, ordered public disclosure of internal company memos and reports previously sealed.

  It appears Glaxo *concealed the fact that its premarket clinical studies with Paxil had demonstrated the drug had an eight-fold increase in the risk of suicide, as far back as 1989.* The key to the disclosure focuses on the "washout" phase preceding a clinical trial. That's when the patients stop taking all other medications to avoid confusion with results from the trial itself. Because the

washout occurs before patients randomly receive either the drug or the placebo control, *adverse events during this time can't be attributable to the trial and are thus excluded from the final results*. However, Glaxo researchers submitting data on Paxil to the FDA in the late 1980s and early 1990s included suicides and suicide attempts from the washout period in the results for the placebo patients, but *not from the Paxil patients.* As a consequence, the extra "placebo" suicides negated suicides attributed to Paxil in the trials, making the drug appear safe. If the washout results had been excluded, the data would have shown that Paxil produced an eight-fold increase in the risk of suicidal behavior in adults.[5]

- July 19, 2006: Five months after the *New England Journal of Medicine* study, the FDA finally issues a warning: "A recently published case-control study has shown that infants born to mothers who took selective serotonin reuptake inhibitors (SSRIs) [including Paxil] after the 20th week of pregnancy were six times more likely to have persistent pulmonary hypertension (PPHN) than infants born to mothers who did not take antidepressants during pregnancy. The background risk of a woman giving birth to an infant affected by PPHN in the general population is estimated to be about 1 to 2 infants per 1000 live births. Neonatal PPHN is associated with significant morbidity and mortality."

  Virtually simultaneous with the warning, the FDA also issues a health advisory, citing another study.[6] "The . . . study illustrates the potential risk of relapsed depression after stopping antidepressant medication during pregnancy. The authors followed pregnant women who in the past had major depression. During their pregnancy, some of these women were not feeling depressed and stopped taking their antidepressant medicines.

Others stayed on their antidepressant medicines while pregnant. The women who stopped their medicine were five times more likely to have a relapse of depression during their pregnancy than were the women who continued to take their antidepressant medicine while pregnant." It should be noted that the patients who relapsed were suffering from *major* depression (see below). The importance of this distinction is not mentioned in the advisory.

- December 13, 2006: The Psychopharmacologic Drugs Advisory Committee meets to address the issue of suicidality in adults taking antidepressant drugs. The committee finds that the data presented by the FDA is consistent with an increased short-term risk for suicidality in younger adult patients using antidepressant drugs. It votes 8–0 to alter the current warning on antidepressant drugs to extend to young adult ages and votes 6–2 that it be a black box warning.

- May 2, 2007: The FDA announces that it has asked all antidepressant manufacturers to expand the current black box warnings to include increased suicidality for young adults (ages 18–24). One should note that it took *almost six months* since the advisory meeting to arrive at this decision—and *one year* since GSK reported the results of its study. Some are critical that the warning stops at age 24—at the suggestion that once an adult hits 25, he or she is no longer at risk.

- February 2008: A study is published in *PLoS Medicine*,[7] assessing the effectiveness of *Paxil* (paroxetine), Prozac (fluoxetine), Effexor (venlafaxine) and Serzone (nefazodone) in the treatment of depression. Following a meta-analysis of 35 different clinical studies, the scientists involved in the study

conclude that when compared to a placebo, there was no difference in benefit from the drugs through moderate levels of initial depression, and significant clinical improvement only occurred at the "upper end of the very severely depressed category." Even at that, they also conclude that the improvement for the severely depressed was attributable to a decrease in responsiveness to the placebo "rather than to increased responsiveness to medication."

- December 31, 2008: Total Paxil sales for the year equal $942 million, even though now competing with generic versions of the drug. That number represented 2.1 percent of Glaxo's total annual revenue.

- August 20, 2009: The *Associated Press* breaks a story about GlaxoSmithKline ghostwriting medical journal articles to promote Paxil. Sound familiar? GSK apparently found the practice beneficial as well. It seems that during litigation over Paxil cases, counsel for the victims found a number of records documenting this means of promotion. A memo, dated April 2000, describes the manner in which its sales staff would approach physicians and either offer to help them write a favorable article about Paxil or have the entire paper ghostwritten by company consultants, with the physician's name added as author. Between 2000 and 2002, such articles appeared in five different medical journals. The program was appropriately designated *CASPPER*. I guess GlaxoSmithKline saw nothing wrong with a little friendly ghostwriting.

- October 13, 2009: A Philadelphia jury, in the case of Kilker vs. Glaxo, awards a child and his family $2.5 million for heart defects it determines were factually caused by his mother's

exposure to Paxil during pregnancy. At this time, there are over 600 more cases waiting to go to trial.

- January 6, 2010: A study is published[8] in the *Journal of the American Medical Association (JAMA)*, exploring the effectiveness of *Paxil* (paroxetine) and Tofranil (imipramine) in the treatment of depression. The meta-analysis of six different studies concludes that although the drugs proved beneficial for patients with *very severe* depression, "The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms." The researchers noted that about 70 percent of all patients seeking treatment for depression have symptoms in the mild to moderate category.

Study 329

Because of its egregious nature and the extent of documentation,[9] the history involving *study 329* will be addressed separately. It is a dramatic example of what has been going on in the drug industry for decades—and continues to this day. In effect, it has become a "way-of-life" on how major pharmaceutical companies test and market their drugs.

Eager to expand Paxil's reach to a broader market, SKB (predecessor to GSK) submitted study designs to assess the effectiveness of the drug for the treatment of major depression in *children and adolescents* in 1993. Principal architect of the protocols was a Martin Keller, MD, Chairman of Psychiatry at Brown University in Rhode Island. Once approved, the purported double-blind study[10] enrolled 275 patients between April 1994 and March 1997. The design included *eight* different defined "outcomes" to

determine the effectiveness of the drug. However, after the investigators eliminated the "blind" aspect of the drug (in October 1997), it was determined that *there was no significant difference between the Paxil and placebo groups on any of the 8 pre-specified measures of a positive outcome.* Put simply: The drug did not work.

It was at this point that Keller and the other investigators began to play with the numbers. *After* discovering who received the drug and placebo, four of the eight negative outcomes were replaced with "positive" ones, to reflect that at some level the drug was working to relieve symptoms of depression. To do this, *19 additional outcomes* were tested before deciding on the final four positives. In reality, there were four positive outcomes (with differing criteria) out of 27 tested (15 percent).

Adverse reactions from the drug, of course, also had to be addressed. And here, Dr. Keller and his colleagues—and the staff at SKB—again got creative. In the study's final report of November 1998, there were several serious and severe adverse reactions in the Paxil group that were significantly more frequent than the placebo group. Among them were patients with suicidal thoughts and behavior, which the researchers chose to refer to as "emotional lability." Five of these six cases were rated in the report as severe and had either harmed themselves or had contemplated suicide. In truth, there were three more of the severe cases that were "overlooked." The actual count was a total of eight severe cases of adolescents in the Paxil group who had self-harmed or had suicidal ideas compared to only one in the placebo group. These numbers were also statistically significant.

The next step was to get the study published. Appearing in a journal was critical, as it would provide a means to push "off-label" prescriptions for children and adolescents, and the FDA had yet to approve the drug for this age group. To accomplish this, SKB turned

to its marketing staff to help ghostwrite the paper to submit to a prestigious journal for publication. Their first choice was the *Journal of the American Medical Association* (JAMA), which received the first of several drafts of the paper in early 1999. But to the disappointment of Keller and SKB, the peer-reviewers were somewhat harsh and suspect. In October 1999 it was finally rejected by JAMA.

Their backup plan was to go to the *Journal of the American Academy of Child and Adolescent Psychiatry* (JAACAP). But even here there were questions. One reviewer wanted clarification on the designed outcomes. Another commented, "Overall results do not clearly indicate efficacy. Authors need to clearly note this." Another stated, "A relatively high rate of serious adverse effects was not addressed in the discussion." Still another noted, "Given the high placebo response rate, are these drugs an acceptable first line therapy for depressed teenagers?"

But with each criticism, SKB and its spin doctors would engage in a little more camouflage. As an example, one of the company's senior scientists, James McCafferty, had drafted some language that at least offered some insight into the risks associated with using the drug: ". . . worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment." But on the same topic, the eventual published version states ". . . only headache (1 patient) was considered by the treating investigator to be related to [Paxil] treatment."

So what did SKB/GSK think of the results of the study? During the course of litigation on a class action case against SKB, the California law firm secured a court order compelling the drug company to turn over thousands of otherwise confidential and unreachable internal documents.[11] Here are some of the comments

when GSK execs thought no one was listening—or reading—from the outside:

> "The results of the studies were disappointing. The possibility of obtaining a safety statement from this data was considered but rejected." [E-mail of October 14, 1998.]
>
> "The best which could have been achieved was a statement that although safety data was reassuring, efficacy had not been demonstrated." [1998.]
>
> "Consultation of the marketing teams confirmed that this would be unacceptable commercially." [1998.]

This, of course, was before the marketing people gave their input to the project. And their skills are clearly at selling, not educating physicians on the risks and benefits of drugs. Indeed, even a GSK executive expressed some concern about twisting the results of the study: "She's going too far in burying bad news. It seems incongruous that we state it is safe yet report so many serious side effects." [e-mail of July 19, 1999.]

Well, perhaps Keller said something. After all, it's his name down there as lead author on the paper. In truth, Keller, who has made as much as $500,000 per year consulting and speaking on behalf of drug companies,[12] including GSK, had very little to do with the final draft of the paper and had no problem with it. Another one of the internal memos shed some light on this as well. When returning a near-complete draft to his ghostwriter, it was accompanied with the following memo from the psychiatrist: "You did a superb job with this. Thank you very much. It is excellent. Enclosed are some minor changes from me . . ."

In point of fact, study 329 was negative for efficacy and positive for harm.[13] But when the study was ultimately published in 2001,[14] it

proudly pronounced to the world that "[Paxil] is generally well tolerated and effective for major depression in adolescents."

In summary, I would ask the following questions: Why should it take a total of 16 to 18 years on the market to learn that an antidepressant drug is not effective in the treatment of mild to moderate levels of depression and *may* only be of some help to those suffering from a severe form of the mental disease? Why should it take a total of 12 years on the market to learn that the use of an antidepressant drug in children and adolescents increases their risk of suicide and other forms of self-harm? Why should it take a total of 14 years on the market to learn that the use of an antidepressant drug in young adults (18–24) increases their risk of suicide and other forms of self-harm?

The answers: *It shouldn't!*

Paxil still remains on the market for the treatment of major depressive disorder in adults and is not approved for pediatric patients. The black box warning currently states in part: "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need." Note that this warning does not *contraindicate* the use of Paxil in children.

In the two years since disclosure of fabricating the results of the Paxil premarket studies, the FDA has yet to publicly address this serious issue.

[1] Barr, et al., *Am. J. Psychiatry* 151 (2) February 1994: 289; Ellison, *J. Clin. Psychiatry* 55,1994: 544–45; Keuthen et al., *J. Clin. Psychopharmacology* 14 (3) June 1994: 206–07; Bloch et al., *The Lancet* 346 (8966) July 1, 1995: 57; Debattista et al., *Am. J. Psychiatry*, 152 (8) August 4, 1995: 1235; Dominguez et al., *Pharmacotherapy* 15,(6) Nov.–Dec. 1995: 778–80; Fava et al., *J. Clin. Psychopharmacology* 15 (5) October 1995: 374–75; Frost et al., *Am. J. Psychiatry* 152, May 5, 1995: 810; Koopowitz et al., *Human Psychopharmacology* 10, 1995: 147–48; Oehrberg et al., *Brit. J. Psychiatry* 167, 1995: 374–79; Phillips, *Am. J. Psychiatry*, 152 (41) 1995): 645–46; Pyke, *Am. J. Psychiatry* 152(1) January 1995: 149–50; Arya, *Aust. NZ J. Psychiatry* 30 (5) October 1996: 702; Bhuamik et al., *Human Psychopharmacology*, 11, 1996: 337–38; Coupland et al., *J. Clin. Psychopharmacology* 16 (3) 1996: 356–62; Mathew, *Australian Adverse Drug Reactions Bulletin* 15, November 1996: 1–2; Pacheco et al., *Brit. J. Psychiatry* 169 (3) September 1996: 384; Reeves et al., *J. Clin. Psychopharmacology* 16 (5) October 1996: 411–12; Stein et al., *J. Clin. Psychopharmacology* 16 (3) June 1996: 218–22; Price et al., *Br. J. Clin. Pharmacology* 42 (6) 1996: 757–63, 1996; Blomgren et al., "SSRI Dose Interruption Study: Interim Data," American Psychiatric Association, 150th Annual Meeting, San Diego, 1997; Landry et al., *J. Clin. Psychopharmacology* 17 (1) February 1997: 60–61; Mackay et al., *Pharmacoepidemiology and Drug Safety* 6, 1997: 235–46; Walker-Kinnear, *Brit. J. Psychiatry* 170, April 1997: 389; Gram, *Ugeskr Loeger* 160 (50) December 7, 1998: 7291–93; Huffstutler, *J. Am. Acad. Nurse Pract*. 10 (4) April 1998: 161–65; Macdonald, *CMAJ* 159 (7) October 6, 1998: 846–47; Rosenbaum et al., *Biol. Psychiatry* 44, 1998: 77–87; Bakker, *Ned Tijdschr Geneeskd* 143 (35) August 28, 1999: 1795; Peeters et al., *Ned Tijdschr Geneeskd* 143 (27) July 3, 1999: 1429–31; Vergouwen et al.,

Ned Tijdschr Geneeskd 143 (35) August 28, 1999: 1794–95; Belloeuf et al., *Ann Med Interne (Paris)* 151 (Suppl.A): April 2000: A52–53; Diler et al., *J. Clin. Psychopharmacology* 20 (5) October 2000: 586–87; Green, *Psychiatry On-Line*, www.priory.com/psych/panes.htm, January 2000; Haddad et al., *Acta Psychiatr Scand* 102 (6) December 2000: 466–68; and Strickland et al., *J. Clin. Psychopharmacology* 20 (2) April 2000: 271–71.

[2] Bogetto et al., *CNS Drugs* 16 (4) April 2002: 273–83.

[3] "Paxil Draws Heightened Warning," *Associated Press*, December 9, 2005.

[4] Chambers et al., *New England Journal of Medicine* 354 (6) February 9, 2006: 579–87.

[5] These findings and conclusions were verified following an extensive review and analysis by a noted Harvard University psychiatrist, Dr. Joseph Glenmullen. He also stated that it was "virtually impossible" for GSK to have misunderstood the data.

[6] Cohen et al., *JAMA*, 295 (5) February 1, 2006: 499–507.

[7] Kirsch et al., *PLoS Medicine* 5 (2) February 2008: 260–68.

[8] Fournier et al., *JAMA* 303 (1) January 6, 2010: 47–53.

[9] Among other sources, see the professional expose' of the whole story in "Clinical Trials and Drug Promotion: Selective Reporting of Study 329." Jureidini et al., *International Journal of Risk & Safety in Medicine* 20, 2008: 73–81 and the January 29, 2007, broadcast by the British investigative TV show "Panorama." Note that paroxetine is sold in Great Britain under the brand name *Seroxat*.

[10] A study is considered *double-blind* when neither the patient nor the investigating physicians know who received the drug and who received the placebo.

[11] My compliments and commendation for that law firm's commitment and dedication to bringing this information to the attention of the general public. Without the actions of such law firms, and the power of the court system in the United States, such conduct would never see the light of day; and what goes on behind closed doors in the drug industry would forever be sealed behind those doors.

[12] See the BBC One "Panorama" TV broadcast of January 29, 2007.

[13] Jureidini et al., *International Journal of Risk & Safety in Medicine* 20, 2008: 75–81.

[14] Keller et al., *Journal of the American Academy of Child and Adolescent Psychiatry* 40 (7) July 2001: 762–72.