

Over Dose: The Case Against the Drug Companies

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Part 1 of 2

Chapter 1: The Race To the Bottom

[Over Dose: The Case Against the Drug Companies: Prescription Drugs, Side Effects, and Your Health](#)

I was in my recliner, headset on, writing this book when the telephone rang.

"Dr. Cohen, my name is Alex. I'm sorry to bother you, but I need to speak to you about problems I'm having with my medication."

I don't get many calls. After twenty years in practice, I've been disabled for ten. I have no office or funding for my research, so I work at home. My telephone number is unlisted. Alex, a young man from the other end of the country, had obviously gone to considerable trouble to find me.

"I'm taking Prozac for panic attacks and depression," Alex told me. "I was nearly housebound by agoraphobia once. I was okay for three years, but things got stressful at work and the problems returned."

"Prozac is a reasonable choice for your disorder," I said. "What's the problem?"

"I've gotten much worse since starting the drug. I get terribly agitated now, and my heart pounds and I can't sleep. I get so shaky sometimes, I'm afraid to go out. I'm withdrawing And depressed again. I think the Prozac is making me worse."

"What do your doctors say?"

"They say that the side effects from the Prozac -- the insomnia and palpitations -- show that it is working, and that I should wait it out."

I sighed quietly. This was awful advice, but not unusual. Although I already knew the answer, I asked, "What dose of Prozac are you taking?"

"Twenty milligrams a day."

Twenty mg -- that's what Lilly and Company, Prozac's manufacturer, recommends initially for otherwise healthy people ages eighteen to sixty-five, and that's what physicians prescribe. Unfortunately, neither Alex nor his physicians knew that early research had already shown that doses one half or even one quarter Lilly's recommended amount are all that some patients need (1, 2).

Anything greater commonly causes side effects including agitation, insomnia, rapid heart rate, and consequent depression and social withdrawal. These are signs that Alex was being over-dosed.

Alex isn't alone. In 1998 an extensive study published in the Journal of the American Medical Association (JAMA) showed that 106,000 people die annually in American hospitals from medication side effects (3).

Medication reactions are the fourth leading cause of death in the United States, dwarfing the number of deaths caused by automobile accidents, AIDS, alcohol and illicit drug abuse, infectious diseases, diabetes, and murder. In addition to the medication-related deaths, the JAMA study also tallied 2,216,000 severe medication reactions in U.S. hospitals annually.

Because of the especially rigorous methods the researchers applied, even these numbers may not present the full picture. The authors defined serious side effects narrowly, including only clearcut reactions causing permanent disability, hospitalization, or death. Thus, they excluded side effects that disable people for weeks or months, side effects such as dizziness or sedation that cause automobile accidents or falls and broken limbs, side effects that require emergency interventions, and side effects that prolong hospitalizations or force people to miss work.

And the authors didn't even try to count the largest category of all -- side effects occurring in outpatients. Overall, the authors excluded side effects that occur far more often than the ones they included.

Despite omitting so many side effects, the JAMA study still recorded numbers reaching epidemic proportions. And, as the authors noted, this side-effect epidemic wasn't new: "The incidence has remained stable over the last 30 years (4)."

Because it is sometimes difficult to place such statistics in everyday terms, consider this: 106,000 deaths a year averages out to nearly **300 deaths a day, every day**. In comparison, about 85 people died from accidents linked to faulty Firestone tires. The Firestone deaths occurred over a period of several years -- medication reactions kill 300 people every day. Yet, it was the Firestone deaths that dominated the news for several weeks and drew Congressional hearings.

Deaths from all major airline crashes in the United States average less than 300 annually, but one airplane crash gets more media attention and governmental scrutiny than the 300 medication-related deaths that occurred not only the same day as the airline crash, but also every day before and after for decades.

Why has this epidemic of side effects gone unrecognized? Deaths from medication reactions rarely look any different than natural deaths. There's no visible wreckage to videotape, no crash sites to horrify and fascinate viewers. As media people say, "No film, no story."

Medication deaths often occur quietly in hospitals, emergency rooms, and homes. When medication-related deaths occur, it is often unclear at first whether the cause was the medication, the illness, or other factors. In other words, to much of the media, there's nothing sexy about side effects.

Moreover, the public likes to believe that our hospitals and medications are safe and that our doctors are taking every reasonable precaution.

Facing the failure of a major industry is never comfortable. How many decades did it take recognize the drunk driving problem? To bring the dangers of cigarettes to public awareness? To mandate seatbelts in cars? Maybe with medication side effects it's the same: We'd rather not know.

It might be different if the public received an accurate account of the scope of the side-effect epidemic. Alex' experience, for example, may have been severe enough to drive him to contact an unfamiliar doctor 2,500 miles away, but his case will never be counted in the side-effect statistics.

His doctors didn't recognize Alex' side effects. and even if they had. they probably wouldn't have

reported them to the FDA. "Most physicians feel that detecting adverse reactions is a professional obligation, but relatively few actually report such reactions [to the FDA]," states Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, one of medicine's most respected drug references (5).

Dr. Brian Strom, former chairman of the department of biostatistics and epidemiology at the University of Pennsylvania, told the *New York Times* in 1997: "Most doctors don't know the system [for reporting medication reactions to the FDA] exists (6)." When speaking to medical groups, Dr. Strom showed a slide of an FDA Medwatch form and asked: "How many of you have ever seen that?" Usually, less than a third raise their hands.

Yet, it is from voluntary reports from physicians that side-effect statistics are derived. Physicians, however, often feel that so-called minor side effects -- the ones that make millions of people like Alex feel merely miserable or unable to function normally -- aren't worth reporting.

Reporting more serious reactions may raise questions about treatment or lead to lawsuits. Another highly regarded drug reference, Melmon and Morrelli's *Clinical Pharmacology: Basic Principles in Therapeutics*, commented: "Drug-induced complications can mimic and therefore be attributed to disease-induced problems.

When therapy fails, we [physicians] frequently can attribute the failure to the disease and escape blame. Probably nowhere else in professional life are mistakes so easily hidden, even from ourselves (7)." The result is that only one in twenty side effects is reported to authorities (8, 9).

Drug companies and medical institutions have their own reasons for underestimating the full scope of the side-effect epidemic. Dr. David Bates, an associate professor of medicine at the Harvard Medical School, wrote in *JAMA*:

Hospitals have had strong incentives not to identify too many of these adverse drug events. Reporting large numbers of adverse events and any serious preventable event brings intense scrutiny from regulators and the public. Thus, most hospitals have relied on **spontaneous reporting, which only identifies about 1 in 20 adverse reactions** and leads to the perception that injuries from ADRs are less common than they really are (10).

Even the Food and Drug Administration acknowledges that adverse drug reactions are grossly underreported. In March, 2000, Dickinson's *FDA Review* reported on its interview with Jerry Phillips, associate director of the Office Of Post-Marketing Drug Risk Assessment at the FDA:

"These reports, however, are generally believed by experts to grossly understate the actual situation, Phillips said. In the broader area of adverse drug reaction data, the **250,000 reports received annually probably represent only 5% of the actual reactions that occur** (11)."

A simple extrapolation from these numbers reveals a total **of five million medication reactions each year** -- and this is still probably an underestimate.

However, one by one, the public is learning about the perniciousness of the side-effect epidemic. Knowledgeable people have told me that their elderly parents died not from their illnesses, but from being prescribed too many too powerful medications. Dozens of websites now exist where patients can discuss medication reactions that have caused major reactions or disabilities that their physicians

have ignored.

Many physicians dismiss anecdotal reports or cases posted on the Internet, but scientific discovery often begins with individual reports of an unrecognized or poorly understood problem. These reports, especially when hundreds of in-depth, medically credible descriptions are listed, should be taken seriously, because they represent another unrecognized aspect of the side-effect epidemic.

It might be different if the side-effect epidemic was caused by a few bad drugs. Every industry produces some lemons. Thus, the FDA has had to remove ten prescription drugs (plus a vaccine and an anesthetic) within the last four years. But, as this book will document, the problem extends well beyond these few. Instead, it involves hundreds of drugs including top-sellers like Viagra, Premarin, Prozac, Lipitor, Celebrex, and Motrin.

Because the problem is so large and so many drugs are involved, blame is difficult to assess. In addition, these same drugs help millions of people, which further obscures the many problems they cause, why they cause them, and how easily many of these side effects, like Alex', could be avoided.

Consider, for example, one class of medications: women's hormones. When I was a medical intern in 1971, I treated a young woman with a blood clot in her lower leg (thrombophlebitis). She required hospitalization and bed rest for nearly two weeks. She was lucky: Hundreds of women like her died each year when such clots broke free and coursed to their lungs.

These clots were caused by birth control pills -- pills that in the 1960s and 1970s contained **three to eight times more estrogen and progesterone than actually needed** (12, 12A). That's 300 to 800 percent more of these powerful hormones than today's pills -- doses that exposed millions of women to greatly increased risks of blood clots, strokes, and death.

The death rate from thromboembolism alone was **600 percent higher with the original high-dose pills**. I don't know where my patient is today, but she probably is now worrying about the increased risks of breast cancer that have been reported with these high-dose pills (13-16). How many women have been harmed by these excessive doses that were prescribed in the United States for twenty-eight years? Some data exist, but the full extent of the damage has never been defined.

Perhaps my patient, after entering menopause, received hormone therapy for hot flashes. If she was prescribed Premarin for hot flashes at the dosage recommended by its manufacturer, Wyeth-Ayerst, she might have received double or even quadruple the amount she actually needed. Wyeth-Ayerst recommended 1.25 mg of Premarin as its initial dose for hot flashes from 1964 through 1999, long after medical experts had shown that 0.625 mg and even as little as 0.3 mg were sufficient for many women (17-19).

Premarin is perhaps the most prescribed drug ever; in 1999 alone, women purchased more than 47 million prescriptions in the United States. Yet even in 2000, after Wyeth-Ayerst finally reduced its recommended starting dose for hot flashes to 0.625 mg, this amount remains excessive for some women (20-22). Similarly, the recommended doses of Premarin for preventing osteoporosis have been unnecessarily high for many women (23, 24).

Meanwhile, **estrogens like Premarin have been linked to increased rates of breast cancer** (25, 26) -- and it is likely that the higher the dose of estrogen, the greater the risk. Has my patient been affected? How many thousands of women have been harmed over the years? We'll

never know, and the side-effect statistics will never reflect them.

Why weren't lower, safer, effective doses of these hormones, as used today, developed decades earlier? The technology existed in the 1960s to determine the lowest, safest doses of these potent drugs. But the intense, fast-paced competition of the medication marketplace frequently spurs drug companies to conduct small, brief, insufficiently extensive studies on the dosages of new drugs (27) -- dosages that will be taken by millions of people.

The result is that only belatedly, years or even decades later, do we discover that lower doses are not only effective, but avoid many side effects. Of course, by this time, tremendous damage has been done to people and their families.

The story is the same with many drugs -- not just obscure drugs, but many top-selling drugs. The problem encompasses the entire field of medication therapy, as recognized experts have attested:

Carl Peck, M.D., former director of the FDA's Center for Drug Evaluation and Research: "There are noteworthy examples in drug development of failing to get the dose right when a drug is first marketed (28)."

Dr. Raymond Woosley, the chairman of the department of pharmacology at Georgetown: "The US society has invested in developing wondrous new pharmacologic therapies but has failed to invest adequately in their safe use (29)."

Dr. Norman Sussman, editor of Primary Psychiatry: "There are lots of problems with the current system of drug testing. Often it fails to detect efficacy and, more often than would be desired, misses significant side effects (30)."

Dr. Marcia Angell, former editor-in-chief of the New England Journal of Medicine: "To rely on the drug companies for unbiased evaluations of their products makes about as much sense as relying on beer companies to teach us about alcoholism (31)."

The result of these shortcomings? Dr. Thomas J. Moore of Georgetown University, Dr. Bruce Psaty of the University of Washington, and Dr. Curt Furberg of Wake Forest University determined that "51% of approved drugs have serious adverse effects not detected prior to approval (32)."

Think about this -- more than half of our drugs, after being deemed "safe" by the FDA and then prescribed to millions of people, are subsequently detected to have previously unrecognized, medically serious side effects. No wonder we have a side-effect epidemic.

When the majority of our drugs are approved with serious risks, the threat isn't small. **Forty-six percent of Americans take at least one prescription drug daily** (33). That's more than 128 million people. Most of these people are taking medications long-term, so their exposures aren't brief. Twenty-five percent of Americans take multiple prescription drugs every day.

In 1999, Americans purchased 2,587,575,000 prescriptions -- that's nine prescription drugs (as well as several over-the-counter drugs) for every person in America.

Americans paid **\$125 billion for these prescriptions -- \$50 per prescription on average.** One would think that with so much cost and utilization, medications would be our most carefully manufactured and safest products. Yet, as Dr. Bates wrote: "Only after drugs leave the trial setting

and are used in sicker patients do their true risks become apparent (34)."

It doesn't have to be this way. As Dr. Bates also wrote, "Although some risks are inevitable, they can be significantly reduced (35)." I agree -- side effects can be significantly reduced, but they aren't. The inadequate methods by which drugs are developed and prescribed are why.

Weary of seeing avoidable side effects affect patient after patient, I began investigating the origins of this problem. With a background in general medicine, pain research, general pharmacology and psychopharmacology, and experience as a staff member at UCLA, UCSD (the University of California, San Diego), and at the world's largest naval medical center at Balboa Hospital in San Diego, I began voicing my concerns publicly in 1988.

First I wrote letters to medical journals and authored health columns in a local newspaper. Beginning in 1996, I began publishing lengthy articles describing my findings in respected medical journals such as the Archives of Internal Medicine (36-38), Postgraduate Medicine (39), Geriatrics (40), The Annals of Pharmacotherapy (41, 42), and Drug Safety (43).

After more than a decade of research conducted without any influences, I found that the drug companies dominate the entire process of medication therapy -- from early research to ultimate usage -- as few other industries control their products today. Drug company research and development often serves marketing strategies more than sound science or patients' safety.

The many ways that drug companies accomplish this is discussed in depth in Chapter 9, but here is a glimpse -- derived from numerous medical journal articles including JAMA (44), the New England Journal of Medicine (45), and Lancet (46) -- of the methods that drug companies use in accomplishing their goals:

Drug companies can choose research study designs that are more likely to produce favorable results rather than designs that might provide more accurate results.

Drug companies can conduct multiple studies on new drugs, and then select and publish the most favorable ones while suppressing the rest.

Drug company studies can measure a drug's effectiveness in multiple ways, then select and publish only the best results. Sometimes these favorable results have little to do with whether the drugs will help patients.

Drug companies hire professional writers to prepare articles according to company guidelines, using favorable phrases and terms selected by the companies.

Drug companies hire high-profile experts to place their names on drug company-generated articles, although the experts have not participated in the studies and their financial connections with the drug companies are not disclosed.

These excesses might be unimportant if drug company research represented a small portion of all medication research. However, the drug companies underwrite 70 percent of all medication research today (47). This gives the pharmaceutical industry tremendous power over the entire medication research effort, including the threat of lawsuits or loss of future funding for physicians wanting to publish unfavorable findings (48).

More and more, drug companies are requiring researchers to sign confidential agreements before

receiving any funding, giving the companies the power to suppress findings they don't like.

The pharmaceutical industry's ability to amass wealth while hospitals and medical centers struggle financially has allowed the drug companies to intrude into the arena of independent academic medicine (49). This intrusion is so great that in 2000, Dr. Angell issued an astonishing article -- "Is Academic Medicine for Sale?" -- in the New England Journal of Medicine:

Academic medical institutions are themselves growing increasingly beholden to industry.... Some academic institutions have entered into partnerships with drug companies to set up research centers and teaching programs in which students and faculty members essentially carry out industry research....

When the boundaries between industry and academic medicine become as blurred as they now are, the business goals of industry influence the mission of the medical schools in multiple ways.... The influences of the marketplace should not become woven into the fabric of academic medicine. We need to remember that for-profit businesses are pledged to increase the value of their investors' stock. That is a very different goal from the mission of medical schools (50).

Despite the concerns of Dr. Angell and other experts, drastic reductions in insurance and Medicare payments have placed great pressure on medical institutions and research physicians to accept the money -- and terms -- of the drug companies.

At the same time, the drug companies spend billions targeting office physicians, as well as new interns and residents, with gifts, free meals, travel subsidies, and subsidized symposia presenting the drug companies' spin on their medications (51, 52).

Beyond these direct influences, drug companies exert broad influence over the drug information received by doctors and consumers. The vast majority of everything physicians and consumers read and know about medications comes from the drug companies. Medication package inserts, drug advertising toward physicians and consumers, and the information in the ubiquitous Physicians' Desk Reference (PDR) (53) come directly from the drug companies.

Where do most doctors turn for medication and dosage information? To the PDR, to drug company representatives who make the rounds of doctors' offices, and to advertising in medical journals. Yet, the medication information offered by these drug company-supported sources is often biased, incomplete, and sometimes inaccurate.