THE PROZAC BACKLASH ■ SPITZER'S NEXT CRUSADE

Fidelity Sets a New Course

FORTUNE

GET A LIFE!

The 24/7 grind hurts—but corporations are helping executives escape it.

HERE'S HOW.

DISPLAY UNTIL DECEMBER 5, 2005

$4.99US $5.99CAN

48

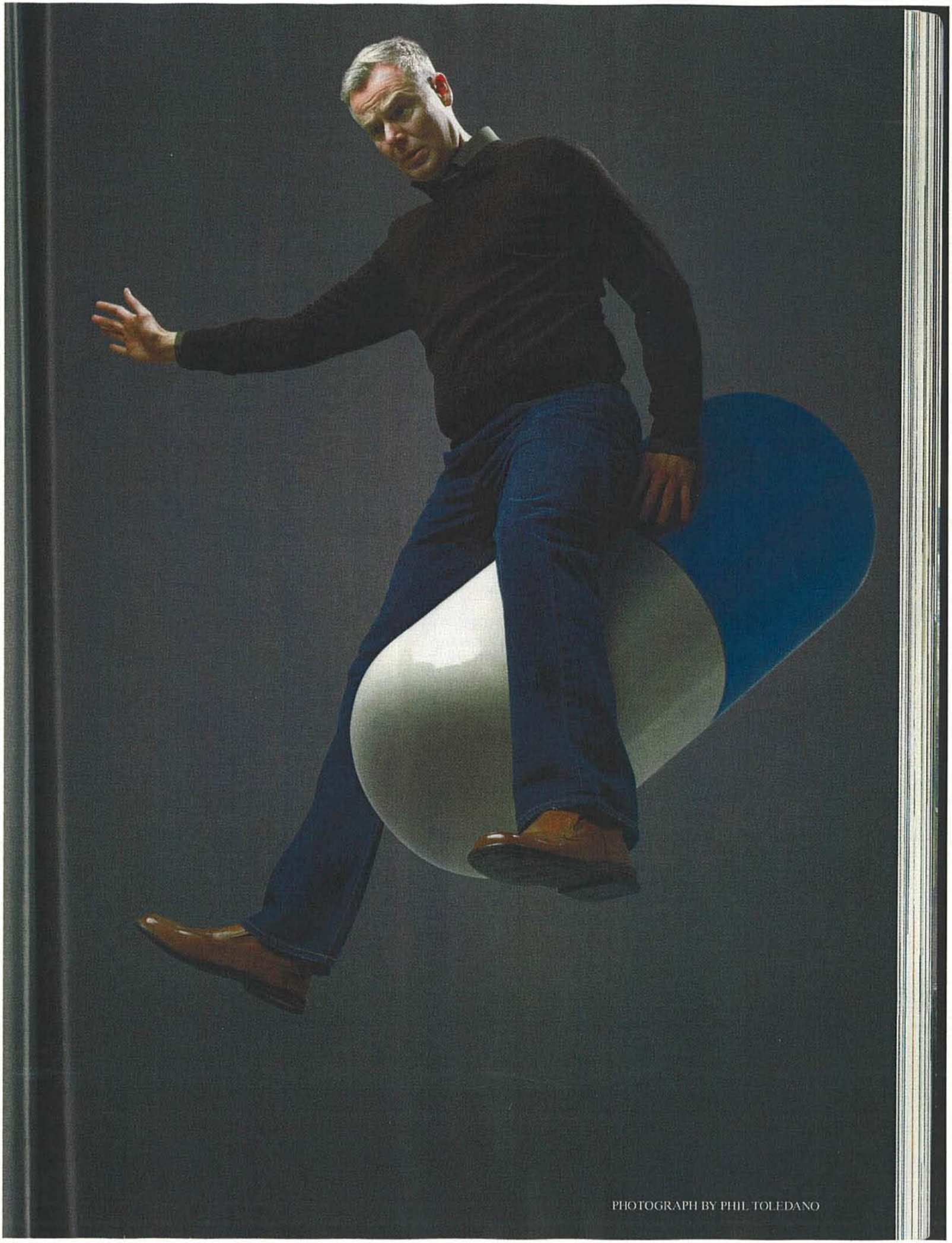
0 70989 10093 0

www.fortune.com (AOL Keyword: Fortune)

TROUBLE IN PROZAC NATION

Wonder drugs of the 1990s, Prozac and its kin have been prescribed to tens of millions of people. But a growing backlash may portend the end of an era. BY DAVID STIPP

Can Prozac make you want to die? The idea seems strange, given that the drug and similar antidepressants are supposed to do just the opposite. Yet that is what Kimberly Witczak believes happened to her husband. Two years ago Tim "Woody" Witczak killed himself at age 37, soon after going on Pfizer's Zoloft—the top-selling member of Prozac's class of drugs, known as selective serotonin reuptake inhibitors, or SSRIs. Her husband was an upbeat, happy man, says Kim Witczak. Shortly before his death he had been named vice president of sales at a startup that sold energy-efficient lighting. When anxiety about the new job caused insomnia, he



PHOTOGRAPH BY PHIL TOLEDANO

was prescribed Zoloft. He began suffering from nightmares, profound agitation, and eerie sensory experiences after a couple of weeks on the medicine—at one point, she says, he said he felt as if his head were detached from his body. Then he seemed to calm down. But about five weeks after his first dose, he hanged himself from the rafters in their garage when Kim was out of town. He left no suicide note.

"Woody's death was the most out-of-the-blue, out-of-character death," she told FORTUNE recently. "He had no history of mental illness." Kim Witczak, who lives in Minneapolis, has sued Pfizer, alleging that Zoloft induced the suicide and that the company failed to warn about the drug's potential to cause perilous side effects. Pfizer declined to comment while the case is in litigation, but a spokesman asserted that there is "no scientifically based" evidence to suggest Zoloft can induce violent acts. It's not the first time SSRI makers have faced complaints related to suicide or other forms of violence. They have fended off or quietly settled scores of such suits over the years without significant injury to their drugs' reputations.

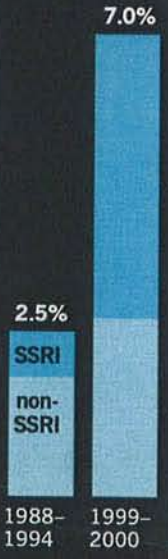
But the Witczak case, which may play out in court next spring, is likely to put SSRIs on trial as never before. For one thing, Kim Witczak has emerged as a formidable crusader. Poised and articulate, she has appeared at congressional and Food and Drug Administration hearings (most recently this month) to tell of her tragedy and the dangers of SSRIs. What's more, her suit is likely to spotlight disturbing information that drug companies and U.S. regulators have been aware of for years—but that most doctors prescribing the drugs have known little or nothing about.

Controversy about SSRIs' side effects flared into national prominence last year when they and older antidepressants were shown to double the risk of suicidal thoughts and behavior in children and adolescents. That discovery prompted the FDA to slap a stern "black box" warning on the drugs' package inserts. (Among other things, it cautions doctors to monitor young patients closely in their first months on SSRIs.)

A black-box warning about suicidal thoughts and behavior in adults may very well be next, say a number of experts interviewed by FORTUNE. "I'm fully expecting that the same [risk found in young patients] will be found in adults," says Dr. Richard Kapit, an ex-FDA official who handled the agency's first safety review of Prozac before its approval in 1987. (He now works as a medical writer and consultant in Bethesda, Md.) In fact, last summer the FDA warned that several recent studies suggest that SSRIs and other antidepressants raise the risk of suicidal behavior in adults as well as kids. The agency added that it is reviewing "all available data" on the issue in an investigation expected to take a year or more.

DOSE ME UP

In the 1990s, Americans reached for antidepressants in a big way, especially SSRIs.



Percent of U.S. adults using antidepressants

FORTUNE CHART / SOURCE: CDC

Risk of suicide isn't the only problem dogging SSRIs. For example, GlaxoSmithKline faces thousands of lawsuits on another side effect, severe withdrawal reactions to its drug Paxil, one of the fastest-acting SSRIs. Last year British policymakers moved to discourage the use of SSRIs to treat mild depression. And a recent scientific analysis has challenged long-held assumptions about how the drugs work. That could undercut drugmakers' assertions that SSRIs are well understood, potentially increasing doubts about their safety.

A black-box warning for adults could have huge repercussions, vaporizing billions of dollars of future sales, increasing pressure on policymakers to curtail direct-to-consumer drug ads, and prompting a slew of lawsuits. It could also complicate drugmakers' efforts to roll out new antidepressants to replace current ones as the drugs go off patent. The ultimate fallout could well equal or exceed that from Vioxx, the Merck painkiller whose saga of potentially lethal risks, dodgy marketing, and damaging courtroom disclosures has given Big Pharma the look of an ethical disaster zone. If so, it would add a sad twist to a tale in which so many people have been helped.

Birth of a Blockbuster

Prozac and its kin have been one of 20th-century medicine's great success stories. Since the debut of Eli Lilly's Prozac in 1988, the drugs have grown into an $11-billion-a-year market in the U.S. alone. Nearly 150 million U.S. prescriptions were dispensed in 2004 for SSRIs and similar antidepressants called SNRIs, according to IMS Health, a Fairfield, Conn., drug data and consulting company—more than for any other drug except codeine. Perhaps one out of 20 adult Americans are on them now, making brands like Zoloft, GlaxoSmithKline's Paxil, Forest Laboratories' Celexa, and Solvay Pharmaceuticals' Luvox household names. Though they don't work for everybody—many people have gone off the medicines because of side effects such as dampening of sexual response—they've done more than any other class of drugs to spur psychiatry's substitution of pills for couches.

In fact, we're popping so many SSRIs that their breakdown products in urine, gushing into waterways, have accumulated in fish tissues, raising concerns that aquatic animals may be getting toxic doses, according to recent research at Baylor University.

The SSRI phenomenon began almost the minute Prozac appeared. Doctors embraced the drugs because of a virtue that seems increasingly ironic: It's hard to commit suicide by overdosing on SSRIs, so they are deemed safer to give to severely depressed patients than are older, more acutely toxic antidepressants such as the so-called tricyclics. Indeed, the drugs once seemed so benign that some psychiatrists

KIM WITCZAK'S HUSBAND hanged himself soon after starting to take Pfizer's Zoloft for job stress. She alleges the drug caused his death.

marveled about how they appear to violate the law of "conservation of mood"—a seemingly universal pattern in which drug-induced emotional lifts are always followed by crashes, resulting in no net gain. Such talk made Prozac seem safer than coffee. That paved the way for massive prescribing by general practitioners with no special training in complex mental disorders—in recent years some 70% of SSRI prescriptions have been written by primary-care doctors.

Within three years of Prozac's launch, annual sales neared $800 million. *Newsweek* put the pill on its cover—a green-and-white capsule floating against a blue sky under a headline that hailed it as a breakthrough drug. Even healthy people were asking for Prozac, the magazine noted. By 1993 the idea caught on that SSRIs could transform lives—curing not only depression but also shyness, low self-esteem, and compulsiveness. Major boosts for the fad came from *Listening to Prozac,* psychiatrist Peter Kramer's eloquent bestseller, and from celebrity endorsements. Recounting his fight with depression, Mike Wallace of CBS's *60 Minutes* told *Newsweek* he expected to take Zoloft for the rest of his life.

But for all the glow about SSRIs, the drugs have been among the most controversial in the history of medicine. Bitter disputes about side effects have seethed for more than a decade, usually out of sight of the mainstream media—in supermarket tabloids, on websites, and in professional gatherings of scientists, regulators, and shrinks.

"Woody's was the most out-of-the-blue, out-of-character death. He had no history of mental illness."

Rare, dangerous side effects of potent medicines like antidepressants often emerge only after the drugs have been prescribed to millions of people for years. But in the case of SSRIs, that is not the whole story. There are signs that manufacturers have downplayed known risks of the lucrative drugs and that regulators and doctors haven't been skeptical enough about them.

Even the theoretical basis for prescribing SSRIs is now in doubt. The drugs have long been said to work by boosting a brain chemical called serotonin, correcting a neural imbalance underlying depression and other ills. That makes them seem the epitome of modern medicine—what could be safer than restoring a natural balance? A growing body of studies casts doubt on the theory, however, according to a provocative report this month in *PLoS Medicine,* an influential peer-reviewed journal published by the nonprofit Public Library of Science. The report points out that scientists have never really understood the drugs' effects in the brain. Yet pharmaceutical ads still cite the serotonin theory as a major reason for prescribing SSRIs—a case of mythmaking "comparable to the masturbatory the-

PHOTOGRAPH BY LISE SARFATI—MAGNUM

ory of insanity," says British psychiatrist David Healy, a longtime SSRI critic. Drug company spokesmen counter that considerable scientific literature supports the serotonin-imbalance idea.

A number of scientists have theorized that while boosting serotonin, SSRIs indirectly inhibit another key neurochemical messenger called dopamine. That means the drugs may actually create a perilous brain imbalance in some people. What's more, there's some evidence that dopamine inhibition underlies several of the rare, serious side effects linked to SSRIs. One is akathisia, a kind of extreme restlessness that has been implicated in suicidal impulses—Witczak believes Zoloft induced akathisia in her husband.

The possibility that SSRIs may occasionally induce deranged mental states conducive to homicide has cropped up again and again in the news. While evidence supporting that idea is scanty compared with data on the risk of suicidal ideas and behavior, it isn't easily dismissed out of hand. Consider some of the testimony at the trial this year of teenager Christopher Pittman, charged with murdering his grandparents. Richard Kapit, the ex–FDA official, testified for the defense—he says he felt compelled to come forward after reading about the case in the news. Kapit told the jury that the teen was "involuntarily intoxicated" by SSRIs when he shot his grandparents. Kapit added that he believes that Pittman, who was being tried as an adult and who was ultimately found guilty, "didn't have the ability to form criminal intent" when he committed the murders at age 12.

"I learned, 'Yeah, something is a little wrong with me, but with medication I can be okay.' "

Many psychiatrists feel that stories about SSRIs' side effects should themselves carry bold cautions against media hype. The risk noted in the FDA black-box warning last year is limited: Suicidal thoughts and behaviors occurred in about 4% of youngsters on antidepressants (mostly SSRIs) in clinical trials, vs. 2% of those taking dummy pills. That doesn't necessarily mean actual suicides occur more often among SSRI takers—there's too little data to answer that question. And the risk must be balanced against the fact that SSRIs help many people—no one disputes that depression is a huge problem, and even some of SSRIs' harshest critics concede the drugs can play a valuable role in treating it when prescribed judiciously.

The uproar, in fact, may be hurting some patients without access to psychotherapy, the main alternative to drugs. Since family doctors are now often afraid to prescribe SSRIs to kids, more depressed young people than ever are probably going untreated, says Gregory Simon, a psychiatrist and health-care policy researcher at Group Health Cooperative, a Seattle HMO. Prescriptions of antidepressants for patients 18 and under have plunged by 20% since the suicide issue hit headlines in early 2004, according to NDCHealth, an Atlanta health-care information provider. (Less than 5% of antidepressant prescriptions are written for youngsters.) Says Jerrold Rosenbaum, psychiatrist-in-chief at Boston's Massachusetts General Hospital: "Most of us [in psychiatry] think the number of patients harmed by failure to treat [due to fear of SSRIs] is much higher than the number who are harmed by treatment."

THE 30-YEAR ITCH

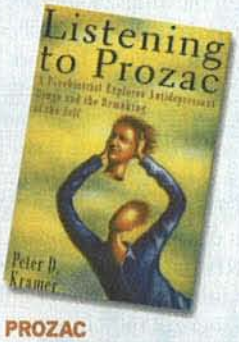
Over more than a century, in roughly 30-year cycles, psychiatry has embraced one popular class of drugs after another to treat mental illness. At first, they have seemed to be miracle workers—but they have usually turned out to be risky. ***— Jia Lynn Yang***

COCAINE
In 1884, a young Freud writes "Über Coca," an ode to "this magical substance" that, he says, can be used to treat depression and even morphine addiction.

AMPHETAMINES
Starting in 1937, amphetamines are available over the counter to treat nasal congestion. During World War II, soldiers take speed to stay alert and improve their moods.

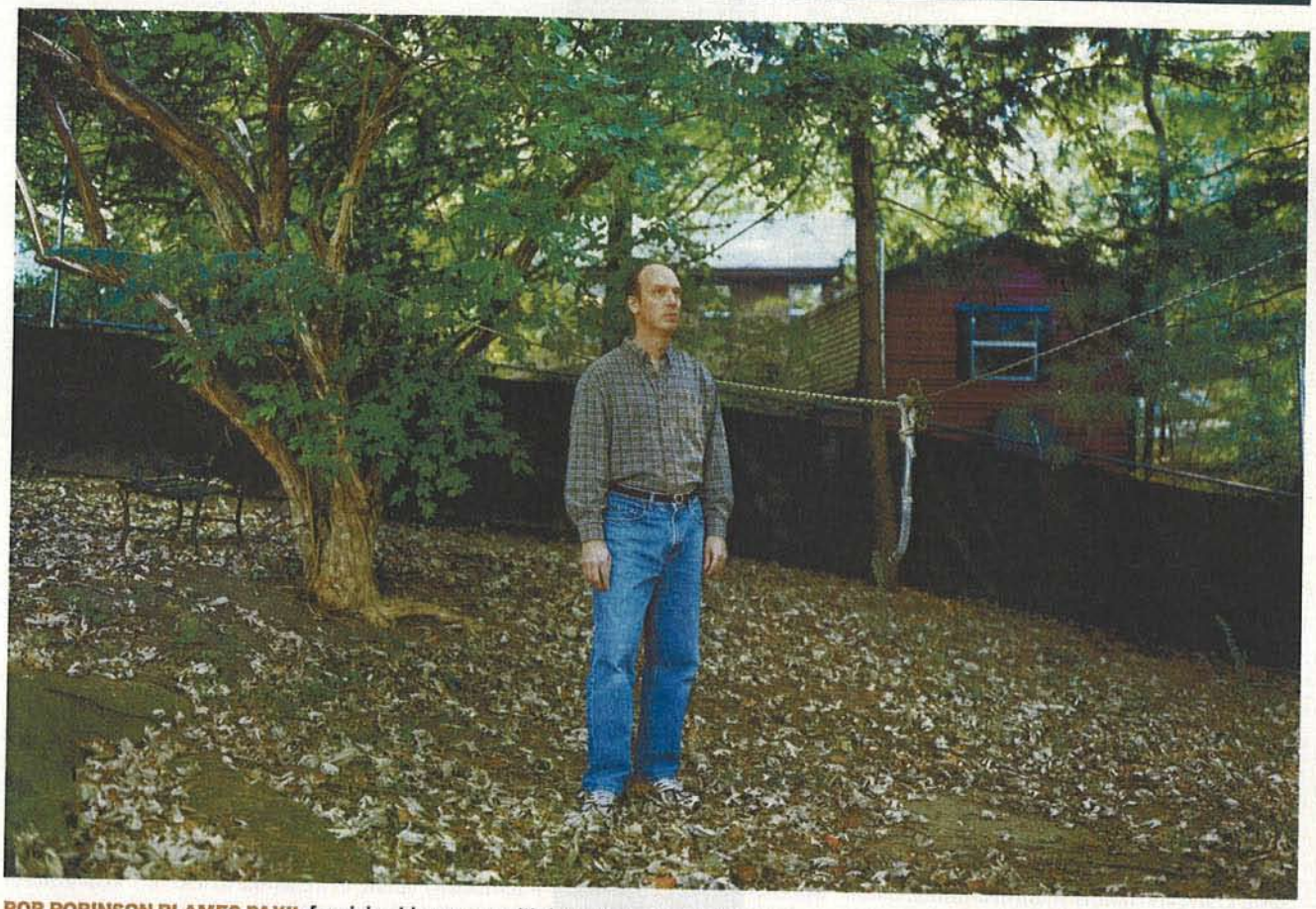
BARBITURATES
In their 1950s and '60s heyday, about 50 types of barbiturates are marketed for medical use. In 1962, Marilyn Monroe dies from an overdose.

VALIUM
In 1978, users pop 2.3 billion Valiums. The drug's ubiquity is immortalized in Jacqueline Susann's novel *Valley of the Dolls*, later made into a movie starring Patty Duke.



PROZAC
The FDA approves Prozac for use in 1987, and within three years annual sales near $800 million. In 1993 psychiatrist Peter Kramer's *Listening to Prozac* is a nonfiction bestseller.

FROM LEFT: MANSELL—TIME LIFE PICTURES/GETTY; GEORGE SILK—TIME LIFE PICTURES/GETTY; ALFRED EISENSTAEDT—TIME LIFE PICTURES/GETTY; GLOBE PHOTOS



ROB ROBINSON BLAMES PAXIL for giving him severe withdrawal symptoms. Now he's organizing protests against the drug's maker, Glaxo.

Of course, many top U.S. psychiatrists, including Dr. Rosenbaum, have worked with drug companies to establish SSRIs as medicines of choice for treating depression. Their views aren't universal in medicine—European authorities have long been more skeptical about the drugs. Soon after the FDA approved Prozac for marketing in December 1987, German regulators rejected it, partly because of concerns that the drug increased the risk of suicide; they later approved it but required Lilly to include a warning in the drug's package insert about the possible need to prescribe sedatives to counter the risk. Last December, Britain's National Institute for Clinical Excellence, which guides that country's health-care policy, recommended that SSRIs and other antidepressants not be prescribed "for the initial treatment of mild depression, because the risk-benefit ratio is poor."

And in April the British House of Commons Health Committee issued a caustic report that may give a preview of things to come in Congress. SSRIs have been "indiscriminately prescribed on a grand scale," the committee concluded, partly due to "data secrecy and uncritical acceptance of drug company views." Further, industry promotions have "worked to persuade too many professionals that they can prescribe [the drugs] with impunity" to treat "unhappiness [that] is part of the spectrum of human experience, not a medical condition." Though Congress isn't likely to buy into the stiff-upper-lip rationale, it may put some very awkward questions about SSRIs to their makers and the FDA in coming months. (Texas Republican Joe Barton and other Congressmen grilled FDA officials for hours just before the agency put the black-box warning on SSRIs for kids.)

"I started having withdrawal symptoms. I finally opened a door on the other side of hell after about 18 months."

"Ownable syndromes"

Drug marketers have been extraordinarily adept at selling SSRIs—even to people who may not need them. Consider that the drugs, once limited to treating major depression, are now prescribed for everything from shyness about peeing in public restrooms to shopoholism. (Such uses aren't approved by the FDA, but there's no law against doctors prescribing SSRIs and other drugs for "off label" indications.)

The explosive growth of the drugs' market is largely a story of clever branding as makers of "me too" SSRIs sought to replicate Prozac's success. Pfizer, for example, positioned Zoloft, launched in 1992, as a versatile antidepressant that could also treat ills such as post-traumatic stress disorder. Glaxo targeted Paxil, launched in 1993, at anxiety disorders such as SAD

PHOTOGRAPH BY LISE SARFATI—MAGNUM

(social anxiety disorder, or excessive shyness) and GAD (generalized anxiety disorder, or unremitting angst)—ills that had received little attention before Glaxo began promoting Paxil to treat them. Lilly countered by expanding Prozac's indications to include PMDD (premenstrual dysphoric disorder, or very bad moods some women suffer before their periods) and depression in children.

Indeed, to marketers, SSRIs have been the pharmaceutical equivalent of Play-Doh. In a remarkably forthright 2003 article, Vince Parry, now a branding expert at Ventiv Health, a Somerset, N.J., healthcare marketing firm, waxed euphoric about psychiatry's "ownable syndromes." Published in a trade journal, the article laid out strategies "for fostering the creation of a [medical] condition and aligning it with a product" like an SSRI. Wrote Parry: "No therapeutic category is more accepting of condition branding than the field of anxiety and depression, where illness is rarely based on measurable physical symptoms." He cites Lilly's positioning of Prozac to treat premenstrual woe as an excellent example of condition branding—the company reinvigorated its aging antidepressant by repackaging it in a lavender pill, dubbed Sarafem, for women with PMDD.

But blaming marketers alone for the SSRI fad isn't fair. Doctors, insurers, regulators—and we eager pill-poppers—are co-conspirators. Cupertino, Calif., resident Ada Spade, for instance, takes an SSRI for a condition that even few psychiatrists know about: compulsive shopping. The problem started about 15 years ago when she was in her 30s, she says. "I'd go to the grocery store and find myself stopping at eight stores on the way to buy something in every one of them. I just could not stop." She tried therapy, budgeting, cash-only purchasing—nothing had lasting effect. Her life changed a few years ago when she took part in a study at Stanford University Medical Center.

"The real scandal [about SSRIs] has been the failure to disclose data."

Funded by Forest Laboratories, it showed that 17 of 24 "compulsive shoppers" given Celexa, an SSRI made by Forest, were greatly improved—they could even visit malls without buying anything. "I learned from the study," she says, "that, yeah, something is a little wrong with me, but with medication I can be okay."

For harried doctors faced with lots of patients complaining of depression, anxiety, or compulsions, drugs billed as versatile and safe can seem a godsend. Prescribing SSRIs "has almost become a way that physicians are regulating demands on their time," says University of Pennsylvania psychology professor James Coyne. "What happens a lot in primary care, though, is that people on the drugs don't get adequate follow-up. About half the time they need an adjustment in dose, which they often don't get," increasing the chance of side effects.

That effectively means a double whammy of risk: It raises the odds that rare patients vulnerable to dangerous reactions will get the drugs as well as the chance that they will spin out of control unmonitored by doctors. Even when patients are monitored, emerging suicidal tendencies are often missed, says Jerome Vaccaro, CEO of PacifiCare Behavioral Health, a mental-health-benefits manager in Santa Ana, Calif. "It's a 'don't ask, don't tell' problem," he says. "Doctors don't ask about it, and patients don't spontaneously volunteer they're feeling suicidal." To SSRI critics, these nitty-gritty considerations should have prompted sterner warnings years ago. Asserts psychiatrist Joseph Glenmullen: "The problem is that when you give these drugs to a large population, you can get lethal side effects."

Mother's Little Helpers

If one had to identify when the sea change on SSRIs started, April 2000 would be a top candidate. That's

ADAPTABLE BLOCKBUSTERS

Introduced to treat depression, Prozac and its current top-selling cousins shown here are now marketed for a broad array of mental ills Freud never heard of. In 2004 the drugs represented the third-largest-selling class of medicines after cholesterol and ulcer drugs.

DRUG	COMPANY	U.S. SALES 2004 ($millions)	SELECTED INDICATIONS
Zoloft	Pfizer	$3,094	Depression, post-traumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD)
Effexor XR	Wyeth	$2,590	Depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD)
Lexapro	Forest Labs	$1,715	Depression and GAD
Celexa	Forest Labs	$977	Depression
Paxil	GlaxoSmithKline	$870	Depression, PTSD, GAD, SAD, panic disorder, obsessive-compulsive disorder (OCD)

when Glenmullen, a clinical instructor at Harvard who also works for its student health service, published a book called *Prozac Backlash*. Playing up SSRI side effects via scary patient vignettes, the book has become to the drugs' bashers what *Listening to Prozac* was to their fans. Glenmullen sipped tea recently at a Cambridge, Mass., coffee shop while laying out provocative historical parallels for the rise and possible fall of SSRIs.

Drug fads in psychiatry, he says, have appeared "like clockwork" in 30-year cycles. The first was cocaine elixirs, which doctors in the late 1800s prescribed for everything from depression to shyness. Freud bolstered the fad by commending cocaine in influential papers. But by the 1920s, cocaine's dangers had become clear, and amphetamines replaced it as psychiatric cure-alls. In the late 1930s uppers like Benzedrine were even sold over the counter to treat nasal congestion. After the dangers of amphetamines rose to the fore, the pattern was repeated with barbiturates and later with habit-forming tranquilizers such as Valium. (Remember "mother's little helpers," from the Rolling Stones song in the 1960s?)

Each fad followed the same trajectory. The medicines were first hailed as wonder drugs for major mental illnesses. Then general practitioners began prescribing them not just for major problems but for all sorts of relatively minor maladies. Next, scattered reports of serious side effects appeared. After 20 years or so of use, sellers of the medicines could no longer plausibly deny the problems, leading finally to sharply curtailed prescribing. Given that SSRIs' popularity took off in 1990, Glenmullen predicts that "we're still five to ten years away" from full disenchantment with them.

Very few doctors agree with his view that SSRIs are as problematic as, say, amphetamines. But a number of his positions—such as the charge that drug companies have selectively used clinical trial data on SSRIs to paint an overly rosy picture of them—no longer seem radical. Says Group Health's Dr. Simon: "The real scandal [about SSRIs] has been the failure to disclose data." Take the revelations that led the FDA to impose the black-box warning about prescribing SSRIs for kids. The story began in 2003 when FDA officials noticed a curious thing while examining the results of a trial with youngsters on Glaxo's Paxil: The company reported that substantially more kids had shown "emotional lability" on the drug than on a placebo.

Emotional lability? When the officials asked what the term meant, Glaxo submitted details showing that "almost all of these events related to suicidality," according to an FDA internal e-mail on the matter in June 2003. (Suicidality is shrink-speak for suicidal ideas or actions; the e-mail was eventually made public at a congressional hearing but got scant media attention.) The implication of higher suicidality on Paxil "has us worried," the FDA's Dr. Russell Katz noted in the message, which he sent to colleague

"The number of patients harmed by failure to treat is much higher than the number who are harmed by treatment."

Dr. Andrew Mosholder, an expert on drug safety. Glaxo, he noted acidly, "has not proposed labeling changes [on Paxil to reflect the discovery], and makes a feeble attempt to dismiss the finding." Agency officials launched a massive reexamination of trial data on antidepressants in children.

That inquiry turned up worrisome data on suicide-related risk—information that caused internal dissension at the FDA. Just before an FDA advisory panel hearing on the issue, the *San Francisco Chronicle* reported that senior agency officials had forbidden Mosholder to go public with his findings on the risk. The agency's top brass feared that the data, which were still tentative, might discourage doctors from giving antidepressants to kids who needed them. But the focus of criticism soon shifted back to Glaxo. In June 2004, New York Attorney General Eliot Spitzer sued the company, alleging that it had fraudulently withheld unfavorable data on youngsters treated with Paxil. (Glaxo, which asserts that the lawsuit was "unfounded," settled by agreeing to post its clinical results on the web.) Last October the FDA finally confirmed that the suicide-related risk is real for a wide array of antidepressants and required the stern warning on their labels.

Clean Bill of Health?

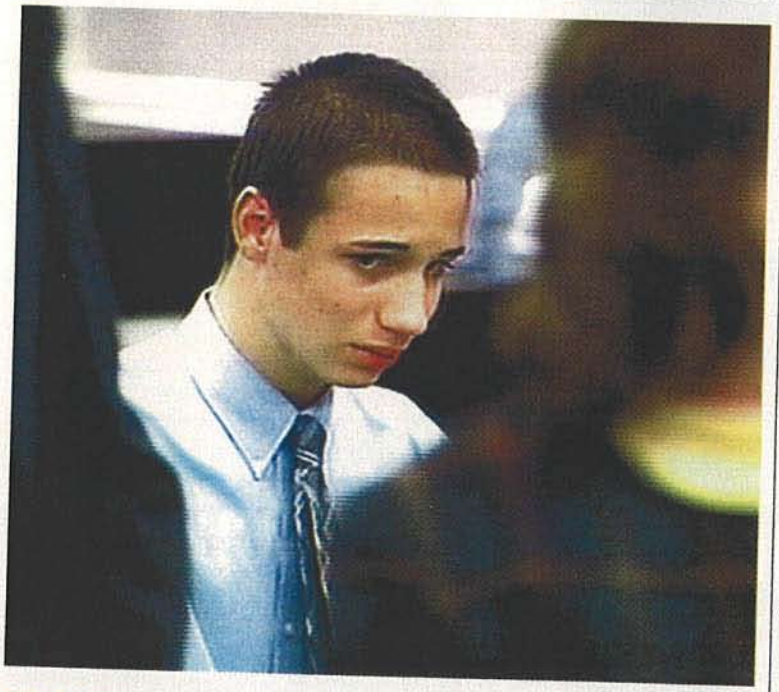
For years, FDA officials had reason to be perplexed. SSRI makers have long maintained there's no reliable scientific evidence that SSRIs cause suicidal or aggressive behavior. Other key factors, like mind-boggling medical complexity, helped obscure the issue. For instance, depression itself can increase suicidal thoughts and behaviors, which makes it extremely difficult to tell whether a drug is to blame. Further, doctors have long believed that antidepressants sometimes "energize" depressed patients before lifting their moods—potentially making them more prone to enact their despair. But over the past 15 years critics have amassed a small mountain of data that point to suicide-related side effects, including reams of medical journal reports, internal FDA memorandums obtained with Freedom of Information Act filings, and unpublished industry documents pried out via discovery in lawsuits.

The commotion about suicide risks dates back to 1990, when Harvard psychiatrist Martin Teicher and colleagues reported that six of their depressed patients had developed "intense, violent suicidal preoccupation" soon after starting on Prozac. The report sparked sensational media stories on the drug's purported dangers. But studies soon made the case that Prozac is no more dangerous than older antidepressants and possibly much safer. The scare was further deflated by revelations that the anti-psychiatry Church of Scientology had helped promote it. In September 1991, an FDA advisory panel concluded there was "no credible evidence" that Prozac promotes suicidal or violent impulses.

A far less reassuring analysis had unfolded behind the scenes, according to internal FDA documents. The documents were later obtained by attorneys representing plaintiffs who sued Lilly, alleging that Prozac had triggered suicidal and violent acts. Lilly has quietly paid an estimated $50 million–plus to settle more than 30 such suits, according to an investigation in 2000 by the *Indianapolis Star*. "Any settlements were based upon business decisions," says Lilly spokesman Dan Collins. "We do not comment on specific details regarding lawsuits."

A few months after Teicher's report, an FDA safety official wrote to his superiors sharply criticizing a study Lilly had submitted to the agency in hopes of quelling the suicide concerns. The memo's author, David Graham, is the same official who made headlines last year by publicly lambasting the FDA's handling of Vioxx. His 1990 memo about Prozac argued that Lilly's "analysis of suicidality does not resolve the issue" because the company had excluded cases of patients who weren't in the company's main clinical trials—Graham had access to data from early Prozac studies that were separate from the ones the drugmakers emphasized. "It can be argued that these exclusions are not justified or appropriate," he wrote. This "apparent large-scale underreporting" of patients with "treatment-emergent suicidality" meant Lilly had not proved that Prozac and violent behavior are unrelated, he argued. Yet when it came time for the FDA to conduct the crucial hearing in 1991, Graham's analysis wasn't mentioned and Prozac was exonerated.

The 12-year-old killer was "involuntarily intoxicated" with SSRIs, the ex-FDA official told the jury.



HE KILLED his grandparents at age 12. Christopher Pittman was convicted despite his claim that an antidepressant made him unable to tell right from wrong.

The clean bill of health is well deserved, Lilly maintains. "More than 54 million patients worldwide have taken Prozac," says Collins; it's "among the most studied medications in history," and its safety "is thoroughly documented."

Yet critics blame the FDA's response largely on coziness between the agency and Big Pharma—and on senior officials' fear of looking careless. Says Kapit: "There's definitely a reluctance by the FDA to come out and say, 'A drug we've approved is really dangerous.'" The problem is compounded, he adds, by the fact that the FDA unit charged with monitoring drugs' post-launch safety is subsumed under the FDA branch that oversees drug approvals. The drug-safety office has no autonomy to go public with its findings. If it could, Graham's analysis of the Prozac data might have come out as early as 1991. (The FDA did not respond to repeated requests for comment.)

An Injection of Itching Powder

SSRIs' darkest side may be the suicide risk. But other adverse effects may pose just as big a problem for drugmakers. In the mid-1990s, for example, horror stories about SSRI withdrawal symptoms began circulating on the Internet, signaling a controversy that is now nearly as bitter as the one about suicide. One of its leading crusaders, Rob Robinson, a building contractor in Signal Mountain, Tenn., recently organized a protest against GlaxoSmithKline at its U.S. headquarters in Philadelphia. He held a BOYCOTT GLAXOSMITHKLINE sign as he paced the sidewalk in front of the high-rise building along with a handful of fellow protesters.

A rock climber of renown—*Climbing* magazine once put him on its cover—Robinson, 45, says his experience with SSRIs started in 1998. He had committed to do a traveling exhibition on climbing, but the project stressed him out and interfered with his sleep, so his doctor prescribed Glaxo's Paxil. After a few weeks on the drug, Robinson says, "I felt calmer. I thought, 'That's good.'" Quitting it after a half-year, though, "I started having what I now know are withdrawal symptoms," he asserts, including muscle spasms, extreme sensitivity to sound, and "horrible electric-shock sensations in my head." He went back on Paxil to alleviate the symptoms. Eventually concluding he had a drug dependency, he found a specialist who took him off the drug in 18 days. That triggered severe symptoms that Robinson claims brought him to the brink of suicide. "I finally opened a door at the far side of hell after about 18 months," he says.

Today Robinson runs a website on Paxil's risks and has sued Glaxo, charging that it deliberately failed to warn about the drug's potential to cause severe withdrawal symptoms. Some 3,000 similar suits against Glaxo have been filed across the country over the past few years, says Karen Barth Menzies, an attorney at Baum Hedlund, a Los Angeles law firm that has handled many SSRI-related suits. AP

Glaxo's drug has become the withdrawal issue's main lightning rod because it washes out of the body more quickly than most other SSRIs. Hence the effects of its absence in the brain can occur with literally dizzying speed. (Doctors recommend gradually tapering doses before quitting to minimize such symptoms.) The symptoms of SSRI "discontinuation syndrome," as psychiatrists call it, include dizziness, headaches, nausea, lethargy, insomnia, irritability, visual disturbances, movement disorders, and electric-shock sensations (known as "electric head" on web chat groups about SSRIs).

Glaxo concedes that such symptoms may occur when people quit taking Paxil abruptly. Discontinuation symptoms, a spokeswoman notes, can also occur with other medicines, such as blood-pressure drugs. But she says allegations that Paxil is addictive, or that Glaxo has tried to hide data on side effects, are groundless. Most discontinuation symptoms, she adds, are "mild to moderate in intensity, resolve on their own within two weeks, and seldom need corrective therapy." It remains to be seen how well such assertions will play in a courtroom if the withdrawal lawsuits, which are still in pretrial proceedings, aren't settled first.

The most consequential SSRI side-effects lawsuit on the industry's horizon, however, appears to be the Witczak case against Pfizer—the one involving the man who hanged himself after taking Zoloft. The symptoms Woody Witczak purportedly experienced suggest the restlessness-causing condition called akathisia. It was first linked to the antidepressants in the 1980s; critics like Glenmullen assert that it is one of SSRIs' most dangerous side effects, in part because it is rarely seen, hence easily missed, by general practitioners who prescribe the drugs. Ironically, a former Pfizer researcher wrote one of the medical literature's most detailed articles on the subject while working for the company. His report, which appeared in the *Journal of Psychopharmacology* in 1998, states that SSRIs "may occasionally induce" akathisia. The condition's name comes from the Greek for "not sitting still," and its cardinal symptom is intense jitters—a patient who has experienced the sensation compares it to an intravenous injection of itching powder. Akathisia is so unbearable for some depressed patients on SSRIs that they apparently feel "death is a welcome result," according to the report.

An internal Pfizer memo on the akathisia report may backfire on the company. Obtained by Kimberly Witczak's attorneys in pretrial proceedings, it makes the remarkable statement, "This article is not suited for distribution to general practitioners, but may be of interest to neurobiologically inclined psychiatrists." Was Pfizer leery of scaring GPs away from Zoloft? Responds company spokesman Bryant Haskins: "It's a bit absurd to allege that Pfizer thought the paper revealed some serious health issue and [then] decided to keep the information hidden by publishing it in a medical journal." He adds that the paper "makes crystal-clear that the scientific basis for any causal connection between SSRIs and akathisia is very weak."

"It's absurd to allege that Pfizer [tried to hide data] by publishing it in a medical journal."

The SSRI backlash is being fueled by people across the political spectrum. Dr. Sidney Wolfe of the liberal watchdog group Public Citizen in Washington, D.C., for example, has long argued that the drugs are overprescribed; conservative activists such as Phyllis Schlafly have launched campaigns against prescribing SSRIs and other psychiatric drugs to children based on mental-health screening programs.

How the controversy will affect Big Pharma revenues and profits isn't clear, though. Since generic SSRIs are now on the market (Prozac's U.S. patent expired in 2001), drugmakers are racing to bring out new versions of antidepressants. Concerns about SSRIs may help speed the transition to such pricier, patent-protected alternatives, offsetting the controversy's fiscal fallout. Or the new drugs could themselves be damaged by the skepticism that has besieged the industry.

The FDA's scrutiny certainly seems to have intensified. Last year Lilly launched a successor to Prozac called Cymbalta. It's an SNRI, a class of drugs that has been hailed as offering significant advantages over SSRIs, such as faster action. (SNRIs are touted as targeting two different chemical messengers in the brain instead of just serotonin, as SSRIs do.) A few months later Lilly dropped plans to seek approval for the drug as a treatment for urinary incontinence in women. Last July the FDA revealed in a public alert that "a higher than expected rate of suicide attempts was observed" in clinical trials with incontinence patients on Cymbalta. Increased suicide risks hadn't been seen in earlier trials of the drug. (A Lilly spokesman says that the Cymbalta suicide-attempt rate, while higher than the rate for the U.S. population, is "consistent" with worldwide suicide rates.) Such problems may someday be resolved by genetic testing. It could take the guesswork out of determining which patients a drug might help and which it might hurt.

Waiting for her day in court, Kim Witczak appeared at another Washington, D.C., forum this month—an FDA public hearing on direct-to-consumer drug ads. "Prescription drugs ... should not be treated in the same manner as cars, soap, or fast food," she told agency officials. Safety has to be No. 1, she added, and all serious side effects ought to be communicated "in a clear, concise, and honest manner, not just those that won't scare people away from thinking twice about taking the drug."

Witczak's comments sounded like points her attorney is likely to make to a jury. But as a success formula for the post-Prozac era, transparency might be just the prescription that pharmaceutical marketers need. F

FEEDBACK *fortunemail_letters@fortunemail.com*