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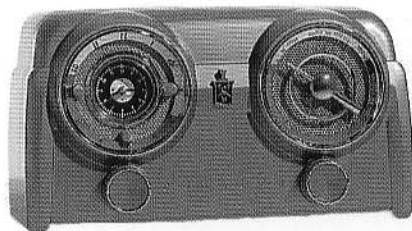
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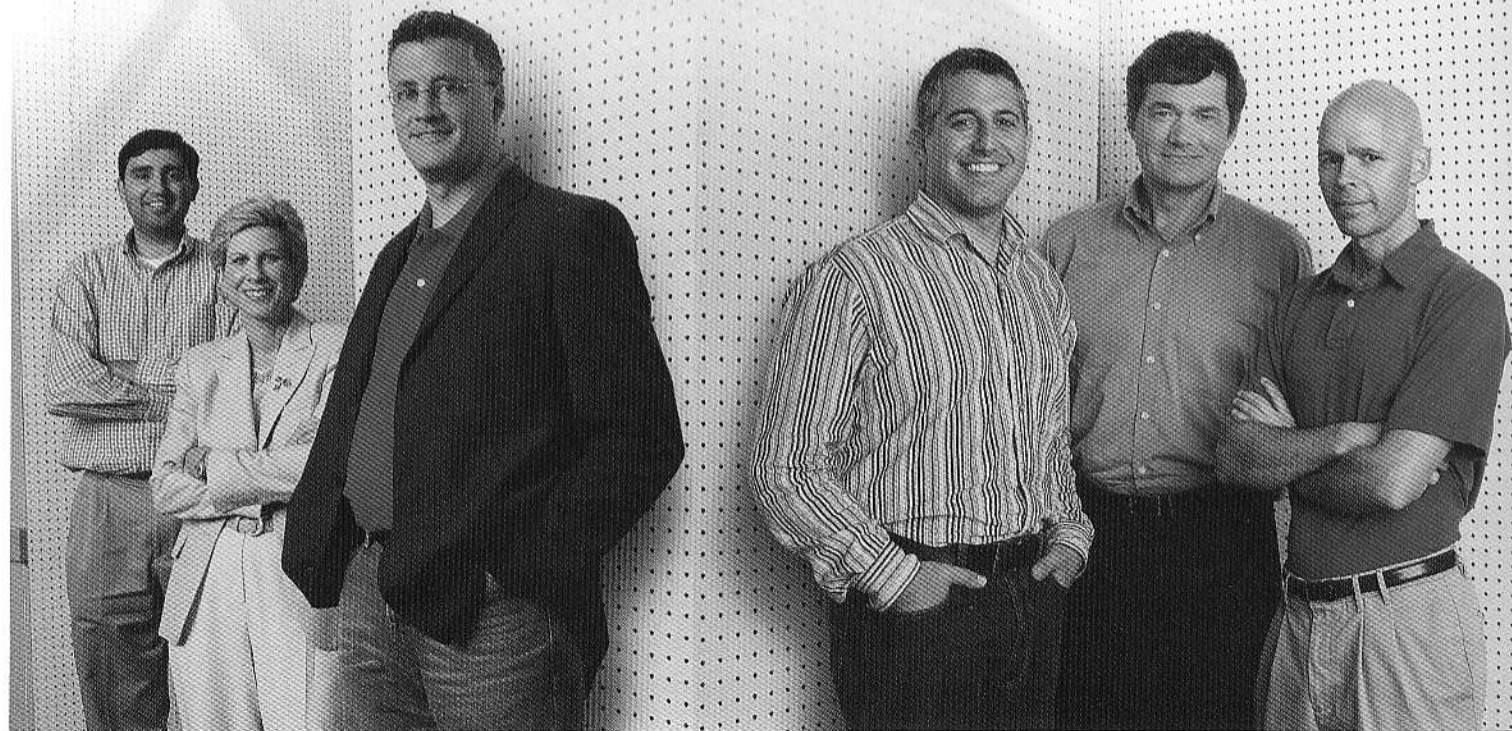
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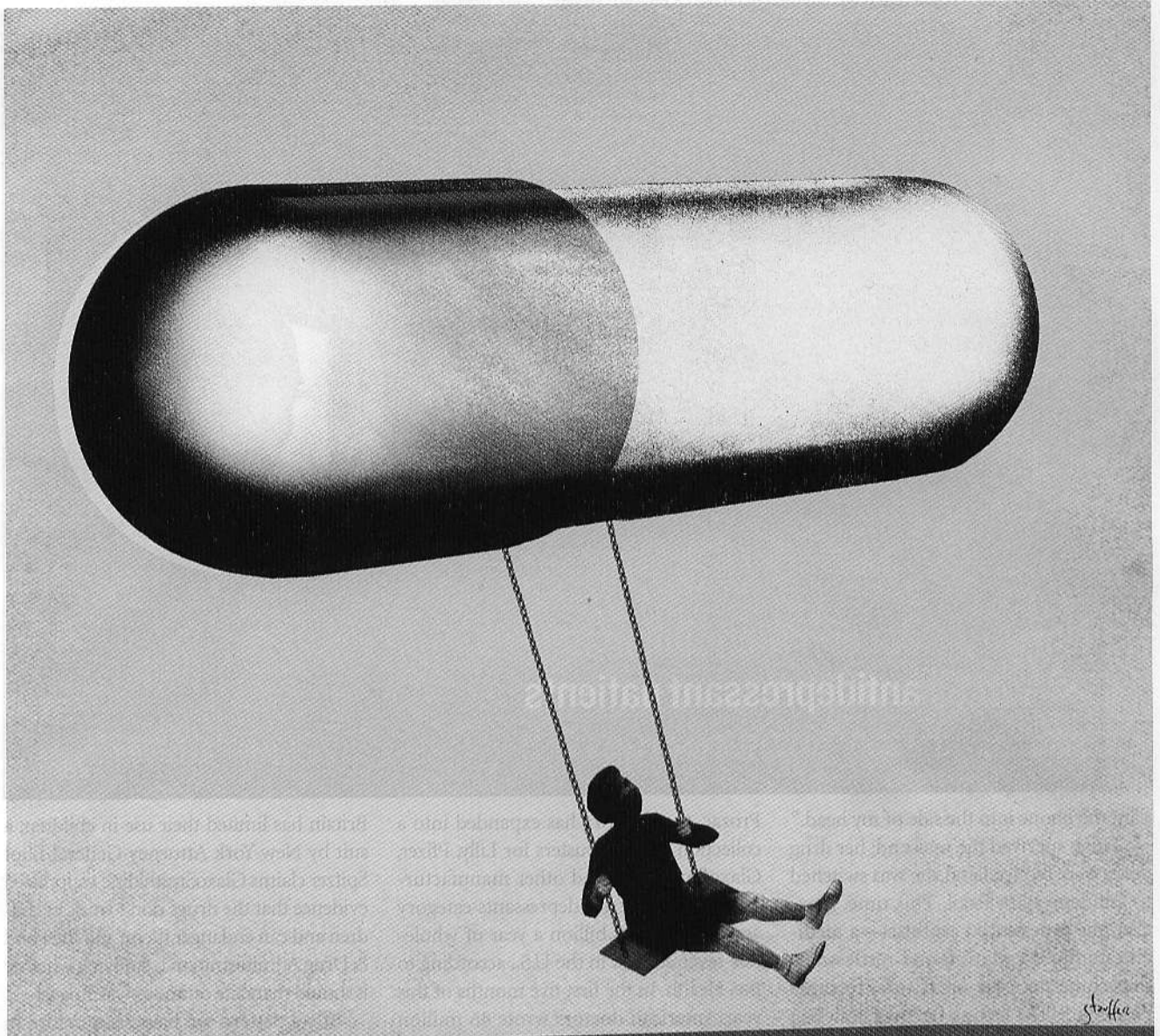
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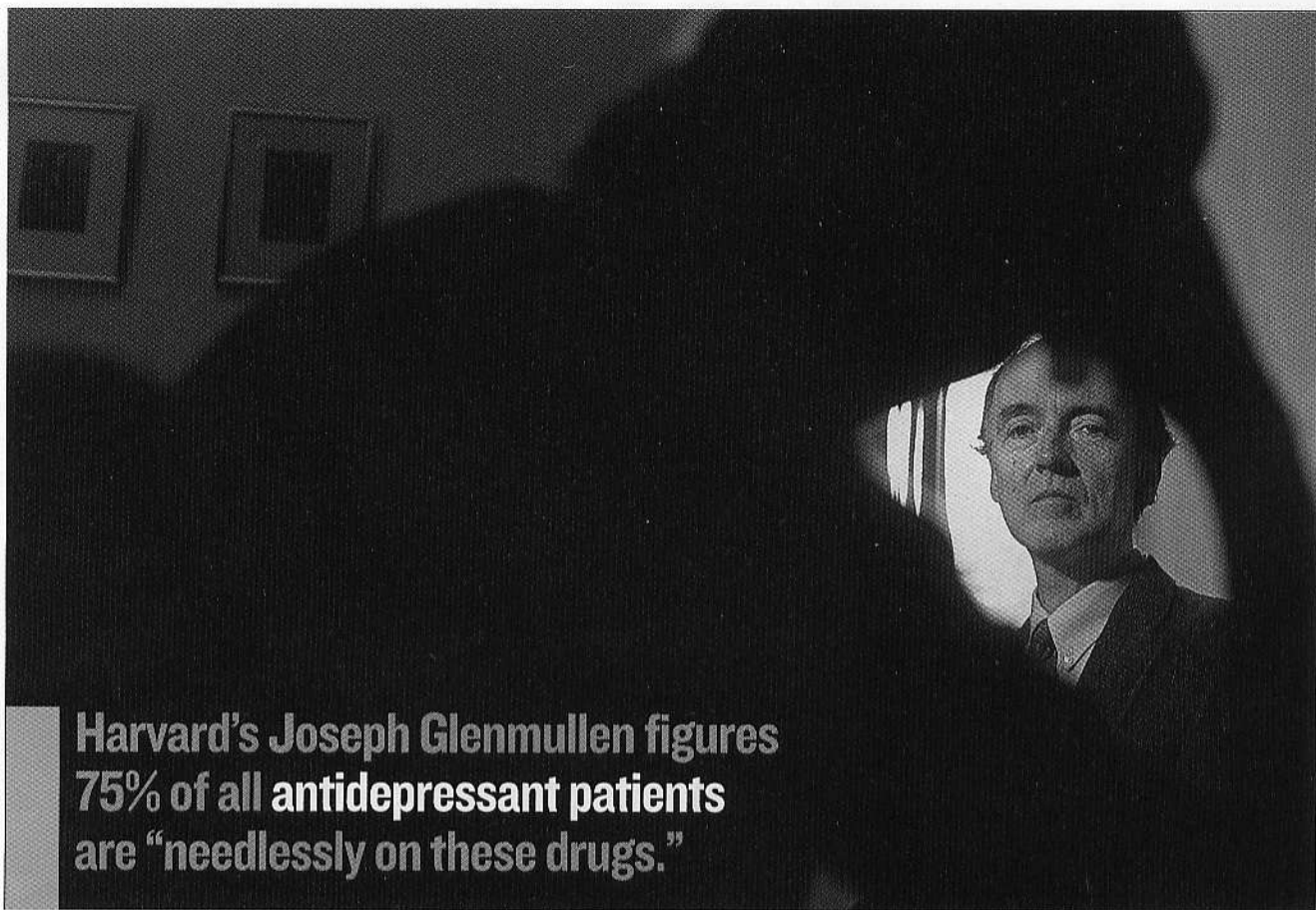
# Prozac Nation: Is the Party Over?

**N**ANCY HUGO, A 57-YEAR-OLD HOUSEWIFE IN CORVALLIS, ORE., HAD recently been prescribed the antidepressant Zoloft by her internist when she found herself in the bathroom, looking at a Bic shaver and wondering if she could get the blade out of its plastic. In the living room she zeroed in on a pair of long scissors she had inherited from her grandmother. "I kept on wanting to pick them up and gouge my eye out," she recalls. Trying to occupy her mind at the computer, she fought the "urge to

BRIAN STAUFFER FOR FORBES

There are three stages in the life of a new mental health drug: euphoria, then medical doubts, then lawsuits.

BY RICHARD C. MORAIS



**Harvard's Joseph Glenmullen figures  
75% of all antidepressant patients  
are "needlessly on these drugs."**

slam the phone into the side of my head."

Hugo survived the weekend; her drug doses were reduced and she was switched to antidepressant Paxil. This time, however, she experienced akathisia—a medicine-induced agitation and restlessness that some patients on antidepressants describe as the feeling of bugs crawling through the skin—and an extreme bout of mania. "What spooks me now is that I thought I'd recognize when I was having trouble with the medications," she says. "But it was a week later before I realized, 'Oh, my God, what have I done?'"

Both Zoloft and Paxil are Prozac-type drugs known as SSRIs, or selective serotonin reuptake inhibitors. Do such drugs cause mania and violent obsessions? That question is now being debated in many a doctor's office, court of law and legislature. Whatever the correct scientific answer, the mere fact that the question is being asked represents a new phase in the evolution of SSRI medications and a threat to the well-being of the companies that make the drugs.

Since SSRIs arrived 16 years ago with the introduction of Eli Lilly & Co.'s

Prozac, the category has expanded into a collection of blockbusters for Lilly, Pfizer, GlaxoSmithkline and other manufacturers. All told, the antidepressants category accounts for \$14 billion a year of wholesale revenues just in the U.S., according to IMS Health. In the first five months of this year American doctors wrote 46 million prescriptions for antidepressants, up 5% over the same period last year, according to NDCHealth. Yes, this is a Prozac nation. Dr. Mark Vanden Bosch, an anesthesiologist at the Berkshire Medical Center in Pittsfield, Mass., who must be alert to drugs that might interact with anesthesia, estimates that a third of the patients checking into his hospital, for a wide range of operations, are on antidepressants.

When Prozac was new, it was heralded (in, for example, the 1993 hit *Listening to Prozac*) as a wonder drug with little in the way of side effects. The few naysayers were for the most part fringe sorts like Scientologists. Now a giant pall of misgiving is descending on SSRIs: Tearful family members are telling their congressmen how the drugs caused their children to commit suicide;

Britain has limited their use in children; a suit by New York Attorney General Eliot Spitzer claims GlaxoSmithkline suppressed evidence that the drugs don't work in children and can endanger them; and the Food & Drug Administration is studying whether it should mandate ominous warning labels.

It's a pattern we have seen before in psychiatric drugs, says Harvard Medical School psychiatrist Joseph Glenmullen. A new class of chemicals creates a wave of euphoria in the medical community, while a handful of celebrities (such as, in the case of SSRIs, Mike Wallace of *60 Minutes*) swear by the new pills. A decade later reports of side effects accumulate and doctors begin to have second thoughts. Another decade later the world discovers a new miracle drug and the old one is relegated to niche uses. It happened to the major tranquilizers (like Thorazine) introduced in the 1950s, and it happened to supposedly less addictive and relatively side-effect-free substitutes for morphine. Dr. Glenmullen made this point about the SSRIs five years ago in his book *Prozac Backlash*. He looks prescient now.



The second-guessing about SSRIs comes just as the earliest patents have expired, or are about to. The combination of potentially dampened prescription volume and new price competition could bring a lot of disappointment to investors in Pfizer and its competitors.

The touchiest issue is whether SSRIs provoke suicides in children. Eric Harris was on Solvay Pharmaceuticals' SSRI, Luvox, when he and Dylan Klebold went on their murder-suicide rampage through Columbine High School in Littleton, Colo. in 1999. Did the powerful drug push him into a dangerous mental zone, like the one Hugo experienced, or was it unable to stop what was already there? It's hard to know. (A Columbine survivor's lawsuit against Solvay was settled out of court, without any admission of liability, and resulted in a token contribution from Solvay to a charity.) The British health authorities have ruled that the side effects of SSRI antidepressants other than Prozac put children at an unacceptable risk of suicide. The National Institute of Mental Health in the U.S., in contrast, says that "some research" points to a drop in suicides among children since the drugs were introduced, "but it is not known if SSRIs are directly responsible."

"The suicides under SSRIs are violent," says Vera Sharav, president of the Alliance for Human Research Protection, a group headquartered in New York City that is crusading for full disclosure of the drugs' side effects. "It's not like someone going into the bathroom and taking pills. It's jumping, knives, hanging. They're in pain. They're jumping out of their skins."

Glenmullen says he himself prescribes SSRIs when appropriate but is dismayed to see patients who have been prescribed antidepressants for every triviality, from nail-biting to boyfriend breakups. It is easy to see where overprescribing could become a habit. General practitioners, internists and family doctors are, at times, penalized by health insurers for making referrals to psychiatrists. These first-line doctors write 73% of all antidepressant scrips in America.

Fact: We now spend more on mood-altering drugs for our children, including antidepressants, than we spend on antibiotics.

Harried GPs do not always discuss with their patients such possible problems as withdrawal symptoms on discontinuance or the need for ever-increasing doses as the drug's efficacy wears off. In 1997 C.W. Tillman, a county official in Missouri, had an anxiety attack and was prescribed Paxil by his doctor; a few days later his adverse reactions included severe agitation, extreme sensitivity to light and noise, claustrophobia, diarrhea and vomiting. His doctor told him to stop taking the drug, let the symptoms

clear up and start again. A month later Tillman had descended into a deep depression and took an overdose. Tillman—subsequently diagnosed as bipolar and now the Web site editor of NAMI, the National Alliance for the Mentally Ill, in Arlington, Va.—is grateful for SSRIs for eventually helping him manage his illness, but says doctors are undertrained in recognizing side effects.

The brain runs on a cocktail of feel-good chemical transmitters, among them adrenaline, serotonin and dopamine. Basically, serotonin flows across a synapse briefly, from one nerve cell to another, after which the cell that sent it out mops up the

## Backlash

Wilton Hall was a 23-year-old up-and-comer at an environmental organization in San Francisco in 1989, but had a tendency toward depression, so he went to a clinic advertised in a newspaper. Referred to a doctor, Hall was handed free samples of a new wonder drug called Prozac.

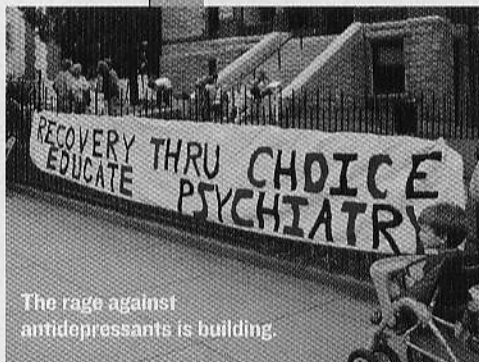
At first Hall thought Prozac was "everything coffee ever promised to be," and he began producing prodigious amounts of work. But weeks later his feel-good buzz had spun into a full-blown mania. A few years later, diagnosed as having a form of schizophrenia, he wound up institutionalized and was given what he calls a "temporary chemical lobotomy."

Today Hall works in a bookstore in Northampton, Mass. and runs the Freedom Center, a self-help group for mentally ill patients that meets every week. He does not take pharmaceuticals anymore—which he claims only exacerbated his illness—but relies on homeopathy, yoga, nutrition and a support network of similar sufferers to keep him from spinning into the abyss. "I do the best I can," he says.

The Freedom Center is one of a collection of grassroots organizations springing up across the country in reaction to the prevalence of medication

in America. It alerts people to the downside of psychiatric drugs but does not try to force people off them; it seeks instead to help sufferers find the best methods of coping, even if their solution is unconventional by the standards of the medical establishment. Similar advocates: the Alliance for Human Research Protection and MindFreedom. The next book by Harvard's Dr. Joseph Glenmullen, due later this year from Simon & Schuster, is a guide to safely tapering off SSRIs without triggering severe withdrawal.

Caution: There are huge numbers of sufferers who really need SSRIs. "Antidepressants provide significant amount of relief for a great number of people," says Thayer Greene, an analyst in Amherst, Mass. "We have to be respectful of what they do, while also raising questions. The reasons underground drug pushers and the pharmaceutical industry make so much money is that so many Americans yearn for release from the nitty-gritty of life. 'Salvation by the pill' does not deliver what it promises. It also takes hard psychological work." —R.C.M.



The rage against antidepressants is building.

excess. SSRIs work by blocking the sending cell's ability to reabsorb the excess serotonin. Result: The receptors in the second cell get a prolonged bath of the feel-good juice. The miracle in this class of drug is that SSRIs are better tolerated than earlier antidepressants and less likely to be fatal in an overdose.

Now the downside: The brain adjusts to the artificial increase in serotonin with a compensatory drop in dopamine. No one knows the long-term effect of this drop in dopamine in the brain. "The gaping loophole in our drug safety system," says Glenmullen, "is long-term safety. It takes decades for enough consumers to have had ill effects for problems to come to the authorities' attention." Pfizer, the manufacturer of Zoloft, says it carefully monitors safety after drugs are approved and shares that information with the FDA.

Doctors and patients have for some time been reporting mild tics and jerks in SSRI users. The tics are usually overlooked, but can develop into tardive dyskinesia (manifested by a freakish "involuntary tongue" that darts out of the mouth, twitching or "running" legs, jerking or wildly swinging arms and gagging). Do patients know they may be in for this? Knowing, they might, of course, still opt for medication. "A little discomfort is a small [price] to pay for a normal level of happiness!" writes Archibald Hart in *Unmasking Male Depression*.

Thorazine, it turns out, creates similar side effects, but it was a while before doctors were aware of how frequently. Prescribed for everything from insomnia to anxiety, this type of tranquilizer was taken by an estimated 250 million worldwide. In 1973, at the 20-year mark, 2,000 cases of tics had been reported. Critics surfaced and were dismissed as alarmists. But by 1980 systematic studies using neurological screening tests discovered that 40% of all patients treated with the Thorazine class of tranquilizers had tics. Reclassified as antipsychotics, the Thorazine-style drugs were given a long list of FDA warnings and are used today only for severe mental illness.

SSRI patients are also reporting memory loss. It's mostly anecdotal evidence at this point. But Harvard's Glenmullen says the reports of memory loss, tics and jerking side effects found in SSRI patients sug-

gests to him the possibility of long-term brain damage. Is there a risk that, a decade hence, we will see an epidemic of Alzheimer's- or Parkinson's-like diseases? The regulators haven't given enough thought to the possibility, he says.

Whatever the true hazards in SSRIs, there is no doubt that tort lawyers can make hay out of the situation. No overall litigation and settlement data are available on antidepressants (opponents claim pharma is settling cases quietly and sealing the records), and there are just the early signs of clustering activity—trial lawyers advertising for SSRI "victims," seminars

could provoke, look at what recently happened to Pfizer. Warner-Lambert's Neurontin was FDA approved for epilepsy, but the company, it was alleged, was encouraging doctors to prescribe it for "off-label" uses like bipolar disorders. A whistleblower triggered federal and state criminal investigations into the marketing, and this May Pfizer (which had subsequently acquired Warner-Lambert) settled with the government, taking a \$427 million pretax hit in criminal and civil fines.

Four days after the settlement the Teamsters Health & Welfare Fund of Philadelphia & Vicinity, joined by Aetna and the Alaska State Employees Association health benefits trust, filed class actions against Pfizer alleging, among other things, that Warner-Lambert suppressed a Harvard Bipolar Research Program study finding that "patients did worse on Neurontin than those who were on a sugar pill." Two years after the study was suppressed, the Teamsters suit alleges, "Neurontin accounted for \$1.3 billion in sales, with over 80% of its use coming

## About to Crash?

America's top-selling antidepressants could soon experience a downturn. Now off-patent, Prozac is no longer a bestseller.

### TOP FIVE ANTIDEPRESSANTS

Drug	Manufacturer	2003 sales <sup>1</sup> (\$bil)
Zoloft	Pfizer	\$2.9
Effexor XR	Wyeth	2.1
Wellbutrin SR	GlaxoSmithkline	1.8
Paxil	GlaxoSmithkline	1.5
Celexa	Forest Laboratories	1.4

<sup>1</sup>Wholesale prices of drugs, not including mail service. Source: IMS Health.

and other legal teamwork—familiar to mass torts, but watch events gather pace.

"We went through a whole period of overprescribing SSRIs," says Jeffrey Kodroff, a Philadelphia lawyer suing Pfizer over Neurontin, an epilepsy drug. "When the market started getting to the point of saturation, the market started emphasizing juvenile use, also for the purpose of getting patent extensions. If the studies show they are not only not efficacious, but cause problems, you're going to see a big backlash in usage of SSRIs."

The New York Attorney General's suit against GlaxoSmithkline, filed in June, alleges that Glaxo committed fraud by suppressing or selectively quoting from clinical studies that showed Paxil to be no better, or even worse, than a dummy pill in treating children with depression. Spitzer has also requested documents from Forest Laboratories, maker of SSRIs Celexa and Lexapro. Glaxo says Spitzer's allegations are bunk; it never targeted kids.

To see what a successful Spitzer prose-

from nonapproved uses, such as treatment of bipolar disorder." Pfizer says it will "vigorously defend" itself against any suits following its Neurontin settlement, and says "it is worth noting that those investigations did not result in a charge of fraud by Warner-Lambert."

A user of SSRIs for almost a decade, who says she can't wean herself off the drugs and spoke to us on the condition of anonymity, recently wrote her former Park Avenue psychiatrist: "I simply pray Glaxo follows the path of [Dow] Corning, who endangered women's lives with silicone implants they knew were dangerous. Bankruptcy."

Even if Pfizer, Glaxo and Lilly are right about the science, they could be on the wrong end of a tort suit. Look at the breast implant cases. Scientific studies showed that there was no connection between silicone and the autoimmune diseases supposedly caused by it. But still the implant manufacturers had to spend billions of dollars to settle lawsuits. **F**