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A risky drug may get wider market

The FDA may approve Zyprexa for kids, despite its significant side effects in adult use.

By ROBERT FARLEY, Times Staff Writer
Published December 16, 2007

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Prescriptions
The numbers peaked in 2004, when Zyprexa was Florida's most prescribed drug to Medicaid fee-for-service patients. The numbers fell as word spread associating the drug with weight gain and diabetes.

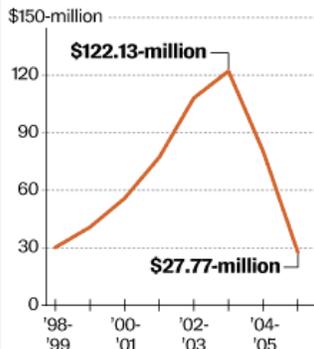
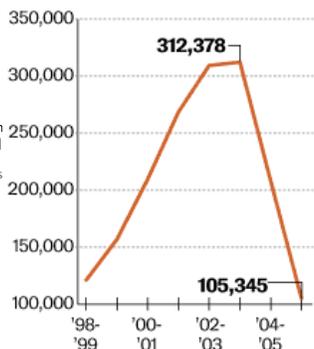
Cost to taxpayers
The new generation of antipsychotic drugs cost 10 times as much as the older generation. Since 1998-99 Florida taxpayers have paid more than a half-billion dollars for Zyprexa used by fee-for-service Medicaid patients.

Zyprexa in Florida

Sources: Florida's Agency for Health Care Administration and a USF analysis

[Times graphics: Ron Brackett]

Zyprexa fast facts



It sounds like a cosmic, FDA joke:

The Food and Drug Administration approves the antipsychotic drug Zyprexa to treat adults with schizophrenia or bipolar disorder. It becomes a market wonder, a bestseller. But the side effects turn out to be dangerous; some patients develop diabetes.

Some 30,000 people sue the manufacturer, Eli Lilly. The pharmaceutical giant shells out more than \$1-billion to settle the cases.

Here comes the punch line:

Though studies show that kids are even more susceptible to Zyprexa's dangerous side effects, now Lilly wants the government's seal of approval for adolescents to use it. And the FDA is about to say yes.

* * *

Like a mounted animal head hung as a trophy from the hunt, a framed copy of a \$2.8-million check from Bayer pharmaceutical hangs in the law office of Joseph Saunders. The check says: It's my business to sue drug companies, and I'm good at it.

Saunders practices in Pinellas Park, but hundreds of lawyers like him across the country have found a niche suing Lilly.

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He has eight Zyprexa clients. Most are psychotic. Most suffer from diabetes, which can cause kidney failure, heart disease, liver damage, blindness.

They were prescribed Zyprexa during the time doctors swooned over the big new thing. Approved by the FDA in 1996, Zyprexa was one of a new class of drugs called atypicals, marketed as powerfully effective for people suffering the dreadful psychotic breaks of schizophrenia and bipolar disorder.

And -- this was key -- the new drugs were less likely to cause the tremors and facial tics that sometimes accompanied older drugs.

Zyprexa was deemed so safe, doctors began prescribing it "off-label" to treat depression, anxiety, ADHD, even sleeplessness. As it turned out, studies would show that Zyprexa may be the most effective of the new class of antipsychotic drugs, but it's also most likely to cause serious weight gain and elevated blood sugar levels.

Saunders says you can't win a lawsuit against a drug company just because you suffer a side effect. But pharmaceuticals do have a legal responsibility to warn doctors about known risks.

The tens of thousands of lawsuits contend that Lilly did not fully disclose risks it discovered during studies conducted to get FDA approval for Zyprexa, risks that became more apparent in the years after the drug hit the market.

The preapproval studies lasted six weeks, not nearly time for diabetes to manifest itself, Saunders says, but there were red flags. Some 29 percent of participants gained significant amounts of weight. Rapid weight gain puts people at higher risk of developing diabetes.

Lilly spokeswoman Marni Lemons allows that a majority of people who take Zyprexa gain a lot of weight. And some of them develop diabetes.

But only a small percentage of those who gain weight on Zyprexa develop diabetes. Also, people with schizophrenia and bipolar disorder are at higher risk of diabetes no matter what drug they take.

"It's a very complicated subject," Lemons said. Bottom line: No data directly finds that Zyprexa causes diabetes.

So why did Lilly pay \$1.2-billion to settle 30,000 claims?

"Even when a company has a really strong defense, as we believe Lilly did, going to court poses very real financial and business risks," Lemons said. "Lilly has a responsibility to its shareholders and employees -- as well as to health care professionals and patients -- to move beyond this litigation at the lowest possible cost."

Saunders counters that Lilly treats lawsuits as a cost of doing business: \$1-billion in settlements sounds like a lot, he says, but it's chump change compared to the tens of billions the company has made since Zyprexa came on the market.

Lilly has more than private attorneys to worry about. Nine states have sued, claiming the company illegally promoted unapproved uses of Zyprexa and downplayed its side effects. The states want to be reimbursed hundreds of millions for Medicaid dollars they paid for Zyprexa.

In 2003, the FDA directed that not only Zyprexa, but all atypical antipsychotics carry a warning about increased risk of hyperglycemia and diabetes.

Lilly continued to market its drug as more effective but no more dangerous than its competitors. Only this fall did the company agree to change Zyprexa's label to state that its tendency to increase blood sugar levels, another diabetes risk factor, is higher than its

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May 27, 2007: A drug's chilling path to market



Joseph Saunders, who has sued Lilly on behalf of eight patients, says it defies common sense that Zyprexa became a bestseller.



James Gottstein heads PsychRights, a group that fights unwarranted forced drugging and electroshock to mental patients.



Dr. David Egilman, facing possible criminal charges, admitted in writing that he violated a court order to keep Lilly documents secret.



Shahram Ahari says Zyprexa salesmen were coached how to deal with doctors worried about weight and diabetes issues.



Dr. David Healy, a pharmacology expert, says that with its side effects, "What you've got is a drug that has very little to recommend it."

Breaking News Video

competitors.

Asked Saunders: "Why did it take 10 years to warn people about something they knew from their clinical trials? The reason is clear: They were making billions and billions of dollars selling it."

* * *

The telephone call that James Gottstein took late last year was a bolt from the blue.

An attorney in Alaska, Gottstein heads a group called PsychRights, which presses litigation against forced psychiatric drugging and electric shock. The caller, a stranger Gottstein never had spoken with, said he had documents that could help lead Gottstein's group to the promised land.

The caller, David Egilman, worked as a consultant for a law firm that had thousands of clients suing Lilly over Zyprexa. In that job, he was given access to thousands of pages of internal Lilly documents, but they were under protective order; it was illegal for him to make them public.

What happened next is disputed, but a quite furious U.S. district judge, Jack B. Weinstein, determined this is how his court order was violated:

At the suggestion of a *New York Times* reporter, Egilman called Gottstein and -- wink, wink -- suggested he find a separate case in which he could subpoena the Lilly documents from him. Gottstein could get copies to the aforementioned reporter before Lilly and the courts could act to stop it.

The deed done, Lilly officials were furious. As Gottstein put it, "They came after me like a Panzer division."

Judge Weinstein, who called it a conspiracy to assist the stealing of protected documents, tried to get the copies back. But they had hit the Internet.

There were internal memos, showing Lilly's marketing strategy aimed at downplaying weight gain and any link to diabetes.

There was a memo from a Lilly employee in 2000 fretting that doctors the company hired to study the diabetes connection had warned that "unless we come clean on this, it could get much more serious than we might anticipate."

There were letters from doctors who raved about the drug's effectiveness but warned Lilly that patients were developing diabetes at an alarming rate. Like this one from 2001, from Dr. Clif Tennon, in Knoxville: "It is troublesome, frustrating and occasionally irritating to repeatedly hear the official line that a relationship between Zyprexa and diabetes is unclear, that diabetes is known to occur more frequently in mentally ill people with or without meds, etc. We know that.

"But we also know that our Zyprexa patients gain weight and that they do develop diabetes. It feels as if our concerns are being dismissed, and that if we would just listen to the experts, we wouldn't worry about this anymore."

Egilman and Gottstein paid a price for making the documents public. Threatened with criminal prosecution, Egilman signed a mea culpathat said he had provided an "incomplete subset" of the Lilly documents. He paid the company \$100,000, which Lilly donated to charity.

Gottstein, who maintains he did nothing improper, says Lilly is still going after him, for civil sanctions that could ruin him financially and for criminal contempt. He says it has threatened to go after his law license.

When he answered the phone that day, who knew what lay ahead? "I do think it was important to get this information out. People should be informed of the risks before they decide to take these drugs. So for me, it was worth it."

* * *

Spring 1998. Like zillions of undergrads, Shahram Ahari was finishing college, looking for that first job. He had finished Rutgers University with a degree in molecular biology, biochemistry and Asian studies.

A friend's brother landed him an interview with Eli Lilly. The job, salesman.

Ahari knew zip about pharmaceutical sales, but he loved what he heard: \$50,000 base salary, \$10,000 to \$15,000 annual bonuses, stock options, a free car, great health benefits. Meals on a hefty expense account.

To hawk Zyprexa, he says, the pitch was simple: "Encourage doctors to be the first on their block with a brand-new toy."

When he made sales calls, he was armed with data from an independent company that tracked every prescription the doctor made that month. It helps to know that the doc you are about to pitch prescribes more of your competitor's drug, say, Risperdal. You can take some gratuitous pot shots at Risperdal in your pitch.

The job mostly was about befriending doctors and leveraging their emotions, Ahari says, though favoring them with goodies didn't hurt. Salesmen wooed doctors with free samples, treated them to expensive dinners and paid them to give speeches at seminars.

"It practically sold itself," said Ahari, who sold Zyprexa in New York from 1998 to 2000.

The gravy train hit some bumps. Reps started hearing from doctors concerned about patients "blimping up." Competitors hammered them on it, derisively twisting Zyprexa's generic name, olanzapine, into "olanza-pig."

The Zyprexa sales reps eagerly awaited word from Lilly's brand team on how they should deal with the weight/diabetes issue. Ahari says this is what they came up with: Tell doctors to instruct patients to drink a glass of water before and after they eat, to suppress appetite.

"We'd have to do it with a straight face," Ahari said, "and after a while, it just became uncomfortable."

With doctors he knew well, he said his pitch was blunt: "Would you rather have a skinny, unwell patient or a fat, stable one?"

Doctors started reporting patients developing diabetes. "That was a big, scary thing," Ahari said. If the FDA required that Zyprexa carry a black box warning about diabetes, "it would have been death, market-wise."

He says sales reps were instructed to deflect the issues of weight gain and diabetes. "We were taught to downplay it and negate it, or to change the topic."

Lemons, the Lilly spokeswoman, says the company can't be certain what every sales manager told their sales reps, but "that has never been our corporate policy." She questioned Ahari's objectivity because she said he is now a paid witness for trial attorneys taking on pharmaceutical companies.

Ahari says he was a paid witness in just one case, which was about preserving the confidentiality of physicians' prescribing patterns.

Today he does public health research on biological disaster preparedness at the University of California, San Francisco. He lectures on how sales reps influence physicians, and he has applied to medical school.

Like many critics, Ahari came to feel Zyprexa was effective, appropriate for many people. But he believed that the brass at Lilly downplayed the weight and diabetes problems because the clock on the patents was ticking. The thinking was, "we may as well milk it while we can."

* * *

Even with all the lawsuits, Zyprexa remains Lilly's best-seller. Some 22-million people have taken it. In just the first six months this year, sales topped \$2.3-billion.

Lilly can ride the Zyprexa money machine until its patent runs out in 2011. But thanks to a carrot offered by the FDA, the company is in line to get an extra six months of exclusivity.

That will allow Lilly to keep making top dollar before generic versions can come on the market and the price falls.

That's where expanding the government's seal of approval to use Zyprexa on adolescents comes in.

Though the FDA approved Zyprexa only for use on adults with schizophrenia or bipolar disorder, psychiatrists prescribe it "off label" to children.

Drug companies had no incentive to study whether giving powerful antipsychotics to kids is safe, not with doctors already prescribing their drugs to children by the fistful.

That's why the FDA offered to extend exclusivity of the atypical antipsychotics by six months if the companies studied their effect in children.

It has made for a bizarre left-hand/right-hand situation.

On one hand, federal and state investigators are looking into whether Lilly and other drug companies downplayed risks and illegally promoted their drugs for unapproved uses.

On the other hand, the FDA is looking into expanding the approved use of the identical drugs. Already this year, the FDA has approved the atypicals Risperdal and Abilify for use in adolescents.

Evidence suggests that the dangerous side effects of Zyprexa in adults are more pronounced in children.

A study published in August compared several atypical antipsychotics in the treatment of early onset schizophrenia. Kids on Zyprexa gained so much weight, the Zyprexa arm of the study was discontinued.

Another study, published in the American Journal of Psychiatry in October, found Zyprexa effective in treating bipolar mania in adolescents. But in the three-week study, kids on average gained more than 8 pounds and had elevated glucose and cholesterol levels.

In an accompanying editorial, Dr. Jon M. McClellan, an associate professor of psychiatry at the University of Washington, wrote that "the long-term consequences of obesity, dyslipidemia and insulin resistance -- and the risk of diabetes and cardiovascular disease -- raise serious questions over the risk-benefit ratio of olanzapine as a first-line treatment in juveniles."

McClellan said in an interview that parents tell him their kids on Zyprexa are always hungry, ravenous even. "A kid comes in and a week later they've gained 4 pounds, they look puffy," he said.

Adults taking Zyprexa may gain 5 to 15 pounds in a year, he says, but kids may gain that in three weeks. Over time, some have gained more than 50 pounds.

A three-person FDA panel that reviewed Lilly's application for approval of Zyprexa for adolescents had reservations about the studies and initially recommended denial. The vote was unanimous.

But Thomas P. Laughren, director of the FDA's Division of Psychiatric Products, said the FDA should not follow the expert panel's recommendation.

Lilly had submitted two studies, with patients roughly split between sites in the United States and Russia. The three-member FDA team was troubled that the positive results mostly came from the Russian sites.

But Laughren noted that FDA inspectors visited the Russian sites and "they found no evidence for fraud."

He said the side effects in children -- weight gain, somnolence, sedation, fatigue, dizziness and dry mouth -- were similar to what has been seen in adults, "however, with some differences in magnitude." Those differences need to be reflected on the labeling, Laughren said in a memo, but he concluded that Zyprexa is "effective and acceptably safe" for treatment of adolescents with schizophrenia and bipolar disorder.

One of the world's most prominent pharmacology experts shudders at the prospect of the FDA approving Zyprexa for adolescents.

Dr. David Healy, a professor of psychiatry at the University of North Wales, says that even in adults, Zyprexa should be used only as a backstop, after other antipsychotics have been tried and failed.

"It ought not to be used in children at all," he said. "It is going to be marketed as a safe and gentle drug. It is not a safe and gentle drug. I think it's an extremely dangerous drug. The idea that it's going to be given to children on a large scale is quite scary."

Times researcher Caryn Baird contributed to this report. Robert Farley can be reached at farley@sptimes.com or (727) 893-8603.

[Last modified December 16, 2007, 01:01:35]

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Comments on this article

by **Arlene**

01/05/08 09:21 AM

VERY interesting. It just shows me that I'm right about ALL depression drugs causing huge appetite and also causing people that have never drank to become alcoholics. My son is on Lexapro with huge appetite and weight gain and is now an alcoholic.

by **Phil**

12/19/07 11:10 PM

Pharmas should be investigated by the FBI as a threat to American citizens, internal memoes and research documents be seized, and evidences not be protected by courts. Like the Enron criminals, Lilly's CEO belongs to two places: prison and hell.

by **kt**

12/17/07 02:18 PM

WHY isn't EVERY newspaper and news outlet reporting on this? It's pretty damn important stuff for people to know. But nope, instead we're going to let a whole generation be drugged into oblivion. "Psychosis" in children used to be called imagination.

by **Tim**

12/17/07 02:06 PM

How can you trust the FDA to protect the public when some members have an association with drug companies? Drug advertising on TV is so unethical by pushing drugs on people. The irony is the whole "war on drugs". Such hypocrisy.

by **PFG**

12/17/07 07:47 AM

And the FDA has nothing to do with the sudden rise in Autism! Hummmm I don't think thousands of parents could be wrong! Greed! If you don't take care of your health no one else will! Do your research...for your kids sake! Can't put your trust in Dr's!

by **Juliana**

12/17/07 02:50 AM

Who believes the FDA today? Why did MD's accept "education" from those who sell the educators' product? Yes, medical doctors really are that lacking in mental ability

by **Lex**

12/16/07 10:46 PM

Drugs & money - Is there really any difference between zyprexa & crack? GREED is their common element. Drug company's are only interested in \$\$\$ - they are legal versions of crack dealers. Drugs & money makes the world, or at least the USA, go round.

by **DrTracy**

12/16/07 09:25 PM

Lilly waited 10 years to warn of diabetes while Wyeth waited 10 years to warn of homicidal ideation with Effexor! One side effect kills the patient, the other kills anyone nearby, ie: the latest-Omaha & Colorado. drugawareness.org, ssrstories.com

by DrTracy 12/16/07 04:29 PM

EXCELLENT ARTICLE!!! A glimpse into reality in the pharmaceutical world. This is FAR FROM a single incident! Drug companies do this kind of thing regularly. Read their internal memos on antidepressants which also increase diabetes. drugawareness.org

by Marcy 12/16/07 03:43 PM

Two of my now-close friends have lost their adult sons to this drug. It is horrifying that the incompetent FDA would take this step. It should be off the market.

by roger 12/16/07 02:35 PM

It is about time this was reported. I gained 60lbs and got diabetes in 6 weeks. How are people supposed to get health insurance with diabetes?

by carlos 12/16/07 02:24 PM

Xyprexa, as most anti psychotics, must be kept out of reach of children. Parental education should be the rule in cases like these, as these drugs are a wildcard in a child's development and easily create lifelong dependency. Educate, not medicate.

by Michael 12/16/07 02:06 PM

This is outrageous that the State of Florida in the financial condition that it is in subsidizes this and other drugs like it. It will stop with a multi billion dollar fine for damages.

by melissa 12/16/07 01:27 PM

This is the exact reason I did my research before my child even received any of his shots! The drug companys are out to make a buck! They don't care about our well being!Do your research before you allow your child any meds/shots!

by Sadness 12/16/07 11:24 AM

What a sad state of affairs. Lilly CEO Taurel is pals with our president. That probably clinched this terrible deal. My son was killed by this horrible drug and it has pretty much ruined my life. Where is our Congress in all this? Nowhere.

by Amy 12/16/07 10:50 AM

Thank you St. Petersburg Times. This article may save a few lives.

by alao 12/16/07 08:07 AM

alot of hype here, pull out of lilly, is what im reading ,,cause its a big scam this drug,,and there giving it to the strung out sugar babies..for no reason except that the parents need to take a month long course on .calorie counting , sugar andfat

by sherry 12/16/07 07:42 AM

Why can't anybody see how dangerous this drug really is. Our government haggles about it and the tv media ignores it. I am a diabetic from taking zyprexa. No history of diabetes or symptoms. Please do not let them start giving this dug to children.

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