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Date: 04/11/2003 02:26:49 PM
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Subject: Re: WSJ article on diabetes and antipsychotics focuses on Zyprexa

Per your request.

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04/11/2003 02:24 AM

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Subject: WSJ article on diabetes and antipsychotics focuses on Zyprexa

Drug Debate: New Antipsychotics Pose a Quandary For FDA, Doctors --- Eli Lilly's Big Seller, Zyprexa, Can Help Schizophrenics; Is It Linked to Diabetes? --- Warnings Abroad, Not in U.S.

By Geeta Anand and Thomas M. Burton
2,529 words
11 April 2003
The Wall Street Journal
A1
English

For more than four years, the U.S. Food and Drug Administration has been mulling a mystery: Is a new generation of big-selling drugs for severe mental illness causing diabetes and, in rare cases, killing patients?

Among the most widely prescribed versions of these medications, Zyprexa, made by Eli Lilly & Co., is the one most frequently associated with serious side effects. Of the millions of patients who took the drug over an eight-year period that ended in 2002, 288 are reported to have developed diabetes. Seventy-five of those people became severely ill, and 23 died. Some researchers see these statistics as significant because in some cases diabetes symptoms came on suddenly after patients began taking Zyprexa, eased after they went off the drug and returned when they tried the medication again.

The company says there isn't conclusive evidence that Zyprexa caused the dire side effects. But pointing to some reports of complications with rival drugs, Lilly also says that if there is a problem, it affects the entire class of medications, known as atypical antipsychotics.

It is up to the FDA to decide whether Zyprexa or any competing drugs are responsible for the illnesses and deaths -- and what to do about it. The stakes are huge for the patients taking the drugs and for the companies making them. In the U.S., sales of antipsychotic drugs, used to treat schizophrenia and other severe mental illnesses, topped $5 billion last year. The market is expanding as doctors try the medicines with patients who have other problems, such as depression, as well as with children. Lilly took in $2.5 billion last year -- 39% of its U.S. sales -- from Zyprexa alone.

The FDA says it hasn't arrived at a definitive answer on whether Zyprexa or any other atypical antipsychotics harm some patients. The resulting quandary illustrates a difficult challenge the agency, manufacturers and physicians regularly face: what to do with otherwise effective drugs that may cause serious side effects.

A big part of that challenge concerns labeling. Japan and the European Union have required Lilly to provide a prominent warning about diabetes-related complications. The safety message must be included in the product-information sheets -- known in the industry as the "label" -- that doctors and patients are supposed to read. Zyprexa's main rival, Risperdal, which is made by a unit of Johnson & Johnson, so far hasn't been hit with similar regulation.

Lilly has resisted such precautions in the U.S., pointing to the inconclusive evidence. The company contends that people with schizophrenia -- a mental illness whose symptoms can include delusions, hallucinations and social withdrawal -- are more likely to get diabetes anyway. Some research psychiatrists agree. They say there is some evidence that schizophrenia patients have high blood-sugar levels -- the condition underlying diabetes -- because of bad eating habits and inactivity. Including a safety message could put Lilly at a commercial disadvantage, causing doctors to prefer competing products.

Meanwhile, many doctors continue to prescribe Zyprexa and rival antipsychotics, unaware of the debate. Thomas Johnson, a general

practitioner in Colorado Springs, Colo., says a 25-year-old patient nearly died last October, two months after she started taking Zyprexa prescribed by her psychiatrist. She arrived in Dr. Johnson's office leaning heavily on her mother, unable to talk, he says. The patient was taken to a hospital, where her blood sugar was recorded at 15 times the normal level -- a life-threatening diabetic state.

The young woman was hospitalized for a week and released, still taking Zyprexa, in addition to insulin, which controls blood-sugar levels. Dr. Johnson says that neither he nor doctors at the hospital initially considered any potential connection between Zyprexa and the patient's blood-sugar problem because the drug's label lacks any alert on the topic. After he found reports on the Internet about the drug and diabetes, he took the patient off Zyprexa. Her blood sugar returned to normal, he says.

Asked about this case, Marni Lemons, a Lilly spokeswoman, says that "there are stories like this on all of the [atypical antipsychosis] drugs." She adds that many patients take multiple medications, making it difficult to attribute side effects to just one drug. "And we know Zyprexa and the other drugs cause people to crave carbohydrates. We often hear of people drinking two-liter bottles of Coca-Cola or juice, and that can drive the blood sugar up," she says. Overall, Ms. Lemons says that "one or two anecdotal reports out of 11 million patients can raise fear among patients and drive them off" helpful medication.

Nearly all drugs have some side effects, and doctors are encouraged to report possible side effects to the FDA, whether or not they can link the problems to the drug. Especially in the early years of a drug's life, it can be hard to tell whether a drug has caused a given side effect. The FDA doesn't have hard-and-fast rules on when to require warnings or bar a medication.

Since 1997, a dozen drugs approved for marketing have been withdrawn, in some cases several years after initial reports of sickness and death. These include cholesterol-lowering Baycol, the diabetes drug Rezulin and the heartburn medicine Propulsid. Waves of lawsuits followed, accusing the companies that made them of dragging their feet in the face of growing evidence the drugs were dangerous.

Antipsychotics block or moderate the level of dopamine, a chemical found in the brain that in excessive amounts is believed to cause abnormal thinking and hallucinations. Atypical antipsychotics -- which include Zyprexa, Risperdal and Clozaril, made by Novartis AG -- have been widely prescribed since coming on the market in the early 1990s. They relieve some psychotic symptoms without causing as much of the stiffness and jerky movement frequently associated with older psychosis drugs. Last year, doctors wrote 7.3 million prescriptions for Zyprexa and 7.6 million for the less expensive Risperdal, the market leaders, according to the information service NDC Health.

In the case of Zyprexa, FDA officials say they are very much aware that requiring a warning could influence doctors to prescribe it less often. They say they don't want to act in a way that might divert patients to other drugs, when it could turn out the rival medications

cause the same problems.

The FDA has approved Zyprexa to treat schizophrenia and bipolar disorder. But in December 2000, Frank Olenick's doctors prescribed the drug to help him with sleeplessness and confusion he suffered while withdrawing from painkillers, says his wife, Christine, who lives in Wintersville, Ohio. Such "off label" prescriptions are legal and not unusual with some drugs. Although she is a nurse, Ms. Olenick says she didn't recognize warning signs two months later -- including excessive thirst -- that might have signaled her 40-year-old husband's blood-sugar level was elevated.

After Mr. Olenick complained of feeling sick, his wife took him to a nearby hospital in Weirton, W.Va. Doctors recorded his blood-sugar level at 20 times the normal level, according to hospital records. He had no history of diabetes, his wife says. After suffering two cardiac arrests, Mr. Olenick died two days later. "Nobody told us to watch for glucose levels, or I would have," his wife says.

In January, Ms. Olenick sued Lilly in a West Virginia state court. Her law firm, Hersh & Hersh, says in court papers that the company "fraudulently withheld relevant information from potential users of Zyprexa." The company says it hasn't yet been served with court papers and so declines to comment in detail. It stresses, though, that Zyprexa hasn't received government approval for treating withdrawal symptoms.

Individual cases aren't sufficient evidence that a medication is causing a side effect, "but they're often the first signal of a link," says P. Murali Doraiswamy, chief of biological psychiatry at Duke University and co-author of several studies on possible side effects of atypical antipsychotics.

The FDA in 1999 launched a broad review of atypical antipsychotic drugs then on the market, after a number of academic studies and individual reports of problems had accumulated. The agency's neuropharmacological division does about 10 such extensive reviews annually, drawn from a much larger number of suggestions it receives of possible side-effect problems. The division also asked manufacturers to check their records for evidence of blood-sugar elevation during clinical trials of antipsychotics.

Officials with the division say that in recent years, they have gradually moved away from requiring manufacturers to warn about "possible" side effects. The division now aims, instead, to define risks with more certainty, the officials say. The idea is that it's better to avoid tentative precautions that later have to be adjusted, because revisions tend to encourage doctors to ignore warnings. This shift doesn't reflect any formal change of policy and hasn't affected the FDA as a whole, the officials say.

By mid-2000, the FDA had gathered some information on the possible link between atypical antipsychotics and diabetes, but making even rudimentary findings proved difficult, agency officials say.

For example, researchers often compare the frequency of a drug's possible bad side effect to the frequency of the malady in the general population. This can provide helpful information if, as is typical, the disorder is relatively rare among people generally. But diabetes is relatively common, so comparing the general-population rate to that of medicated psychosis patients doesn't prove or disprove whether antipsychotic drugs cause diabetes.

Separately, company records of clinical trials weren't of much use because researchers hadn't focused on blood-sugar levels. The medical literature didn't offer conclusive answers either, the FDA officials say.

A team of researchers, led by Elizabeth Koller, a former FDA official, and Dr. Doraiswamy of Duke, catalogued the number of diabetes-related complications reported to the FDA in patients taking Zyprexa and Risperdal, the drug made by Johnson & Johnson unit Janssen Pharmaceutica. The researchers reported the possible Zyprexa side-effect cases last July in the journal Pharmacotherapy: Over an eight-year period, 288 diabetes cases, of which 75 resulted in severe illness and 23 in death. Of the millions who had taken Risperdal over an overlapping nine-year period, Dr. Koller's group found 132 diabetes cases, 31 of which involved life-threatening complications and five that ended in death. The findings were based on voluntary reports to the FDA, which scientists estimate reflect between 1% and 10% of actual cases.

Based on this and other research, Johnson & Johnson says Risperdal has a lower risk of diabetes than Zyprexa. But Lilly says its research undercuts this contention. A study led by a Lilly consultant looked at prescription records of AdvancePCS, the giant pharmacy-benefits manager. Published in the February 2003 issue of the Journal of Epidemiology, the study found that patients on a selection of antipsychotics were two to three times as likely as the general population to have diabetes. But the study found no difference in the rate of diabetes among patients taking the various drugs.

Robert W. Baker, a senior clinical research scientist at Lilly, says the company has spent millions of dollars on research evaluating the diabetes question. Roughly a quarter of Zyprexa patients gain more than 25 pounds while on the medication, Lilly researchers say, and obesity is linked with diabetes. But Dr. Baker says the evidence suggests Zyprexa itself doesn't cause diabetes-related problems. He says the research suggests that the Zyprexa patients who developed diabetes probably had elevated blood-sugar levels before taking the medication.

He says, however, it is still possible that antipsychotic drugs in rare cases cause some health problems. Lilly continues to evaluate

evidence and discuss research with the FDA, Dr. Baker says.

As some researchers themselves concede, each of the studies of antipsychotics has had limitations precluding firm conclusions. Some had too few subjects; others lacked a scientifically proper comparison, or "control," group.

Even so, Novartis, the maker of Clozaril, agreed to alert doctors to possible diabetes-related complications, beginning in 1997. Novartis says it agreed to this step to make sure physicians and their patients were aware of the potential side effect. The precaution isn't thought to have affected sales very much, however. Since Clozaril came on the market in 1990, the FDA has required that its label carry other warnings and that patients get weekly blood tests in early treatment. Those safety steps probably had already lessened Clozaril sales.

Dr. Koller, the former FDA official, has reported 384 diabetes cases among Clozaril patients. Fifty-five were life-threatening, and 25 were fatal. The drug is prescribed far less often than the big two, but Novartis says its side effects may be recognized more often since patients are monitored weekly for the other potential medical problems.

Some psychiatrists say the FDA's approach on Zyprexa and other leading antipsychotics is understandable, given the many confounding factors. "The short answer is, we just don't know yet," says Paul Keck, a professor of psychiatry at the University of Cincinnati.

Others think FDA action is long overdue. These doctors typically don't believe Zyprexa and similar drugs ought to be pulled from the market but say some sort of precaution is warranted because of cases such as that of Douglas Ferguson.

The 31-year-old Fort Worth, Texas, rock musician was rushed to the emergency room in February 2002, the day before he was to see a doctor for a range of symptoms. His family found a note in his handwriting, listing excessive thirst, frequent urination and other symptoms associated with high blood-sugar levels, his brother, Matt Ferguson, says. Douglas had been taking Zyprexa for four months, his brother says. "We didn't know these were symptoms of something life threatening," adds Matt, a physics graduate student.

Doctors at Fort Worth's John Peter Smith Hospital recorded Douglas's blood sugar at about 10 times the normal level, his brother says. The patient's organs progressively failed, and he died days later, his brother says. Nobody at the hospital raised any potential connection with Zyprexa, Matt Ferguson says. But his mother, a reference librarian, found studies and cases describing a possible link on the Internet.

Ms. Lemons, the Lilly spokeswoman, reiterates that cases such as this one aren't unique to Zyprexa. There are similar accounts involving patients on other psychosis drugs, she says. She adds that many patients take more than one drug and that making too much

of such cases may encourage other patients to stop taking medication that drastically improves their lives.

Dr. Doraiswamy of Duke University favors label language that would caution doctors about diabetes-related complications in patients taking Zyprexa. "No one is denying the benefit of these drugs," he says. "The real issue is trying to avoid unnecessary harm."

Peter Landers contributed to this article.

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