SLATE

Drug Secrets

What the FDA isn't telling.

By Jeanne Lenzer

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Traci Johnson's body was discovered on Feb. 7, 2004, hanging by a scarf from a shower rod in an Indianapolis laboratory run by the drug company Eli Lilly. The 19-year-old college student had been serving as a test subject in a clinical trial of the experimental antidepressant duloxetine. Investigators from the Food and Drug Administration rushed to Indianapolis to determine whether the experimental drug was related to her death. The probe was inconclusive.

This left researchers in a quandary: Was the drug safe or not? Could duloxetine trigger suicide, as some experts suggested? Or was Johnson's death an "isolated tragedy," as Eli Lilly claimed? When drug manufacturers fail to publish negative study results, as studies show is often the case, the best source of information about these questions is the FDA. The agency—which was rocked last week by the sudden resignation of Commissioner Lester Crawford—requires companies seeking approval for a drug to provide data from randomized controlled trials, studies in which some patients are given the drug and others are given a placebo. But when researchers and the press started asking about duloxetine, the FDA didn't scour its database and go public. It kept quiet. The FDA gave a legal rationale for its silence: Some clinical trial data are considered "trade secrets," or commercially protected information, and thus are exempted from release under the Freedom of Information Act. Since the FDA doesn't routinely perform comprehensive reviews of drugs once they are on the market, when uncommon but deadly side effects tend to be picked up, independent researchers are often the only hope of catching such flaws. But the trade-secrets rule can leave researchers in the dark about the most worrisome data—negative results that support a failed application to market a drug.

The argument for secrecy is that failed efforts at drug development need protection lest entrepreneurs suffer a competitive disadvantage when other companies aren't forced to expend the same time and money exploring dead ends. And at first blush, there would appear to be little need for clinical data on a drug that isn't in use. The problem is that many drugs have multiple uses. Duloxetine, for example, is marketed under the brand name Cymbalta to treat depression. Traci Johnson committed suicide while taking duloxetine during tests for selling the drug to treat stress urinary incontence, under the brand name Yentreve. If a drug is on the market for one use and studies about another use suggest disquieting risks—as the death of Traci Johnson may—do the benefits of keeping the study data secret outweigh the costs?

The FDA approved Cymbalta to treat depression in August 2004. By the end of that

year, Cymbalta sales topped $61.3 million. At some point—the date is undisclosed—Eli Lilly began testing Yentreve. In January 2005, as Cymbalta sales climbed to $106.8 million for the first quarter, Lilly announced that it was withdrawing its application for Yentreve. Then it cited the trade-secret rule in refusing to disclose why the drug did not win approval. Perhaps the rationale was harmless—the drug didn't work for incontinence. But duloxetine has been approved as a treatment for incontinence in Europe since August 2004.

Over four months beginning in January, I filed several Freedom of Information Act requests on behalf of the *Independent on Sunday*, a British newspaper, for all safety data related to Cymbalta and Yentreve. I received a database that included 41 deaths and 13 suicides among patients taking Cymbalta. Missing from the database was any record of Johnson, or at least four other volunteers known to have committed suicide while taking Cymbalta for depression.

When I asked the about the missing results, FDA officials cited a federal regulation that they said prohibited the agency from releasing study data—or acknowledging the existence of an application—for a drug that fails to win FDA approval. Since the FDA never approved Yentreve, all the data about it were off limits. The agency may have used a similar rationale in failing to release safety data about the pain reliever Bextra, which Pfizer, its manufacturer, withdrew from the market in April for fear of links to an increased rate of heart attack.

In its Web-site database, Eli Lilly initially listed no suicides and two deaths among patients enrolled in seven clinical trials of Cymbalta for depression. (Lilly's database won the company praise in a May *New York Times* article for being "the company that has gone furthest in disclosing results.") Today the Web site lists 10 clinical trials of Cymbalta and five of Yentreve, with one suicide and five deaths combined. Based on the dates of the trials and the circumstances of the deaths, it's clear that the Web-site numbers do not include any of the five suicides missing from the FDA database. Lilly admits that it has never made public at least two of those deaths. Lilly spokesman David Shaffer said that data was unavailable because some of the studies were still in progress. He also said that two of the suicides "took place in depression studies run by another company," and that "the decision about how and when to disclose such information rests with that company." Shaffer was referring to the Japanese firm Shionogi & Co., which partners with Lilly to market duloxetine in Japan.

Meanwhile, my sources (sorry, they're gun-shy and anonymous) were telling me that duloxetine caused suicidal tendencies in patients who took the drug for incontinence—and who were not depressed. That news was potentially explosive. In the face of questions about a link between antidepressants and suicide, industry experts have long insisted that it's depression, not the drugs used to treat it, that causes patients to kill themselves. Johnson's death appeared to call that claim into question. She entered the clinical trial as a healthy, nondepressed volunteer in order to help pay her college tuition. And she was only approved for the study after undergoing thorough medical testing to screen out depression or suicidal tendencies.

Because one patient's reaction can't prove anything one way or the other, it was critical for researchers to analyze the results of all the patients in Lilly's duloxetine studies. Instead, the FDA's interpretation of the trade-secrets rule left only the positive data from the Cymbalta trials available for review.

In June, after the *Independent* article, the FDA (without issuing a press release) noted on its Web site that one suicide "was reported in a Cymbalta clinical pharmacology study in a healthy female volunteer." The agency added that new data from stress urinary incontinence trials showed that middle-aged women taking duloxetine had a suicide attempt rate of 400 per 100,000 person-years, more than double the rate of about 160 per 100,000 person-years among other women of a similar age. These findings had been withheld from the public, and the researchers asking for them, for five months after the FDA had reviewed data showing the increased risk.

The FDA claims it has no choice but to resist releasing information about drugs it doesn't approve. "My hands are tied," said Dr. Robert Temple, FDA's director of medical policy. "This is something only Congress can change." That may be as much a matter of the FDA's interpretation as it is of the law, however. Experts disagree about whether congressional action or a federal court ruling is needed to make data like Johnson's death available, or whether the FDA could choose to disclose more itself.

The voluntary guidelines promoted by the drug industry, however, are not a solution. These guidelines encourage companies to list every clinical trial they initiate. Registration would be helpful. But it would not compel companies to release the data from, or even the outcomes of, their trials, as long as they companies can argue that this information is "commercially protected."

The use of trade-secret laws to conceal deaths and serious side effects linked to drugs has the obvious flaw of putting profits before public health. It also subverts the covenant between researchers and study volunteers. Subjects like Traci Johnson are told that even if they do not personally benefit from a new drug, the scientific knowledge gained from the study in which they've participated will benefit others. The volunteers should be told instead that scientists will learn about their experience only if it's good news for the drug they're helping to test.

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