

The Washington Post

A Silenced Drug Study Creates An Uproar

By Shankar Vedantam
Washington Post Staff Writer
Wednesday, March 18, 2009; A01

The study would come to be called "cursed," but it started out just as Study 15.

It was a long-term trial of the antipsychotic drug Seroquel. The common wisdom in psychiatric circles was that newer drugs were far better than older drugs, but Study 15's results suggested otherwise.

As a result, newly unearthed documents show, Study 15 suffered the same fate as many industry-sponsored trials that yield data drugmakers don't like: It got buried. It took eight years before a taxpayer-funded study rediscovered what Study 15 had found -- and raised serious concerns about an entire new class of expensive drugs.

Study 15 was silenced in 1997, the same year Seroquel was approved by the Food and Drug Administration to treat schizophrenia. The drug went on to be prescribed to hundreds of thousands of patients around the world and has earned billions for London-based AstraZeneca International -- including nearly \$12 billion in the past three years.

The results of Study 15 were never published or shared with doctors, even as less rigorous studies that came up with positive results for Seroquel were published and used in marketing campaigns aimed at physicians and in television ads aimed at consumers. The results of Study 15 were provided only to the Food and Drug Administration -- and the agency has strenuously maintained that it does not have the authority to place such studies in the public domain.

AstraZeneca spokesman Tony Jewell defended the Seroquel research and said the company had disclosed the drug's risks. Since 1997, the drug's labeling has noted that weight gain and diabetes were seen in study patients, although the company says the data are not definitive. The label states that the metabolic disorders may be related to patients' underlying diseases.

The FDA, Jewell added, had access to Study 15 when it declared Seroquel safe and effective. The trial, which compared patients taking Seroquel and an older drug called Haldol, "did not identify any safety concerns," AstraZeneca said in an e-mail. Jewell added, "A large proportion of patients dropped out in both groups, which the company felt made the results difficult to interpret."

The saga of Study 15 has become a case study in how drug companies can control the publicly available research about their products, along with other practices that recently have prompted hand-wringing at universities and scientific journals, remonstrations by medical groups about conflicts of interest, and threats of exposure by trial lawyers and congressional watchdogs.

Even if most doctors are ethical, corporate grants, gifts and underwriting have compromised psychiatry, said an editorial this month in the American Journal of Psychiatry, the flagship journal of the American Psychiatric

Advertisement

	age	male
10-Yr Level Term Life Insurance	35	\$15.75
\$500,000 Policy	40	\$20.56
(monthly premiums)	45	\$31.06
	50	\$45.06

ACCUQUOTE Get A Free Quote!

Association.

"The public and private resources available for the care of our patients depend upon the public perception of the integrity of our profession as a whole," wrote Robert Freedman, the editor in chief, and others. "The subsidy that each of us has been receiving is part of what has fueled the excesses that are currently under investigation."

Details of Study 15 have emerged through lawsuits now playing out in courtrooms nationwide alleging that Seroquel caused weight gain, hyperglycemia and diabetes in thousands of patients. The Houston-based law firm Blizzard, McCarthy & Nabers, one of several that have filed about 9,210 lawsuits over Seroquel, publicized the documents, which show that the patients taking Seroquel in Study 15 gained an average of 11 pounds in a year -- alarming company scientists and marketing executives. A Washington Post analysis found that about four out of five patients quit taking the drug in less than a year, raising pointed doubts about its effectiveness.

An FDA report in 1997, moreover, said Study 15 did offer useful safety data. Mentioning few details, the FDA said the study showed that patients taking higher doses of the drug gained more weight.

In approving Seroquel, the agency said 23 percent of patients taking the drug in all studies available up to that point experienced significant weight increases, compared with 6 percent of control-group patients taking sugar pills. In 2006, FDA warned AstraZeneca against minimizing metabolic problems in its sales pitches.

In the years since, taxpayer-funded research has found that newer antipsychotic drugs such as Seroquel, which are 10 times as expensive, offer little advantage over older ones. The older drugs cause involuntary muscle movements known as tardive dyskinesia, and the newer ones have been linked to metabolic problems.

Far from dismissing Study 15, internal documents show that company officials were worried because 45 percent of the Seroquel patients had experienced what AstraZeneca physician Lisa Arvanitis termed "clinically significant" weight gain.

In an e-mail dated Aug. 13, 1997, Arvanitis reported that across all patient groups and treatment regimens, regardless of how numbers were crunched, patients taking Seroquel gained weight: "I'm not sure there is yet any type of competitive opportunity no matter how weak."

In a separate note, company strategist Richard Lawrence praised AstraZeneca's efforts to put a "positive spin" on "this cursed study" and said of Arvanitis: "Lisa has done a great 'smoke and mirrors' job!"

Two years after those exchanges, in 1999, the documents show that the company presented different data at an American Psychiatric Association conference and at a European meeting. The conclusion: Seroquel helped psychotic patients lose weight.

The claim was based on a company-sponsored study by a Chicago psychiatrist, who reviewed the records of 65 patients who switched their medication to Seroquel. It found that patients lost an average of nine pounds over 10 months.

Within the company, meanwhile, officials explicitly discussed misleading physicians. The chief of a team charged with getting articles published, John Tumas, defended "cherry-picking" data.

"That does not mean we should continue to advocate" selective use of data, he wrote on Dec. 6, 1999, referring to a trial, called COSTAR, that also produced unfavorable results. But he added, "Thus far, we have buried Trials 15, 31, 56 and are now considering COSTAR."

Although the company pushed the favorable study to physicians, the documents show that AstraZeneca held

the psychiatrist in light regard and had concerns that he had modified study protocols and failed to get informed consent from patients. Company officials wrote that they did not trust the doctor with anything more complicated than chart reviews -- the basis of the 1999 study showing Seroquel helped patients lose weight.

For practicing psychiatrists, Study 15 could have said a lot not just about safety but also effectiveness. Like all antipsychotics, Seroquel does not cure the diseases it has been approved to treat -- schizophrenia and bipolar disorder -- but controls symptoms such as agitation, hallucinations and delusions. When government scientists later decided to test the effectiveness of the class of drugs to which Seroquel belongs, they focused on a simple measure -- how long patients stayed on the drugs. Discontinuation rates, they decided, were the best measure of effectiveness.

Study 15 had three groups of about 90 patients each taking different Seroquel doses, according to an FDA document. Approximately 31 patients were on Haldol. The study showed that Seroquel failed to outperform Haldol in preventing psychotic relapses.

In disputing Study 15's weight-gain data, company officials said they were not reliable because only about 50 patients completed the year-long trial. But even without precise numbers, this suggests a high discontinuation rate among patients taking Seroquel. Even if every single patient taking Haldol dropped out, it appears that at a minimum about 220 patients -- or about 82 percent of patients on Seroquel -- dropped out.

Eight years after Study 15 was buried, an expensive taxpayer-funded study pitted Seroquel and other new drugs against another older antipsychotic drug. The study found that most patients getting the new and supposedly safer drugs stopped taking them because of intolerable side effects. The study also found that the new drugs had few advantages. As with older drugs, the new medications had very high discontinuation rates. The results caused consternation among doctors, who had been kept in the dark about trials such as Study 15.

The federal study also reported the number of Seroquel patients who discontinued the drug within 18 months: 82 percent.

Jeffrey Lieberman, a Columbia University psychiatrist who led the federal study, said doctors missed clues in evaluating antipsychotics such as Seroquel. If a doctor had known about Study 15, he added, "it would raise your eyebrows."

Post a Comment

[View all comments](#) that have been posted about this article.

Comments that include profanity or personal attacks or other inappropriate comments or material will be removed from the site. Additionally, entries that are unsigned or contain "signatures" by someone other than the actual author will be removed. Finally, we will take steps to block users who violate any of our posting standards, terms of use or privacy policies or any other policies governing this site. Please review the [full rules](#) governing commentaries and discussions. You are fully responsible for the content that you post.

© 2009 The Washington Post Company