FDA to review "missing" drug company documents

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The US Food and Drug Administration has agreed to review confidential drug company documents that went missing during a controversial product liability suit more than 10 years ago. The documents appear to suggest a link between the drug fluoxetine (Prozac), made by Eli Lilly, and suicide attempts and violence.

The missing documents, which were sent to the *BMJ* by an anonymous source last month, include reviews and memos indicating that Eli Lilly officials were aware in the 1980s that fluoxetine had troubling side effects and sought to minimise their likely negative effect on prescribing.

The documents received by the *BMJ* reportedly went missing during the 1994 Wesbecker case that grew out of a lawsuit filed on behalf of victims of a workplace shooting in 1989. Joseph Wesbecker, armed with an AK-47, shot eight people dead and wounded another 12. He then shot and killed himself. Mr Wesbecker, who had a long history of depression, had been placed on fluoxetine one month before the shootings.

One of the internal company documents, a report of 8 November 1988, entitled "Activation and Sedation in Fluoxetine Clinical Trials," found that in clinical trials "38% of fluoxetine-treated patients reported new activation but 19% of placebo-treated patients also reported new activation yielding a difference of 19% attributable to fluoxetine."

The FDA recently issued a warning that antidepressants can cause a cluster of "activating" or stimulating symptoms such as agitation, panic attacks, insomnia, and aggressiveness. Dr Joseph Glenmullen, a Harvard psychiatrist and author of *The Antidepressant Solution*, published by Free Press, said it should come as little surprise that fluoxetine might cause serious behavioural disturbances, as it is similar to cocaine in its effects on serotonin.

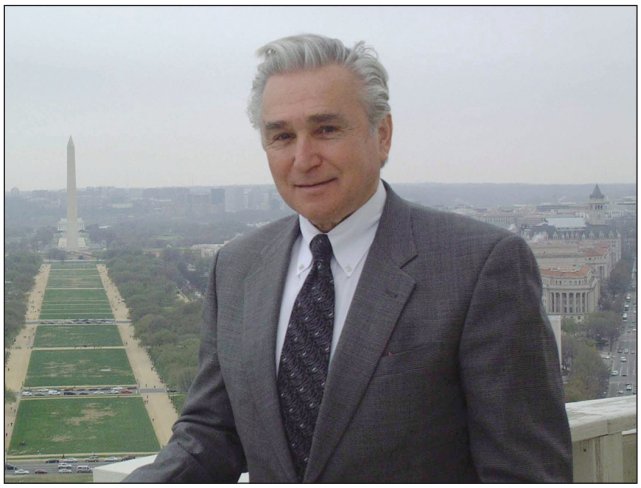
Dr Richard Kapit, the FDA clinical reviewer who approved fluoxetine, said he was not given the Lilly data. "These data are very important. If this report was done by Lilly or for Lilly, it was their responsibility to report it to us and to publish it."

Congressman Maurice Hinchey's office is currently reviewing the documents to determine whether Lilly withheld data from the public and the FDA. Mr Hinchey (Democrat, New York) said: "This is an alarming study that should have been shared with the public and the FDA from the get-go, not 16 years later.

"This case demonstrates the need for Congress to mandate the complete disclosure of all clinical studies for FDA-approved drugs so that patients and their doctors, not the drug companies, decide whether the benefits of taking a certain medicine outweigh the risks."

The plaintiffs in the Wesbecker product liability sought to show that Eli Lilly withheld negative study data from the FDA and that fluoxetine tipped Wesbecker over into a homicidal rage. Lilly won a 9 to 3 jury verdict in late 1994 and subsequently claimed that it was "proven in a court of law … that Prozac is safe and effective."

The trial judge, Justice John Potter, suspecting that a secret deal had been struck, pursued Lilly and the plaintiffs, eventually forcing Lilly in 1997 to admit that it had made a secret settlement with the plaintiffs during the trial. Infuriated by Lilly's actions, Judge Potter ordered the finding changed from a verdict in Lilly's favour to one of "dismissed as settled with prejudice," saying, "Lilly sought to buy not just the verdict but the court's judgment as well."



CONGRESSMAN MAURICE HINCHEY

Congressman Maurice Hinchey said that the internal Lilly data "should have been shared with the public"

David Graham, currently associate director in the FDA's Office of Drug Safety, criticised the analysis of post-marketing surveillance data submitted by Lilly to the FDA. After discovering that Lilly failed to obtain systematic assessments of violence and had excluded 76 of 97 cases of reported suicidality, Dr Graham concluded in a memo dated 11 September 1990 that "because of apparent large-scale underreporting, [Lilly's] analysis cannot be considered as proving that fluoxetine and violent behavior are unrelated."

An FDA advisory panel was convened in 1991 to review the fluoxetine data. It concluded that fluoxetine was safe despite the concerns raised by Dr Graham and others, leading critics to point out that several of the panellists had financial ties to Eli Lilly.

Dr Glenmullen said the missing documents obtained by the *BMJ* provide "the missing link" between the recent advisory issued by the FDA and what Lilly scientists knew 16 years ago.

Since the 1991 FDA hearings Dr Peter Breggin, who served as the medical expert in the Wesbecker case, has warned that the stimulant effects of fluoxetine can cause suicide and violence. He cautions that the 38% activation rate reported in the missing document is probably low because "it doesn't include other symptoms of activation such as panic attacks, hypomania, and mania."

Dr Kapit, the original reviewer for fluoxetine, told the *BMJ*, "If we have good evidence that we were misled and data were withheld then I would change my mind [about the safety of fluoxetine]. I do agree now that these stimulatory side effects, especially in regards to suicidal ideation and homicidal ideation, are worse than I thought at the time that I reviewed the drug."

Lilly declined to be interviewed but issued a written statement saying, "Prozac has helped to significantly improve millions of lives. It is one of the most studied drugs in the history of medicine, and has been prescribed for more than 50 million people worldwide. The safety and efficacy of Prozac is well studied, well documented, and well established." □