Did GSK trial data mask Paxil suicide risk?

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Jim Giles

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An inappropriate analysis of clinical trial data by researchers at GlaxoSmithKline obscured suicide risks associated with paroxetine, a profitable antidepressant, for 15 years, suggest court documents (897kb, requires Acrobat Reader) released last month. Not until 2006 did GSK alert people to raised suicide risks associated with the drug, marketed as Paxil and Seroxat.

An analysis of internal GSK memos and reports, which were released to US lawyers seeking damages, suggests that the company had trial data demonstrating an eightfold increase in suicide risk as early as 1989. Harvard University psychiatrist Joseph Glenmullen, who studied the papers for the lawyers, says it's "virtually impossible" that GSK simply misunderstood the data - a claim the company describes as "absolutely false".

Glenmullen's report rests on documents obtained by lawyers in Los Angeles, who are bringing around 30 cases against GSK linking suicides and suicide attempts to the use of Paxil. The report was under seal at a district court in Sacramento, California, until 18 January, when the judge agreed to make parts of it public.

Several pages from the report were withheld by the judge, but Chuck Grassely, a Republican senator for Iowa, wrote to GSK on 6 February asking that the missing sections be made public.

"With new questions about when GlaxoSmithKline knew about risks for suicidal behavior compared to when it let the public know about those risks, it seems like it'd be in the drug maker's best interest to provide every bit of information about this issue," said Grassely. "At this point, any sense that more information is being withheld only leads to more suspicion about what went on and what still might be going on. The public has a right to know what there is to know about this and other drugs."

The analysis focuses on the "washout" phase preceding a trial, when subjects stop taking most or all medications to avoid confusion with results from the trial itself. Because the washout occurs before patients randomly receive either the drug or the placebo control, adverse events during this time can't be attributable to the trial and so are seldom if ever included in final results.

However, GSK researchers submitting data on Paxil to the US Food and Drug Administration in the late 1980s and early 1990s included suicides and suicide attempts from the washout period in the results for the placebo arms of trials, but not from the Paxil arms. Glenmullen alleges that these extra "placebo" suicides negated suicides attributed to Paxil in the trials, making the drug appear safer than it really was. He says that if the washout results had been excluded, the data would have showed that Paxil increased eightfold the risk of suicidal behaviour in adults.

GSK spokeswoman Mary Anne Rhyne says inclusion of the washout data "was intended to present the full picture of events that occurred in all phases of the clinical trials - starting from the time patients

were enrolled, before they were randomised". She says that even without the washout data, Paxil still came out as safe as the placebo in this trial. She accused Glenmullen of incorrectly analysing the data to reach the opposite conclusion, but didn't respond to a request for numerical proof that Glenmullen's verdict was wrong.

Glenmullen suggests that the FDA would have acted differently had the use of the washout data been made more explicit. Rhyne says that material still under seal shows the FDA to be fully aware of how the washout data was being used. But Glenmullen quotes Martin Brecher, the FDA official who reviewed Paxil's safety, as agreeing during a pre-trial hearing that the use of the washout data was "scientifically illegitimate".

Independent researchers say it was wrong to use washout data as GSK did. "I can't imagine circumstances in which it would be appropriate," says Bruce Psaty of the University of Washington in Seattle.

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