ETHICS

Paxil study under fire

Trial researcher alleges paper exaggerated antidepressant benefits.

BY MEREDITH WADMAN

The contentious issue of drug-industry influence over medical-research writing erupted on the campus of the University of Pennsylvania in Philadelphia this week. A professor of psychiatry has alleged that several colleagues — including the chair of his department — allowed their names to be added to a manuscript while ceding control to the global pharmaceutical giant GlaxoSmithKline (GSK). The professor, Jay Amsterdam, also claims that the manuscript, written with an unacknowledged contractor paid by GSK, unduly promotes the company's antidepressant drug Paxil (paroxetine), the subject of the study.

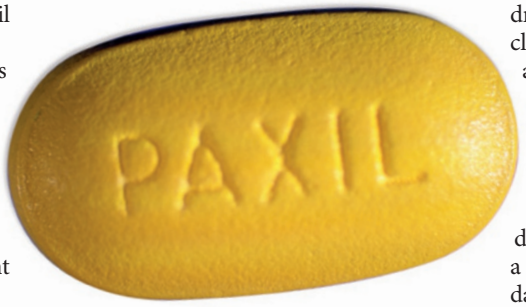
"The published manuscript was biased in its conclusions, made unsubstantiated efficacy claims and downplayed the adverse-event profile of Paxil," Amsterdam's lawyer wrote in an 8 July letter to the Office of Research Integrity (ORI), the body responsible for investigating research misconduct in US Public Health Service agencies and its grant recipients.

The letter accuses the study's academic authors of engaging in scientific misconduct by allowing their names to be attached to the manuscript (C. Nemeroff *et al. Am. J. Psychiatr.* **158,** 906–912; 2001), which has been cited more than 250 times. Documents accompanying Amsterdam's complaint are offered as evidence that "most if not all" of the authors were handpicked by GSK, working in conjunction with the medical-communications company Scientific Therapeutics Information (STI) in Springfield, New Jersey, to lend credibility to a result that Amsterdam says places Paxil in an overly favourable light. In one such document, Karl Rickels, a psychiatrist not involved with the study who looked at the issue for the department in 2001 said that "apparently … [academic] participants never had a chance to review or even just see the manuscript before it went to press".

"It has always been GSK's policy and practice for the primary author(s) to have final approval on manuscripts," the company says. "The proper use of medical writers serves a legitimate role in facilitating the timely analysis and presentation of clinical-trial data for public consideration."

Amsterdam had recruited patients for the trial but was not included as an author; he protested at the time to his boss, department chair Dwight Evans. Amsterdam was prompted to file his current complaint with the ORI after seeing allegations late last year that Evans had lent his name to an editorial (D. L. Evans and D. S. Charney *Biol. Psychiatr.* **54,** 177–180; 2003) written by an STI writer who was being paid by GSK (the payment was not acknowledged in the publication). At the time, the university decided that the allegation of ghostwriting was unfounded.

Amsterdam's charges could prove awkward for the president of the University of Pennsylvania, Amy Gutmann, who is also the chair of US President Barack Obama's bioethics commission. In an 11 July letter to Obama, the Project on Government Oversight (POGO), a watchdog group based in Washington DC that Amsterdam contacted while developing his complaint, called for Gutmann's ousting as chair. The letter takes issue with Gutmann's handling of the earlier ghostwriting allegations. "We do not understand how Dr. Gutmann can be a credible Chair of the Commission when she seems to ignore bioethical problems on her own campus," POGO's executive director, Danielle Brian, wrote.



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The university said on 11 July that its School of Medicine will investigate the new allegations. The school's policy, adopted last year, states that medical researchers "are prohibited from allowing their professional presentations of any kind, oral or written, to be ghostwritten by any party, including Industry". The published paper acknowledged that GSK funded the study, but did not note that STI had been employed in the manuscript's preparation, or that three of the co-authors were GSK employees while the study was being conducted. The GSK authors are not included in Amsterdam's complaint.

The five authors whom Amsterdam accuses are Evans, Charles Nemeroff, now chairman of psychiatry at the University of Miami in Florida; Laszlo Gyulai, a psychiatrist at the University of Pennsylvania who has now retired; Gary Sachs, a psychiatrist at Massachusetts General Hospital in Boston; and Charles Bowden, chairman of psychiatry at the University of Texas Health Science Center in San Antonio.

Evans and Gyulai did not respond to interview requests, but the university stated that "both Penn faculty members have been advised of the allegations in the complaint and while they believe them to be unfounded, have made clear to the University that they will fully cooperate with the investigation". Bowden says: "I provided input that was incorporated into the manuscript … I never had any sense that the manuscript was 'ghostwritten'."

Sachs says he strongly agrees and that he "went physically from Boston to Philadelphia to draft the first draft" with Gyulai. The multi-site clinical trial was conducted in the mid-1990s and funded by GSK (SmithKline Beecham when funding was initiated). It compared Paxil — marketed as Seroxat outside the United States — the firm's new antidepressant, with imipramine, an older, cheaper, antidepressant, and with placebo in treating depression in people with bipolar disorder — a condition with a high suicide risk. Amsterdam alleges that the study: didn't enrol enough patients to come to definitive conclusions; made specious distinctions between subsets of subjects that allowed it to claim a positive result for Paxil in some patients; and played down the side effects of the drug. Nemeroff, the paper's first author, says that the data used withstood rigorous peer review in a process that sent the paper back to the authors for revisions several times. "Right in the abstract under 'results' we report that 'Differences in overall efficacy among the three groups were not statistically significant'," he says. "I don't know how much more straightforward we can be than that."

He adds that "with a 2011 magnifying glass, obviously one would have included in the published paper the use of an editorial assistant". Still, he says: "All [STI] did was help collate all the different authors' comments and help with references. We wrote the paper."

Paul Root Wolpe, a bioethicist at Emory University in Atlanta, Georgia, who reported to Evans and collaborated with Amsterdam while on the faculty of psychiatry at the University of Pennsylvania, says that the documents imply but do not prove that the manuscript was ghostwritten. But, he says, they indicate "a troubling level of control of pharma over the academic product".

Wolpe adds: "This is not an isolated case, but a systemic problem that needs a coordinated, systemic solution." ■

GENETICS

How to build a better mouse

The Collaborative Cross project will boost diversity and help the hunt for disease genes.

BY EWEN CALLAWAY

It has taken nearly a century, but mouse geneticists are finally finishing the work started by Abbie Lathrop. The former schoolteacher from Massachusetts bred many of what became the first laboratory strains of mice in the early 1900s, yet her animals carried only a sliver of the genetic diversity found in wild mice. The hundreds of strains of laboratory mice used today still have a pretty narrow range of traits, which hampers the search for disease-causing genes.

Now, the Collaborative Cross, an ambitious project to create hundreds more mouse varieties representing a wider range of genetic diversity, is beginning to deliver its first animals. The new mouse strains have some very visible differences from one another — from variations in fur colour to tail length — and are already yielding clues to genes that help fend off fungal infection, which might not have been easily uncovered with standard lab strains[1–3].

Many classic laboratory strains, such as C57BL/6 — the first mouse to have its genome sequenced — owe much of their genetic make-up to the same handful of ancestors. These strains differ from each other in certain ways, such as the ability to battle infection, but not nearly as much as do wild mice. Huge chunks of the genomes of these strains are essentially identical, making it difficult and time-consuming to link particular traits to single genes within these genetic blind spots.

"Everyone realized there's a truckload of variation that we aren't seeing at all," says Richard Mott, a statistical geneticist at the University of Oxford, UK, who is involved in the project.

Begun at the US Department of Energy's Oak Ridge National Laboratory in 2005, the Collaborative Cross project selected five classic inbred strains, along with three more recently developed wild-derived strains, and began to breed them and their offspring together to reshuffle their genes.

To create genetically uniform inbred strains, brothers and sisters were mated for many generations. So far, the Collaborative Cross has established about 30 fully inbred mouse lines, says Gary Churchill, a mouse geneticist at the Jackson Laboratory in Bar Harbor, Maine, one of the researchers who conceived the project.

The mice are already beginning to pay dividends. Fuad Iraqi, a geneticist participating in the Collaborative Cross at Tel Aviv University, Israel, tested 66 nearly inbred strains for their susceptibility to infection by *Aspergillus fumigatus*, a soil fungus that causes a respiratory disease in humans.

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Mouse strains with greater genetic differences are ready to enter the lab.

Depending on the strain, the mice survived between 4 and 28 days after infection. On the basis of genotype information for the new strains and the genome sequences of the eight founder strains, Iraqi's team mapped these differences in survival time to just a handful of genomic regions, containing a small number of genes[3]. Future studies in 'knockout' mice lacking these genes should pin down exactly which ones are responsible for fungal resistance, Iraqi says.

Getting to this point with the Collaborative Cross mice took only a year, compared with the decade and a half Iraqi estimates it would have taken with the classic strains. "It is amazing," he says. His team is taking the same approach to map genes involved in defence against the bacterium *Klebsiella pneumoniae* and other traits.

"I don't think results are going to trickle out, they're going to be bursting," Churchill says.

Rudolph Balling, director of the Luxembourg Centre for Systems Biomedicine, believes that the Collaborative Cross mice will become even more valuable when researchers start pooling their knowledge so that they can draw connections between seemingly distinct traits that have common genetic origins. "There has to be integrated database. That's the key to the whole thing," Balling says.

Steve Brown, director of the Mammalian Genetics Unit at MRC Harwell, UK, says the Collaborative Cross will mesh well with another project — the International Knockout Mouse Consortium — to create thousands of knockout strains collectively lacking nearly every mouse gene (see *Nature* **474,** 262–263; 2011). For instance, a gene knockout that affects a mouse's sensitivity to diabetes could be linked to other traits of the syndrome, such as altered glucose metabolism, through the Collaborative Cross.

No database exists to help scientists forge such connections at present, and there is little capacity to shuttle hundreds of different mouse strains all over the world. So those involved with the Collaborative Cross are working with the University of North Carolina in Chapel Hill to colonize the world's labs with the new mice. They plan to send out breeding pairs of the first strains by the end of this year, with up to 100 strains available by 2012. "The idea is to make these available as broadly as possible," Churchill says. ■

1. Aylor, I. *et al. Genome Res.* http://dx.doi.org/10.1101/gr.111310.110 (2011).
2. Philip, V. *et al. Genome Res.* http://dx.doi.org/10.1101//gr.113886.110 (2011).
3. Durrant, C. *et al. Genome Res.* http://dx.doi.org/10.1101/gr.118786.110 (2011).

CORRECTION

The News story 'Paxil study under fire' (*Nature* **475,** 153; 2011) gave the wrong affiliation for Charles Bowden. He is a clinical professor of psychiatry and pharmacology at the University of Texas Health Science Center, San Antonio.