

FEATURE



RESEARCH CONDUCT

No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility

As a new data analysis adds weight to calls for retraction of a paper on paroxetine in adolescents, **Peter Doshi** examines the resistance to action of a professional society, its journal, and an Ivy League university

Peter Doshi *associate editor, The BMJ*

A major reanalysis just published in *The BMJ* of tens of thousands of pages of original trial documents from GlaxoSmithKline's infamous Study 329, has concluded that the antidepressant paroxetine is neither safe nor effective in adolescents with depression.¹ This conclusion, drawn by independent researchers, is in direct contrast to that of the trial's original journal publication in 2001, which had proclaimed paroxetine "generally well tolerated and effective."² The new paper, published under the restoring invisible and abandoned trials (RIAT) initiative,³ has reignited calls for retraction of the original study, putting additional pressure on academic and professional institutions to publicly address the many allegations of wrongdoing.

Troubled from the start

Few studies have sustained as much criticism as Study 329, a placebo controlled, randomized trial of paroxetine and imipramine carried out by SmithKline Beecham (which became GlaxoSmithKline (GSK) in 2000). In 2002, a US Food and Drug Administration officer who formally reviewed the trial reported that "on balance, this trial should be considered as a failed trial, in that neither active treatment group showed superiority over placebo by a statistically significant margin."⁴ Yet this same year, according to the New York State Attorney General's office, which sued GSK, over two million prescriptions were written for children and adolescents in the United States, all off-label, after a marketing campaign that characterized Study 329 as demonstrating "REMARKABLE Efficacy and Safety."

The disparity between what the manufacturer and study authors claim the trial found and what other parties say the data show was an important element in the US Department of Justice's criminal charges against GSK. In 2012, GSK was fined a record \$3bn (£2bn; €2.7bn), in part for fraudulently promoting paroxetine.

Then there are the matters of "editorial assistance" and undisclosed financial conflicts of interests of one of the paper's authors. The first draft of the manuscript ultimately published in the *Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP)* was not written by any of the 22 named authors but by an outside medical writer hired by GSK. And the paper's lead author—Brown University's chief of psychiatry, Martin Keller—had been the focus of a front page investigation in the *Boston Globe* in 1999 that documented his under-reporting of financial ties to drug companies. Senator Charles Grassley, who led a congressional investigation and published a report on ghostwriting in the medical literature, reportedly wrote to Brown University about Keller.

It is often said that science self corrects. But for those who have been calling for a retraction of the Keller paper for many years, the system has failed. None of the paper's 22 mostly academic university authors, nor the journal's editors, nor the academic and professional institutions they belong to, have intervened to correct the record. The paper remains without so much as an erratum, and none of its authors—many of whom are educators and prominent members of their respective professional societies—have been disciplined. This propelled University of Adelaide child psychiatrist Jon Jureidini, who led the reanalysis team, and his colleagues into action. "The RIAT initiative offered us a chance to report Study 329 ourselves, so as to correct the record, and perhaps finally embarrass the authors, institutions and the journal into taking the actions they have so far resisted."

Journal's response

Disputes in science are often put down to differences of opinion. But in the case of Study 329 no epistemological acrobatics would seem able to reconcile the differences between the 2001 *JAACAP* paper and the RIAT republication. They cannot both

be right. Take, for example, the straightforward issue of reporting the trial's primary outcome. In the *JAACAP* paper, Keller and colleagues describe "response" as a "primary outcome measure" and says it "separated statistically from placebo." But according to the RIAT team, the effect of paroxetine was not significantly different from placebo for any prespecified primary or secondary outcome measure.

Such stark differences between the original paper and the rewrite are bound to put particular pressure on Andrés Martin, Yale University professor and current editor in chief of *JAACAP*. Martin has been under pressure to retract the paper for years, including from within his own society.

Last October, Martin was compelled to address the academy's assembly about Study 329. According to the minutes, members heard how Martin had investigated the matter thoroughly by consultation with the authors, the Committee on Publication Ethics (COPE), clinical experts, "a whole range of attorneys, and more." Martin's assessment, completed in July 2010, concluded that no further action was necessary. A follow-up inquiry, again by Martin, in 2012, after GSK was fined \$3bn, similarly concluded "no basis found for editorial action against the article."

No specific findings from Martin's investigation are recorded in the minutes, and Martin did not respond to multiple requests for comment from *The BMJ*.

Ivan Oransky, cofounder of the Retraction Watch blog, says that transparency is vital. "GSK agreed to pay a \$3bn fine and you're [Martin] saying you had completely different results? Great. Show me."

Oransky described Martin's silence as part of the "typical scientific playbook." "It has certainly been our experience that journals and researchers and institutions can be incredibly stubborn about failing to retract a paper, about ignoring calls, or not responding favourably to calls to retract."

The academy

It has proved no easier to get the professional society to talk. Several of the authors of the *JAACAP* paper are members of the American Academy of Child and Adolescent Psychiatry (AACAP). *The BMJ* sent four requests for comment to the academy's president, Paramjit Joshi, and past president Martin Drell, but received no response.

Others have had better luck. In 2012, Mickey Nardo, a retired psychiatrist who subsequently joined the RIAT team, wrote to the AACAP ethics committee with a plea to retract the Keller paper. "It's the right thing to do and a right time to do it."

"The letter was received warmly by the president of the AACAP, the president elect, and the chair of the ethics committee, who assigned a member of the committee to work with me . . . We had several amicable exchanges," Nardo later commented in his blog.⁵ Then, silence.

Behind the scenes, Nardo's letter had impact. Minutes of an AACAP Council teleconference obtained by *The BMJ* confirm that the topic was formally discussed in a call that included *JAACAP*'s editor in chief. Martin said, "that while the [Keller et al] article is not perfect, the ethical concerns raised by the GSK lawsuit are not substantiated," according to the minutes. Furthermore, the journal editors "believe that there is little to gain in responding and that doing so would simply 'fuel the fire.'" The agenda item ends: "Action: if council members receive any inquiries about Study 329, please direct these to Andrés Martin."

What does not appear in the minutes is any mention of AACAP's ethics committee and its role in handling complaints about members. "The AACAP leadership has asked us to defer any comments representing the organization on this matter to them so we have forwarded your request to the current president and CEO," AACAP ethics committee cochairs, Arden Dingle and Gail Edelson, told *The BMJ* in an email. They added that their committee has never had an "investigatory role" within the academy, leaving unclear how—and indeed if—the academy investigates allegations of misconduct against its members.

The AACAP ethics committee's lack of an investigatory role seems to be unusual. Related professional organizations, including the American Psychiatric Organization, American Psychological Association, and the American Psychoanalytic Association all have ethics committees charged with responding to allegations of ethical misconduct within their respective societies.

Discontent within the academy

The refusal of AACAP's leadership to call for retraction of the Keller paper has become a rallying point for some in the academy who view Study 329 as symbolic of fundamental ethical problems within the profession. One regional chapter, the Northern California Regional Organization of Child and Adolescent Psychiatry (NCROCAP), features the Study 329 story on its homepage.

Ed Levin, a Bay Area based child psychiatrist who has held many offices in the chapter, including that of president, has led the charge. Warning for more than two years that a RIAT rewrite of Study 329 could be expected, he has urged the academy leadership to take action on Study 329 and to review its policies on relationships with the drug industry. Financial reports that AACAP makes available show the organization has received between \$500 000 and \$1m from the drug industry each year since 2003, roughly 5-20% of its annual revenue.^{6,7}

But after successfully bringing the topic to the national agenda at last October's annual meeting, Levin describes an "increasing defensiveness of the leadership." He and former NCROCAP president George Stewart increasingly think that going public may be the only route forward. As an example, Levin says the academy began advance screening of emails to be submitted to the assembly listserv. Following that, the chair of the assembly "would not allow me to post on the assembly listserv my thoughts about how s329 was handled at the last assembly meeting." And he added, "AACAP leadership also set up first time ever rules controlling communication between different regional organizations—just after we requested, and were denied, the email addresses of the presidents of the other ROs."

Distress over Study 329 has caused at least one person to resign from the academy. Mary Olowin, former president, secretary and treasurer of the Northern California regional group, told *The BMJ* that she first withheld her academy dues in 2014.

"When the journal did not retract the article and AACAP leadership did not press for the editor to do this by the time the annual meeting ended in October, I sent in a letter of resignation, explaining why I was leaving." The academy did not acknowledge her letter.

"We're not out here to destroy the academy; we're trying to protect it before it hits the mainstream media because it's going to make us look like fools," Levin said.

One topic the media may soon pick up on is that the incoming president elect of AACAP, Karen Wagner, is a coauthor of the *JAACAP* paper. Wagner, a psychiatrist at the University of

Texas, is also named eight times in the 2011 US Department of Justice complaint against GSK. According to the complaint, Wagner promoted paroxetine at a 1999 GSK sales force event. A GSK newsletter cited in the complaint quotes Wagner as telling the sales force that major depression was “a lethal disorder and it requires treatment.” Based on the results of Study 329, which were at the time still unpublished, “Dr Wagner said: ‘We can say that paroxetine has both efficacy and safety data for treating depression in adolescents.’”

The newsletter also states that the “clinical study demonstrating the success of Paxil in treating depression among adolescents will be published in a peer reviewed journal during first quarter 2000.” The manuscript, however, was rejected by *JAMA* in late 1999 before *JAACAP* ultimately published it in 2001.⁸

Wagner did not respond to *The BMJ*'s requests for comment.

University keeps silent

It's often argued that fairness in journalism requires getting “both sides” of the story, but in the story of Study 329, the “other side” does not seem interested in talking.

“I would caution you not to confuse the University's policy of confidentiality with inactivity,” wrote Edward Wing, former Brown University dean of medicine and biological sciences. Wing was responding to Jureidini, who had written to the university's president, Ruth Simmons, requesting retraction of the Keller paper.

Simmons gained national attention as the first African American president of an Ivy League university and had appointed a steering committee to examine how the school benefited from slavery in the 18th century. But on Study 329, the university did not take such a transparent course of action.

“The University takes seriously any questions about the soundness of faculty-conducted research. While we cannot comment on individual personnel cases, we do take appropriate actions whenever we receive substantive concerns about the conduct of research. The University gathers relevant information, conducts internal reviews if appropriate, and makes any adjustments or corrections that may be warranted,” read Wing's letter to Jureidini in late 2011.

The BMJ has been unable to determine whether Brown ever investigated the university's or faculty's involvement in Study 329.

Mark Nickel, interim director of the news and communications office, said that such matters are considered confidential. “I'm not confirming or denying anything regarding what the university may or may not have done.”

David Savitz, Brown's vice president for research, said: “I appreciate your interest, but having been in my position for only the last 1.5 years, I have no personal insights into this case. While there are issues in what can be disclosed, in my case there is simply the absence of knowledge of the case other than through the media.” Savitz is the integrity officer for the university, and in this role helps assess allegations of research misconduct at Brown. However, he explained that “these matters have to be handled with complete confidentiality regarding particular allegations and individuals.” The university also said it does not report aggregate data regarding how many such allegations it investigates or their outcome.

Roy Poses, president of the Foundation for Integrity and Responsibility in Medicine and clinical associate professor of medicine at Brown, says he has never heard of a formal investigation of Keller or Study 329. “There were claims that

some person or persons in the Brown administration had looked into the cases, but not in a formal way, in particular not using an open process, and I don't believe any formal results of any such investigation were ever made public.”

“The big story is that there was no story. There was no formal investigation, no hearing, no faculty forum, no real public discussion,” says Poses.

“I don't understand how Brown has gotten away with what it's doing. It has essentially decided to ignore the whole thing,” says Paul Thacker, a journalist that investigated Study 329 and Brown as part of his work as a former congressional staffer for Senator Grassley. “The only real investigation we've had on the Brown University campus on this drug has been by the *Brown Daily Herald*,” he said, referring to the student newspaper. The Herald has run at least six stories since 2008 that probe Study 329, Keller's relationship with the pharmaceutical industry, and Senator Grassley's investigations into conflicts of interest in clinical research.

“I think this is the most thoroughly examined case study of research misconduct in the 2000s, and I don't know how it has not been retracted yet,” Thacker told *The BMJ*. “Why would you send your kid to Brown University and pay all that tuition when the only people who seem to know what's right are the kids on campus?”

Retraction Watch's Oransky says he is not surprised by Brown's silence. “Universities have become more corporate than many corporations.”

Oransky argues that institutions like Brown should confront the problem. Instead of silence, the message from Brown should be: “There is fraud in science; it's pretty rare, but here is what we're doing to get rid of it because we're upset about it.”

“The controversy will not end if they simply stop talking about it. If anything, it will get worse.”

Competing interests: I have read and understood BMJ policy on declaration of interests and declare I am the first author of the RIAT declaration, which was coauthored by David Healy, who is part of the group that reanalysed Study 329. I served as a formal peer reviewer for the reanalysis manuscript and provided the Jureidini team with unpaid advice on the RIAT process before the paper was submitted and while it was under review. I am also a graduate of Brown University and member of a Cochrane review of neuraminidase inhibitors that is based in part on clinical study reports provided by GSK for zanamivir. I initiated an inquiry in 2012 that resulted in additional information from clinical study reports of Study 329 and eight other studies being posted on GSK's website.

Provenance: Commissioned, not externally reviewed.

- 1 Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015;351:h4320.
- 2 Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 2001;40:762-72.
- 3 Doshi P, Dickersin K, Healy D, Vedula SS, Jefferson T. Restoring invisible and abandoned trials: a call for people to publish the findings. *BMJ* 2013;346:f2865.
- 4 FDA. Clinical review: paroxetine. www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM371260.pdf.
- 5 Simply fuel the fire, 6 April 2014. <http://1boringoldman.com/index.php/2014/04/06/45376/>.
- 6 American Academy of Child and Adolescent Psychiatry. Treasurer's report. 2014. www.aacap.org/App_Themes/AACAP/docs/about_us/transparency_portal/financial_reports/aacap_treasurers_report_201404.pdf.
- 7 American Academy of Child and Adolescent Psychiatry. Treasurer's report. 2012. www.aacap.org/App_Themes/AACAP/docs/about_us/transparency_portal/financial_reports/aacap_treasurers_report_201212.pdf.
- 8 Jureidini J. Paxil Study 329: paroxetine vs imipramine vs placebo in adolescents. 2010. www.healthyskepticism.org/global/news/int/hsin2010-01/.

Cite this as: *BMJ* 2015;351:h4629

© BMJ Publishing Group Ltd 2015