

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

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 address publicly the many allegations of wrongdoing.

Troubled from the start

Few studies have sustained as much criticism as Study 329, a placebo controlled, randomised trial of paroxetine and imipramine carried out by SmithKline Beecham (which became GlaxoSmithKline (GSK) in 2000). In 2002, a US Food and Drug Administra-

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tion 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 characterised 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 ghost-writing 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

SHORT HISTORY OF PAROXETINE AND STUDY 329

1992 >>>

FDA approves paroxetine for adults with depression



1994–1998 >>>

SmithKline Beecham conducts Study 329, a randomised placebo controlled trial of paroxetine in 275 adolescents with depression



2001 >>>

Keller and colleagues publish Study 329 in the *Journal of the American Academy of Child and Adolescent Psychiatry*. Authors conclude that "paroxetine is generally well tolerated and effective"

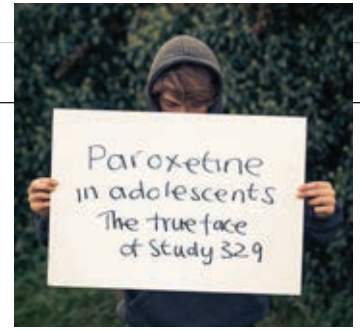


2002 >>>

FDA states that Study 329 "should be considered as a failed trial." This year, over two million paroxetine prescriptions are written "off-label" for US children and adolescents. A *Panorama* investigation takes a critical look at Seroxat use in the UK

2003 >>>

UK Committee on Safety of Medicines recommends that paroxetine not be used in children and adolescents with depression, citing concerns of increased risk of self harm and potentially suicidal behaviour



WHAT YOU NEED TO KNOW

- The widely used antidepressant paroxetine is neither safe nor effective for adolescents with depression, according to a reanalysis of GSK data just published in *The BMJ* (p 11)
- The influential original report of the study, published in 2001 in the *Journal of the American Academy of Child and Adolescent Psychiatry*, portrayed paroxetine as “generally well tolerated and effective” in adolescents with depression
- Despite subsequent FDA and MHRA warnings about increased risks of suicidal thinking and behaviour and GSK receiving a record fine, partly for illegal off-label promotion of the drug, the original report has not been retracted or even had a correction
- Academic and professional institutions have failed to publicly address the many allegations of wrongdoing
- None of the named authors has intervened to correct the record. An internal inquiry by JAACAP in 2010 concluded that no further action was necessary
- Brown University remains silent over its involvement in the study. It refuses even to confirm or deny whether any investigation took place

its authors—many of whom are educators and prominent members of their respective professional societies—has 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.”

“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

2004 >>>

FDA places black box warning, its most serious warning, on all antidepressants, stating that they increase the risk of suicidal thinking and suicidal behaviour in these age groups

2012 >>>

GlaxoSmithKline agrees to pay £2bn in largest ever US healthcare fraud settlement, partly for fraudulently promoting paroxetine



2013 >>>

April-May: Jon Jureidini (right) writes to GSK requesting help in getting Keller and colleagues’ paper retracted; GSK responds that “GSK does not agree that the article is false, fraudulent or misleading”

June: *The BMJ* publishes the restoring abandoned and invisible trials (RIAT) declaration; GSK expresses its support for RIAT, stating that “by making the clinical study reports available we are very happy for others to publish on the records if they wish to and if journals consider the work to be of scientific merit”

July: Jureidini announces his team’s intent to republish Study 329 in accordance with the RIAT initiative



2015 >>>

The BMJ publishes RIAT reanalysis of Study 329. The seven restorative authors conclude: “Neither paroxetine nor high dose imipramine showed efficacy for major depression in adolescents, and there was an increase in harms with both drugs”

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."

Unusually the society's ethics committee has no investigating role, leaving it unclear how—and indeed if—the academy investigates allegations of misconduct against its members.

Related professional organisations, 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.

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 that a RIAT rewrite of Study 329 could be expected, he has urged the academy leadership to take action and to review its policies on relationships with the drug industry. Financial reports that AACAP makes available show the organisation 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

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"increasing defensiveness of the leadership." 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."

"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.

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," 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.

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.

"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 who 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.

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

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

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