Conflicted Medical Journals and the Failure of Trust

Jon N. Jureidini, Ph.D., M.B., and Leemon B. McHenry, Ph.D.

1Discipline of Psychiatry, University of Adelaide, Adelaide, South Australia
2Department of Philosophy, California State University, Northridge, California, USA

Journals are failing in their obligation to ensure that research is fairly represented to their readers, and must act decisively to retract fraudulent publications. Recent case reports have exposed how marketing objectives usurped scientific testing and compromised the credibility of academic medicine. But scant attention has been given to the role that journals play in this process, especially when evidence of research fraud fails to elicit corrective measures. Our experience with The Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP) illustrates the nature of the problem. The now-infamous Study 329 of paroxetine in adolescent depression was negative for efficacy on all eight protocol-specified outcomes and positive for harm, but JAACAP published a report of this study that concluded that “paroxetine is generally well tolerated and effective for major depression in adolescents.” The journal’s editors not only failed to exercise critical judgment in accepting the article, but when shown evidence that the article misrepresented the science, refused either to convey this information to the medical community or to retract the article.

Keywords: clinical trials, conflict of interest, consumer fraud lawsuits, ghostwriting, GlaxoSmithKline, Journal of the American Academy of Child and Adolescent Psychiatry, medical journals, paroxetine (Paxil, Seroxat), retraction, scientific misconduct, Scientific Therapeutics Information, SmithKline Beecham

INTRODUCTION

Evidence about medicines will be reliable only if the sponsor company and investigators design, conduct, and report the results of clinical trials with integrity. Many have expressed skepticism about a system that allows industry to test its own products (Angell, 2005). Recent case reports about rofecoxib, rosiglitazone, and gabapentin have exposed how marketing objectives usurped scientific testing and compromised the credibility of academic medicine (Ross et al., 2008; Nissen, 2010; Steinman, 2006). But scant attention has been given to the role that journals play in this process, especially when evidence
of research fraud fails to elicit corrective measures. When editors refuse to acknowledge incontrovertible evidence of scientific misconduct postpublication and refuse to retract the publication in question, they jeopardize their scientific standing and moral responsibility to prescribers and patients. Retraction has occurred (Wakefield et al., 2010), but there is a worrying disconnect between the strong statements made by present and former editors of major journals and the behavior of many current editors (DeAngelis, 2006; Angell, 2005; Smith, 2006). Our experience with The Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP) illustrates the nature of the problem.

Information in the case discussed below is based largely on our review of over 10,000 confidential documents in litigation against SmithKline Beecham (SKB) (now GlaxoSmithKline, GSK), of which selected documents identified for de-designation were released by GSK to the public after plaintiffs’ attorneys at the law firm of Baum, Hedlund, Aristei & Goldman challenged their confidential status. A subset of these unsealed documents is posted on the Healthy Skepticism Web site and is available at http://www.healthyskepticism.org/global/news/int/hsin2010-01. Both authors attest that no document in the litigation against GSK contradicts any of our account below.

**PUBLICATION OF GSK’S STUDY 329**

We have previously shown that the now-infamous Study 329 of paroxetine (and imipramine) in adolescent major depression was negative for efficacy on all eight protocol-specified outcomes and positive for harm (Jureidini et al., 2008). We outlined in detail how the published article (Keller et al., 2001) incorrectly represented the outcomes of the study. Briefly, the Study 329 protocol specifies two primary and six secondary outcome measures, and all eight proved negative (SKB, 1996). The published article incorrectly represented one of the primary outcomes, and deleted all six pre-specified secondary outcomes, replacing them with more favorable measures. This provided the means to claim falsely the statistically significant superiority for paroxetine over placebo on one primary and three secondary measures. Examination of SKB’s final report reveals that at least eight adolescents in the paroxetine group had self-harmed or reported emergent suicidal ideas compared to only one in the placebo group (SKB, 1998a). The report of this study published in JAACAP concluded that “paroxetine is generally well tolerated and effective for major depression in adolescents” (Keller et al., 2001).

An internal SKB document showed that the company was aware that their adolescent depression trials failed to demonstrate superiority of paroxetine over placebo. This “position piece on Phase III clinical studies” reads: “It would
be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.” It appears, therefore, that SKB’s strategy was to report selective data from Study 329 in conference posters and in the JAACAP publication “to effectively manage the dissemination of these data in order to minimise any potential negative commercial impact” (SKB, 1998b; see also, Kondro and Sibbald, 2004).

The ghost-written article ultimately attributed to Keller and his twenty-one co-authors began life as a manuscript prepared by medical communications company, Scientific Therapeutics Information (STI), for SKB (McHenry and Jureidini, 2008). According to the STI contract and related documents, the first draft was written by STI employee Sally Laden rather than any of the named authors. The documents reviewed demonstrate to us that SKB maintained tight control of the article’s content throughout its development. STI managed the submission process to the Journal of the American Medical Association (JAMA), who rejected the manuscript. STI then modified it, and facilitated its submission to JAACAP. JAACAP’s editorial process missed the fact that the article significantly misrepresented primary outcomes and adverse events. However, their peer-reviewers did note that “Results do not clearly indicate efficacy for Paroxetine” and questioned the potential for the article to misdirect practice, asking, “Given the high placebo rate, are SSRIs an acceptable first-line therapy for depressed teenagers?” (SKB, 2000). Nevertheless, JAACAP accepted the article, and it became the basis of SKB’s aggressive marketing strategy. It was prominently cited by key opinion leaders delivering presentations at psychiatric conferences, in Med Query Letters distributed to doctors, and in an SKB-sponsored Continuing Medical Education program called “The Hidden Diagnosis” (STI, 2002). Reprints were attached to a memo sent to sales representatives selling Paxil, encouraging them to use the paper to promote Paxil’s “REMARKABLE Efficacy and Safety in the treatment of adolescent depression” (SKB, 2001).

The Keller et al. article became one of the most cited in the medical literature in support of (off-label) antidepressant therapy in children and adolescents. By June 2010, at least 184 articles made reference to efficacy in Keller et al. These citations have perpetuated false claims about the efficacy and safety of paroxetine for adolescent depression right up to the present. Seventy-five articles (40%) reproduced false claims about outcome from Keller et al. Another 63 articles (34%) implied that Study 329 was positive (Jureidini and Jureidini, 2010).

CONCERNS ABOUT STUDY 329 IN THE PUBLIC DOMAIN

Consumer fraud lawsuits, including The People of the State of New York vs. SmithKline Beecham Corp. (Case No. 04-CV-5304 MGC), Beverly Smith vs.
SmithKline Beecham Corp. (Case No. 04 CC 00590), Engh vs. SmithKline Beecham Corp. (Case No. PI 04-012879), Teri Hoormann vs. SmithKline Beecham Corp. (Case No. 04-L-715), and Julie Goldenberg and Universal Care vs. SmithKline Beecham Corp. (Case No. 04 CC 00653), alleged that SKB had withheld and concealed results of clinical trials showing paroxetine ineffective and unsafe for adolescent depression and promoted paroxetine off-label. These lawsuits brought to light thousands of internal industry documents that provided the opportunity to investigate the interactions between industry, the “authors” named on the Keller et al. article, the ghost-writer (STI), and JAACAP. In a settlement with the State of New York, GSK was forced to post all results of clinical trials online. Other consumer case settlements resulted in GSK paying over $U.S. 100 million, and refunding parents and third-party payors (such as insurance companies) for pediatric paroxetine prescriptions. Additionally, numerous cases involving paroxetine in child and adolescent suicides and suicide attempts were settled. The results of the consumer fraud lawsuits were reported in major media such as The New York Times, The Los Angeles Times, The Washington Post, and The Chicago Tribune.

Study 329 became the focus of a British Broadcasting Corporation (BBC) Panorama Programme “The Secrets of the Drug Trials” in 2007, in which JAACAP’s editor, Dr. Mina Dulcan, was interviewed. Additionally, a book published about Study 329, Alison Bass’s Side Effects, was prominently reviewed by major medical journals and newspapers (Bass, 2008). This included among others The New England Journal of Medicine, The Boston Globe, and the New York Review of Books (Friedman, 2008; Leddy, 2008; Angell, 2009). Most of this information could have been expected to come to the attention of JAACAP’s editors.

DRAWING JAACAP’S ATTENTION TO CONCERNS ABOUT THE KELLER ET AL. ARTICLE

When they received the article, JAACAP’s editors had no way of knowing about many of the deceptions about authorship and content. Some problems, we believe, should have been apparent. Based only on information available in the published article, a letter published in JAACAP pointed out the misrepresentation of adverse outcomes (Parsons, 2002). At around the same time, Jureidini (with Tonkin) wrote to JAACAP pointing out that, in our opinion, there was misleading reporting in the Keller et al. article, and explicitly questioning editorial scrutiny (Jureidini and Tonkin, 2003). Editor Dulcan, who had accepted the Keller et al. article, published the letter with a response from the authors but did not publish any response to our criticisms of editorial accountability.

At the time when the Keller et al. article was published, JAACAP had in place conflict of interest and authorship policies. The January 2000 issue contained the following statement:
Base authorship credit only on substantial contributions to (a) conception and design or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and (c) final approval of the version to be published . . . Each author is required to have participated sufficiently in the work to take public responsibility for the content. (JAACAP, 2000)

In our opinion, the article violated this policy. JAACAP previously stated that it endorsed the position of the International Committee of Medical Journal Editors (ICMJE) on Conflict of Interest, but this statement has recently disappeared from their Web site. Regarding scientific misconduct and breach of publication ethics, the JAACAP Web site now states:

Scientific misconduct includes fabrication, falsification, and plagiarism with the intent to deceive by the authors. Honest error or differences in interpretation are not considered misconduct. Breaches of publication ethics include: failure to reveal financial conflicts of interest; omitting a deserving author or adding a non-contributing author. (JAACAP, 2010)

In 2005, McHenry e-mailed Dulcan and the managing editor, Ms. Sherri Willoughby, to alert them that we were concerned the Keller et al. article violated their journal policy. Dulcan replied that: “Unless there is a specific accusation of research fraud, it is not the role of scientific journals to police authorship” (Dulcan, 2005).

FACTS POINTING TO RESEARCH FRAUD COMMUNICATED TO JAACAP

By the time criticism had been published about the manner in which the Keller et al. article misrepresented Study 329, Dulcan was no longer editor of the journal. We wrote to the new editor, Dr. Andrés Martin, in December 2009, to bring just such a specific accusation of research fraud, as Dulcan had required, and to request retraction of the article. We enclosed three publications in which we spelled out the extent of misconduct in Study 329 (Jureidini et al., 2008; McHenry and Jureidini, 2008; Jureidini and McHenry, 2009), and our letter listed the following, which, as we viewed the evidence, violated JAACAP policy:

1. Failure to disclose financial conflict of interests of “authors”;
2. GSK concealed commercially damaging data via the medical communication company, STI, and the “authors” (as had been its stated intention since at least 1998, see SKB, 1998b);
3. Fabrication (creation of a strong false impression that one primary outcome measure, response, was positive by deliberately confusing it with another measure, remission);
4. Falsification (post hoc changes to secondary outcome measures and misrepresentation of serious adverse events);

5. Plagiarism (submitting a ghostwritten manuscript).

That the authors of the Keller et al. article failed to disclose conflict of interest by JAACAP policy alone is clear. Several authors did not disclose membership on SKB's advisory board and speaker's bureau, the true role of the ghostwriter and STI in the production of the manuscript was concealed, and the article included a substantial number of non-contributing “honorary” authors among the 22 listed on the article. But this alone does not constitute sufficient reason for a journal retraction. The more serious charge of scientific misconduct justifying retraction concerns the manner in which the publication misrepresented the data in order to conclude “Paroxetine is generally well tolerated and effective for major depression in adolescents” (Keller et al., 2001).

Martin did not respond to our December 2009 letter. We then submitted a 300 word letter to the editor to make public our request for retraction. It took JAACAP’s editors five months to reject our submission; in July 2010, Martin wrote to us that the peer review process in assessing the Keller et al. article “conformed to best publication practices prevailing at the time” (Martin, 2010). He acknowledged a responsibility “as part of our duty to readers and the wider community” to “reconsider previously published papers that have been subsequently found to contain scientific errors in their data” but stated: “We have found no evidence for such errors nor any justification for retraction according to current editorial standards and scientific publication guidelines. We therefore will not proceed further with your request” (Martin, 2010). It may be that some of the issues we raised did not violate JAACAP rules as they applied in 2001, but, as we demonstrated above, the Keller et al. article did violate JAACAP authorship policy at that time. Moreover, we fail to understand how Martin concluded that the Keller et al. article did not contain scientific errors.

CONCLUSION

Journals like JAACAP promulgate ideals of scientific rigor and ethical integrity at odds with the reality of the journal’s editorial decisions and failure to acknowledge scientific misrepresentation when it is brought to their attention (Martin et al., 2008). JAACAP was the most important instrument through which the results of Study 329 were misrepresented to physicians. The journal’s editors not only failed to exercise critical judgment in accepting the article, but when shown that the article, in fact, had misrepresented the science, refused either to convey this information to the medical community or to retract the article.
The case of Study 329 leads us to ask how many industry-sponsored publications of clinical research are equally flawed. It is unclear to what extent one can extrapolate from Study 329 since relatively few industry-sponsored clinical trials have been exposed to this level of legal scrutiny. Given, however, the vast operations of “publication planning” conducted by pharmaceutical marketing, there is little doubt about the degree to which industry-sponsored research is suspect (McHenry, 2010). The general problem of conflict of interest rendering the content of journals untrustworthy will not be resolved as long as industry is permitted to spin its data in journals. As we have seen in the case of Study 329, the problem is then compounded when the journal editors are either unable or unwilling to police the journal’s content. We see no alternative than to endorse Richard Smith’s proposal that publication of industry trials should be banished from the journals. Pharmaceutical companies should be obliged to post results of their trials on Web sites, leaving journals to independently and critically examine the raw data and conclusions. In this manner, journals will no longer be subject to the complaint that they have become little more than the marketing arm of the pharmaceutical industry (Smith, 2005).

**Chronology**

1998 Wilson memo re: SKB publication strategy
1999 Keller et al. manuscript rejected by *JAMA*
2001 Keller et al. published by *JAACAP*
2002 Parsons letter published by *JAACAP*
2003 Jureidini/Tonkin letter published by *JAACAP*
2004 *People of New York vs. SmithKline Beecham*
2005 *Beverly Smith vs. SmithKline Beecham*
2005 McHenry contacts editor *JAACAP*, Dulcan
2007 Jureidini/McHenry article on Study 329 rejected by AACAP Conference
2007 BBC Panorama Programme: The Secrets of the Drug Trials
2008 Jureidini et al. article on Study 329 selective reporting published in *International Journal of Risk and Safety in Medicine*
2008 McHenry/Jureidini article on Study 329 ghostwriting published in *Accountability in Research*
2008 Bass’s *Side Effects* published with details of the misrepresentation of Study 329
2008 Jureidini letter to editor about continued misleading citation of Keller et al. rejected JAACAP

2008 Martin (editor JAACAP) et al. publish article entitled “Conflict of Interest” in JAACAP

2009 Jureidini/McHenry editorial published by Psychotherapy and Psychosomatics

2009 McHenry/Jureidini write to Martin calling for retraction of Keller et al. (unanswered for 8 months)

2010 Jureidini/McHenry letter to editor submitted JAACAP (rejected July 2010)

DISCLOSURES AND ACKNOWLEDGMENTS

Jureidini, who is a child psychiatrist, had read the Keller et al. article several times before he recognized that it misrepresented data. Following the publication of his letter to the editor of JAACAP (with Tonkin), he was approached by the law firm of Baum, Hedlund, Aristei & Goldman of Los Angeles, California, to provide expert opinion about GSK documents that they had obtained in the course of legal action. McHenry was acting for the firm as a research consultant in medical ethics. Both authors have examined over 10,000 pages of GSK documents, and have prepared a number of scientific papers on the subject. Both contributed to all drafts of this paper. Jureidini is the guarantor. No funding supported the preparation of this manuscript. Both authors are members of Healthy Skepticism, an organization that aims to improve health by reducing harm from misleading health information. The authors would like to thank David B. Resnick and Sheldon Krimsky for helpful suggestions arising from peer review and Ron Goldman of Baum Hedlund for legal advice.

REFERENCES


