

On the Origin of Great Ideas: *Science in the Age of Big Pharma*

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The vision most people used to have of medical research is that professors gain funding from universities or government agencies, go to the lab for careful observation and experiment, and after some years publish their hard-won results in scholarly, peer-reviewed medical journals. This is probably a simplified story that never played out quite as envisioned. As a result of commercial interests in the outcome of medical research, we are now even further from it. Pharmaceutical companies' marketing departments have developed a novel strategy. The old vision allowed costly failures when reality did not cooperate with the company's plans for its new molecular entities. With the rising price of bringing a new drug to the market, a method that guaranteed success was needed. Instead of fitting the conclusion to the evidence, the industry's strategy now is to "defend the molecules": Select the data that promote the drugs, file away the results that are unfavorable, and then buy just the right academic credentials to sign on to ghostwritten articles produced by the marketing department staff or by public relations agencies employed by the company. Publish these articles in the most respected

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medical journals. Complete the circle of evidence by citing the published ghostwritten journal articles in “Dear Doctor” letters and other promotional materials, as if they were independent verification of the effectiveness and safety of the drugs.

To some extent, academic medicine has long involved ghostwriting. Scientific writers have often written up the results of studies. But while this practice deprives the authors of the credit they rightly deserve, it does not threaten to undermine the scientific integrity of medical research. What is relatively new on the scene is industry-sponsored ghostwriting. Drug promotional materials masquerade as legitimate scientific research, and competition between the pharmaceutical companies for the market share is fought out using “key opinion leaders” who are paid to sign on to the ghostwritten articles.

What follows is an account of one such case. The documents that build the case were filed into the public record by GlaxoSmithKline’s lawyers on June 23, 2004 (docket numbers 290 and 291) in the *In re Paxil Products Liability Litigation* MDL 1574. They were then used in an *ABC Primetime* program on antidepressants that aired on December 9, 2004.¹ The author is a research consultant for Baum-Hedlund, the Los Angeles-based law firm that filed the suit on behalf of individuals suffering from withdrawal symptoms upon discontinuing Paxil, which is one of the antidepressants known as selective serotonin reuptake inhibitors (SSRIs).

As it turns out, the differences in efficacy among the SSRIs are minimal, so their side effects profiles can make all the difference in how doctors prescribe them. In the mid-1990s, Eli Lilly, which manufactures Prozac (another of the SSRIs), began attacking Paxil, manufactured by GlaxoSmithKline—at that time, SmithKline Beecham—on just these grounds. In 1996-97, Lilly sponsored conferences and journal supplements focusing attention on the side effects caused by Paxil.² Paxil has a short “half-life”—the time after taking a drug at which half of the dose remains in the body—and therefore a short wash-out period when compared to Prozac. Paxil’s half-life is twenty-one to twenty-four hours; Prozac’s four to sixteen days. Because of the short half-life, a patient who abruptly ceases therapy with Paxil tends to have more severe withdrawal symptoms.

Lilly’s strategy was to play up the problems associated with Paxil’s short half-life. One key paper sponsored by Lilly was Jerrold F. Rosenbaum and John Zajecka’s “Clinical Manage-

ment of Antidepressant Discontinuation,” presented at a closed symposium titled “SSRI Discontinuation Events” and later published in a supplement of the *Journal of Clinical Psychiatry*.³ In this short paper, Rosenbaum and Zajecka stressed the importance of gradually tapering all SSRIs *except fluoxetine* (Prozac). They also suggested substituting fluoxetine in cases where symptoms of “discontinuation”—as they now called withdrawal—persevere even when the SSRI is tapered slowly.⁴ Both citations for this claim refer to cases of paroxetine withdrawal.

SmithKline Beecham wasted no time counterattacking. Their “Business Plan Guide,” dated December 1, 1997-May 31, 1998, announced new strategies against Lilly, including instructions to sales reps regarding the manner in which they were to address the problem of discontinuation with physicians and psychiatrists.⁵ Instructions included bullet points under categories such as “Minimize concerns surrounding discontinuation symptoms” and “Maximize benefits of optimal 24-hour half-life.”⁶

Part of the SmithKline Beecham response involved the use of the medical journals to get their message into the right hands. The public relations agency Ruder-Finn was hired by SmithKline Beecham’s marketing department to help prepare publications in the “Paxil Discontinuation Response.” The documents in this case show how Ruder-Finn and SmithKline Beecham’s marketing de-

partment worked together to disguise the authorship of these publications. In a memo of June 5, 1997, Ruder-Finn wrote to SmithKline Beecham marketing that “We’ve written two draft letters to the editor regarding the Lilly discontinuation supplement. One is from Drs. [Bruce G.] Pollock, [Ranga] Krishnan and [Charles B.] Nemeroff. The other would be authored by Ivan [Gergel].”⁷ Ruder-Finn also notes that letters in *Journal of Clinical Psychiatry* are written as case reports, so “if this is a requirement, we’ll need to ask one of the physicians to provide one.” They also note that the references listed for discontinuation symptoms with all SSRIs are the same for both letters, “and complete duplication will look fishy if we decide to submit both.” They ask: “Are there other references we could draw on for the various drugs? At the very least, we can’t have the references appear in the same order.”

Both draft letters make essentially the same points in response to Rosenbaum and Zajecka: (1) discontinuation symptoms have been reported with all SSRIs; (2) discontinuation symptoms with SSRIs are relatively mild and transient; (3)

In the new, industry-sponsored ghostwriting, pharmaceutical companies fight for market share using “key opinion leaders” paid to sign on to articles authored by marketing departments.

symptoms are less severe than those associated with discontinuation of tricyclic antidepressants; (4) incidence of adverse effects after abrupt discontinuation of paroxetine has been very low; and (5) the short half-life of paroxetine is a benefit when flexibility is desired in situations where switching or discontinuation of a medication is required. Both drafts contain handwritten editing by SmithKline Beecham marketing.

One of the two letters was published in the *Journal of Clinical Psychiatry* under the name of Bruce G. Pollock.⁸ The piece, “Discontinuation Symptoms and SSRIs,” is an expanded version of the original Ruder-Finn letter that bears his name but emphasizes points (1) and (2) above, in addition to another point that was in the original draft of this letter—that patients who abruptly stop treatment with a long-acting agent may not associate a symptom that occurs several weeks later with discontinuation of therapy. Overall the letter defends Paxil by showing that SSRIs with longer half-lives, like Prozac, also leave patients with discontinuation symptoms when the patient stops taking them. The letter does not acknowledge that SmithKline Beecham marketing or Ruder-Finn had any role in writing it, nor that Bruce Pollock has any financial relationship to SmithKline Beecham.

The letter was published in October 1998. In SmithKline Beecham’s “Business Plan Guide,” references to “The Pollack [sic] Letter” show up as part of the marketing strategy for sales reps. Interestingly, the Business Plan Guide appeared well before the letter was published. How SmithKline Beecham knew the letter was forthcoming one can only guess. The Guide says:

This letter to the editor authored by Bruce Pollack [sic], M.D. in the *Journal of Clinical Psychiatry*, October, 1998 is a great resource for addressing the issue of discontinuation. Dr. Pollack [sic] clarifies that discontinuation symptoms have been reported to occur with all SSRIs with onset and duration mediated by drug half-life. Most importantly, he balances the risk benefit of a short vs. long half-life, noting the control offered by shorter half-life agents. . . . You may order reprints of the Pollack [sic] letter electronically.⁹

The Business Guide also makes it clear that part of the strategy for educating physicians about Paxil should include emphasizing that a short half-life offers the benefit of a “drug holiday.”¹⁰ A common side effect of the SSRIs is sexual dysfunction, but the short half-life of Paxil allows a patient to wash the drug out of his system quickly in anticipation of sexual relations.

In a recent House of Commons health committee investigation, witnesses from GlaxoSmithKline strongly denied that the company practiced ghostwriting. Dr. Stuart Dollow, from GlaxoSmithKline, went as far as to state: “The issue of ghostwriting, as alleged, is not something I recognize at all.”¹¹ The *Journal of Clinical Psychiatry* likewise denies that it allows ghostwriting. It claims “to adhere to the highest ethical standards of scholarly peer-review and publication.” Journal policy “requires that authors name all persons who have made substantial contributions but who do not fulfill authorship

criteria and disclose the named individuals’ pertinent professional or financial relationships; contributions include writing or editing assistance. *JCP* policy requires that all such acknowledgments and disclosures are printed along with the accepted article or letter.”¹² The “Authorship Statement, Copyright Transfer, Financial Disclosure, and Acknowledgement Permission” form on the journal’s website requires disclosure of a range of financial relationships, including consulting relationships, grant/research support, speakers or advisory boards, “and other financial or material support.” This policy has been in place since the journal’s inception.

One final piece in this collection of documents provides a fitting conclusion to this case study. It appears to be part of a PowerPoint presentation to SmithKline Beecham marketing or sales reps. The slide is headlined: “Discontinuation: why this is an issue.” The text reads: “’97 Seroxat/Paxil sales to the end Sept already exceed \$1 BILLION.” Below the text is an image of a bag of money.¹³

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1. These documents can be viewed at <http://abcnews.go.com/Health/story?id=311956&page=1>.
2. 6th World Congress of Biological Psychiatry, “Interruption or Discontinuation of Antidepressant Therapy: A Critical Consideration in Patient Management,” Nice, France, 1997, and “SSRI Discontinuation Events,” Phoenix, Arizona, 1996.
3. J.F. Rosenbaum and J. Zajecka, “Clinical Management of Antidepressant Discontinuation,” *Journal of Clinical Psychiatry* 58 (suppl. 7) (1997), 37-40.
4. *Ibid.*, 39.
5. SmithKline Beecham Business Plan Guide, Sales Cycle 2, 1997, December 1, 1997-May 31, 1998, 0290-0297.
6. *Ibid.*, 0264.
7. Sandra Stahl, Ruder-Finn memo, June 5, 1997, 0260.
8. *Journal of Clinical Psychiatry* 59, no. 10, October 1998, 535-36.
9. SmithKline Beecham Business Plan Guide, 0297.
10. *Ibid.*, 0296.
11. House of Commons Health Committee, *The Influence of the Pharmaceutical Industry*, Fourth Report of Session 2004-05, volume I, March 22, 2005, 54.
12. Email correspondence from Meg M. Waters, Director of Editorial Services, Physicians Postgraduate Press, April 7, 2005. See “Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication,” at www.icmje.org/#conflicts.
13. See http://abcnews.go.com/images/Primetime/paxil_moneybag.pdf.