Beyond the JAMA "Flap"

Laura S. Boylan, MD
laura.boylan@nyumc.org

The events below are germane to a clinical trial reporting benefit for treating depression before it happens in people who've had a stroke . There was a big "flap" associated with this study because the editors of JAMA reacted strongly against the "messenger" who brought first author Dr. Robinson's undisclosed conflicts of interest (COI) to JAMA's attention. Other sources have detailed this absurdity. But the problem goes beyond a comedy of manners.

Big pharma would love to see people without psychiatric problems take psychiatric medicines. The "flap" led me to look in detail at the paper's methods and analysis. One thing led to another, and this timeline resulted.

I look to institutions like JAMA, the NIH, universities, and the peer review process to keep the public interest at the fore and maintain information integrity. It seems to me there is much room for improvement. So while there are certainly elements of a comedy of manners in this tale, at bottom, it's really no joke.

Date	Event	Source
1999-2001	Patient enrollment period for Daiichi/Prestwick industry sponsored phase II trial of nefiracetam for poststroke depression. Robinson was first author on the eventual publication that indicated that he was paid consultant on study design.	Robinson et al 2008 J Neuropsychiatry Clin Neurosci
2002	Robinson awarded NIH grant R01MH065134 through University of Iowa to study prevention of post stroke depression (PSD). The proposed study published on NIH (CRISP) database was a four-arm study: nortriptyline, citalopram, psychotherapy, and placebo. Endpoints not specified.	CRISP, NIH database
8/02	Product launch/FDA approval of Lexapro (escitalopram), manufactured and developed by Forest and Lundbeck (latter is Danish company). A "patent extending" variation of Celexa (citalopram).	Link to a discussion of the FDA approval and marketing of Lexapro
9/02	Robinson PSD project start date.	CRISP document, Clinicaltrials.gov
7/03	Forest patent on citalopram (Celexa) expires, generics become available	everydayhealth.com
7/03	Patient enrollment in PSD trial begins. The paper reports on a three-arm trial: Lexapro, psychotherapy and placebo. The paper states that escitalopram (Lexapro) was used instead of citalopram because of empirical evidence of possible superiority. Cites two references. The first (Tamminga et al) is a "thought piece", not empiric evidence, and does not mention escitalopram (Lexapro). The second citation, a	Robinson 2008 JAMA Robinson et al 2000, AJP,

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	Lundbeck sponsored study published in 2005 can't have been the basis of a decision made, at the latest, in 2003. Nortriptyline is not mentioned although Robinson's 2000 study supported superior efficacy of nortriptyline over fluoxetine (another SSRI, like citalopram and escitalopram). In 2009 Lexapro costs over 5 times as much as nortriptyline and over twice as much as generic citalopram.	drug prices: http://www.drugstore.com
9/03	Beginning of the "5 year window of reporting" offered by Robinson in his corrected COI disclosure to JAMA. This month attended at conference in Spain paid for by Lundbeck. Lexapro had already replaced the two generic medications initially proposed to NIH.	Robinson letter to JAMA editor vis disclosure
10/29/03	PSD trial first registered at clinicaltrials.gov.	Clinicaltrials.gov Study NCT00071643
9/04	JAMA announces policy that inadequately registered clinical trials will not be considered for publication. Ongoing studies must be registered by 9/13/2005. In order to ensure the integrity of data analysis, complete registration requires a priori specification of study primary and secondary endpoints.	JAMA's policy on trial registration
6/23/05	Oldest version of PDS trial registration data available on clinicaltrials.gov site. Includes no endpoints.	First version on clinicaltrials.gov
4/16/07	Robinson submits final revisions on Daiichi and Prestwick sponsored trial for poststroke depression paper based on data from 1999-2001. A subset of patients who benefitted from nefiracetam was identified in an otherwise negative study. Disclosures include financial COI with Daiichi/Prestwick .	Robinson et al 2008 J Neuropsychiatry Clin Neurosci (abstract only)
8/2/07	Neuren Pharmaceuticals announces acquisition of Hamilton (only product is nefiracetam) and plan to seek funding for further trials in post stroke depression	fiercebiotech.com
5/27/08	USA Today quotes Robinson as saying "I think every stroke patient who can tolerate an antidepressant should be given one to prevent depression,"	USA Today
5/28/08	Publication of PDS trial in JAMA. Robinson discloses financial COI only with Hamilton and Avanir. Daiichi, Prestwick, Forest, Lundbeck, Pfizer, Neuren not included.	Robinson 2008 JAMA
7/16/08	Publication of Cochrane Review of interventions for post stroke depression. Cochrane is a highly respected source for systematic evidence based reviews: "This review of 14 trials, involving 1515 participants, found no evidence that antidepressant drugs prevent depression or improve physical recovery after stroke. Two trials showed that psychological therapy could improve patients' mood and prevent depression, but did not improve other outcomes." (Robinson 2008 data from 176 patients not included in review).	Cochrane Reviews
8/13/08	Hamilton application for "Use of Nefiracetam for treating post-stroke neurodegeneration", filed in 2001, becomes public information	freepatentsonline.com

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8/20/08	Revisions are made to the clinicaltrials.gov study website for the PSD study. For the first time primary and secondary endpoints are registered.	clinicaltrials.gov revisions
10/15/08	Publication of Robinson's acknowledgement that psychotherapy and escitalopram did not significantly differ in efficacy in his 2008 study.	Robinson JAMA letters to the editor
10/16/08	Dr. Leo email to JAMA questions COI completeness	DeAngelis editorial, link from this site
2/5/09	Following investigation, JAMA accepts letter of correction from Robinson with "five year reporting window"	DeAngelis editorial, above
2/25/09	US dept of justice files claim charging that Forest "sought to induce physicians and others to prescribe Celexa and Lexapro by providing them with various forms of illegal remuneration, including cash payments disguised as grants or consulting fees, expensive meals and lavish entertainment and other valuable goods and services, all in violation of the federal anti-kickback statute."	US Dept of Justice Charges
3/7/09	Robinson gives a presentation on novel treatments for stroke and depression at a conference in Hawaii. States: "Nothing to disclose".	AAGP Meeting program
3/11/09	JAMA publication of Robinson letter and correction with "five year window" of disclosure reporting. COI with Lundbeck, Forest and Pfizer (but not Daiichi/Prestwick/Neuren) are added to previous disclosures.	JAMA correction, Robinson letter
3/11/09	JAMA editorial announces that those who report COI irregularities to JAMA are obliged to maintain confidentiality while JAMA investigates.	DeAngelis editorial, link from this site
4/09	Robinson publication of lead editorial "Prevention of first-episode depression: progress and potential" in British Journal of Psychiatry (last revision 12/08). Robinson says we should consider "universal prevention'" for healthy individuals and "not set our sights too low." States he has no conflicts of interest.	BJP abstract with disclosure
4/20/09	Boylan email to DeAngelis indicating that there is an "apparent irregularity" in clinical trial registration for PSD study such that it would not meet JAMA requirements to consider a manuscript. DeAngelis replies stating there's "no irregularity".	
4/24/09	Boylan letter to BMJ Rapid Response reports that PSD study clinical trial registry on clinicaltrials.gov was inadequate to meet JAMA requirements and that the "five year reporting interval" doesn't cover the study period.	BMJ.com