Pradaxa: More Evidence of Drug Firms Manipulating Science

Thanks to Dr. Roy Poses at Health Care Renewal:

http://hcrenewal.blogspot.com/2014/02/cant-this-be-avoided-how-corporate.html

--for calling attention to two articles in the *New York Times* by Katie Thomas:

http://www.nytimes.com/2014/02/06/business/study-of-blood-clot-drug-pradaxa-unnerved-its-maker-documents-suggest.html?_r=0

http://www.nytimes.com/2014/02/08/business/new-emails-in-pradaxa-case-show-concern-over-profit.html

Let me give some medical background and then review the contents of Thomas's articles, relay Dr. Poses' take on the matter, and then end with a reflection of my own.

For many years, the most commonly used oral anti-clotting drug (commonly referred to mistakenly and misleadingly as "blood thinners") has been warfarin. Warfarin has a number of disadvantages. First, it has a very narrow safety range—let blood levels get too low and the person is at risk for forming potentially fatal clots; let them get too high and the person is at risk for a potentially fatal bleeding episode. That leads to the second disadvantage—that patients taking warfarin have to report regularly for blood tests to measure the levels and to adjust the dose if needed. So if anyone succeeds in developing a new-generation replacement for warfarin, but without these problems, then it would qualify as a better mousetrap par excellence.

Recently, several firms have proclaimed the advent of the better mousetrap; one version is Pradaxa (dabigatran) made by the German firm Boehringer Ingelheim. Pradaxa has been marketed for preventing clots in one of the most common conditions for which such drugs are prescribed, the irregular heartbeat known as atrial fibrillation, and the company claims it is at least as good as warfarin without

requiring any inconvenient blood testing. Warfarin works by blocking the step in the clotting process that's controlled by Vitamin K, so that if a patient taking warfarin starts bleeding dangerously, an intravenous dose of Vitamin K will immediately reverse the drug's effects. Pradaxa and the other new drugs work at a different point in the clotting cycle and there's no available antidote if a patient bleeds—leading some experts to advise that the drug is too dangerous to use for that reason alone. The FDA has received reports of 1000 deaths attributed to Pradaxa (out of some 850,000 patients prescribed the drug, netting Boehringer the hefty revenues of $2B).

It's patients suing the drug firm over Pradaxa-related harm that led to the articles in the *Times*. The judge ordered release of some documents related to the case that include internal company e-mails about a research study coordinated by a company scientist, Paul A. Reilly. Reilly's study showed that a part of the safety problem with Pradaxa was that some patients had too high a blood level and some patients too low (sound familiar?). He concluded that a blood test that measured drug levels could be helpful for at least some patients in avoiding dangerous reactions. (Such a blood test is available now in Europe but not the U.S.)

A draft of Reilly's paper that included these findings unleashed a storm of e-mails from other company scientists and officials. They argued that publishing a paper with these conclusions would undermine the company's primary marketing point in favor of Pradaxa, the result of a fine-tuned marketing effort going back a decade. Moreover, some feared that if the paper were published, it would be that much harder to get the government regulators to hold off demanding blood tests. The end result was that the paper was published recently but with many of the offending details removed.

Boehringer Ingelheim insists that this was a simple matter of scientific review and refinement. A draft was circulated, others chimed in with appropriate criticisms, and in the end the final paper was suitably modified to better present the actual facts. Nobody here but us scientists, boss.

Other experts aren't buying that, and Dr. Poses appropriately asks how often such censoring of scientific findings in the name of marketing occurs with no friendly judge to force the release of the secret company documents.

One of the common complaints from pharmapologists is that pharmascolds quite

unfairly would have physicians distrust a scientific paper merely because it's sponsored by a drug company, when ideally, they should read the paper carefully, review the methods, and believe the paper or not based solely on its merits. Dr. Poses comes out with a powerful contrary statement: ***"I strongly advocate that those who author authoritative systematic reviews, meta-analyses, and clinical practice guidelines... assume the likelihood that all commercially sponsored published clinical research has been manipulated..."***

Now for my own comment—this sounds very much like a replay of the case of the so-called atypical antipsychotics that we previously discussed:

http://brodyhooked.blogspot.com/2009/01/are-second-generation-antipsychotic.html

Recall there that a new class of drugs was introduced with great fanfare and said to be far superior to the original class of drugs, and only after years of use did it become clear in hindsight that the supposedly new drugs were in fact hardly different at all from the old ones, except in the eyes of the company marketers, who managed to bamboozle the entire medical profession very neatly, much to the harm of patients.

Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: The REL-Y Trial (Randomized Evaluation of Long-term Anticoagulation Therapy). *Journal of the American College of Cardiology* 63:321-328, 2014.