Selective reporting of pharmaceutical data leads major medical journals to change editorial policy

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The publication in Fall 2000 of the CLASS and VIGOR trials in *JAMA* and the *New England Journal of Medicine* (respectively) provided strong evidence for the cyclooxygenase (COX)-2 hypothesis: that COX-2 selective NSAIDs confer a gastrointestinal (GI) safety advantage over predecessor NSAIDs such as ibuprofen, naproxen or diclofenac.[1,2] The publicity resulting from these trials helped prolong a multibillion dollar boom[3] in North American sales of celecoxib (Celebrex) and rofecoxib (Vioxx), which are the first COX-2 agents licensed in the US and Canada. But more complete information recently submitted to the US Food and Drug Administration (FDA) has prompted an outcry that Celebrex manufacturer Pharmacia and prominent US clinical investigators did not present their trial data fairly.

On Aug. 5, 2001, the *Washington Post* published a story entitled, "Missing data on Celebrex: Full study altered picture of drug."[4] The article recounts *JAMA*'s publication of the CLASS study, which concluded that celecoxib might confer a GI safety advantage over ibuprofen and diclofenac. Boston gastroenterologists Drs. David R. Lichtenstein and M. Michael Wolfe had written a cautiously favourable editorial about the study in the same issue of *JAMA*.[5] However, last February, when Dr. Wolfe was shown the full study as a member of the FDA Arthritis Advisory Committee, he saw that the complete trial data painted a different picture, and that celecoxib did not appear to offer a significant safety advantage over the older, less expensive medications.

"We were flabbergasted," said Dr. Wolfe,[4] after learning that what the authors had represented as a single 6-month trial was actually a combined analysis of the first 6 months of 2 separate 12-month trials. The authors had omitted the second 6-month data set, in which the apparent celecoxib advantage melted away. *JAMA* Editor Catherine D. DeAngelis said the journal was not informed about the missing data. "I am disheartened to hear that they had those data at the time that they submitted to us. We are functioning on a level of trust that was, perhaps, broken."[4]

This and similar incidents, plus the fact that research is now funded to a very large extent by pharmaceutical firms who have vested financial interests in the results, prompted the 11 editors of the Vancouver Group (International Committee of Medical Journal Editors) to issue new requirements for acceptance for publication of research funded by industry sponsors.[6] The requirements permit journal editors to review protocols and research contracts between the companies and investigators. Contracts that inhibit the full freedom of researchers to conduct the studies as they see fit and publish when they want may not be published.

University of British Columbia clinical pharmacologist Dr. James Wright is cited in the *Washington Post* article for having alerted *JAMA* to the misreporting of the CLASS trial data. Wright and colleagues at the UBC Therapeutics Initiative (www.ti.ubc.ca) submitted a letter to *JAMA* in July 2001 suggesting that the complete data from the CLASS trial indicate that celecoxib may cause more serious adverse events than ibuprofen or diclofenac (Dr. J. Wright, UBC Therapeutics Initiative, Vancouver: personal communication, 2001).

In its Aug. 22/29, 2001, issue,[3] *JAMA* published a Cleveland Clinic meta-analysis of the CLASS and VIGOR trials, 2 smaller unpublished robecoxib trials, and the full trial data submitted to the FDA, focussing on the risk of cardiovascular events associated with selective COX-2 inhibitors. This post-hoc analysis suggests that both rofecoxib and celecoxib may increase the risk of thrombotic cardiovascular events, including myocardial infaction, unstable angina,

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sudden death and ischemic stroke, when compared with other NSAIDs or with placebo. Rofecoxib was also associated with more frequent hypertension in the VIGOR trial, with mean blood pressure increases (systolic, 4.6 mm Hg; diastolic, 1.7 mm Hg) comparable but opposite to the mean effect of ramipril in the HOPE[7] trial. Equivalent data were not available from the CLASS study. Pending clarification from a prospective trial specifically assessing cardiovascular effects of COX-2 selective NSAIDs, the authors suggest "we urge caution in prescribing these agents to patients at risk for cardiovascular morbidity."

Competing interests: Dr. Perry works part time for the University of British Columbia Therapeutics Initiative.

References

1. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284(10):1247-55.

2. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR [Vioxx Gastrointestinal Outcomes Research] study group. N Engl J Med 2000;343:1520-8.

3. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286(8):954-9.

4. Okie S. Missing data on Celebrex: Full study altered picture of drug. Washington Post 2001 Aug 5;Sect A:11.

5. Lichtenstein DR, Wolfe MM. COX-2–selective NSAIDs: New and improved? [editorial]. JAMA 2000;284(10):1297-9.

6. Davidoff F, DeAngelis CD, Drazen JM, Nicholls MG, Hoey J, Hojgaard L, et al. Sponsorship, authorship and accountability. CMAJ 2001;165(6):786-8.

7. Yusef S, Sleight P, Pogue J. Bosch J, Davies R, Dagenais G, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53.

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Editor's note: My *Concise Oxford Dictionary* defines the adjective *honest* as "free of deceit; truthful and sincere." It defines *ethical* as, "of or relating to moral principles or the branch of knowledge concerned with these." These are simple enough concepts and ones that those in the health care professions should naturally embrace.

Pharmaceutical companies play a large role in our health care system. They have gained academic credibility by infiltrating prominent universities and courting influential physicians. Drug company funded studies now comprise a substantial proportion of all research published in peer-reviewed medical journals, and their increasing influence on medical practice is a growing controversy. For-profit companies wish to portray their products in a positive light, and physicians should interpret research findings with this in mind; but if the "industry standard" is to release only selected trial data to clinical investigators and medical editors, how can we believe anything we read?

The recent scandal surrounding the CLASS study was perhaps the last straw, and 11 of the world's most prominent medical journals have joined forces to try to ensure articles have a sound, non-industry biased foundation. The editors of these journals may now refuse to print pharmaceutical-sponsored studies unless the researchers involved are guaranteed scientific independence and full access to the data.

CJEM applauds this move and encourages readers to cultivate and maintain their own critical appraisal skills.

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PS: The next time you're gorging yourself at a drug company sponsored event, take time to reflect on the line that separates knowledge enhancement from marketing.

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