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## Journal still questions Canadian-led Vioxx study, despite drug's removal

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TORONTO (CP) - The New England Journal of Medicine continues to question a Canadian-led study of Vioxx it published more than five years ago, even though the once-blockbuster anti-inflammatory drug has been pulled from the global market.

In an online editorial Wednesday, the NEJM reaffirmed its "expression of concern" over the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which the journal published in November 2000.

Wednesday's editorial was issued along with the researchers' lengthy response to the journal's original expression of concern, published last December. In that missive, the NEJM rebuked at least two of the VIGOR authors, alleging that data on three heart attacks among subjects taking Vioxx were withheld when the study was submitted for publication.

"The information we have indicates that the VIGOR article, because it did not contain relevant safety data available to the authors more than four months before publication, did not accurately reflect the potential for serious cardiovascular toxicity with rofecoxib (Vioxx)," wrote executive editor Dr. Gregory Curfman, managing editor Stephen Morrissey and editor-in-chief Dr. Jeffrey Drazen.

The VIGOR study was led by Dr. Claire Bombardier, a prominent rheumatologist at Toronto's Mount Sinai Hospital, and was funded by the maker of Vioxx, Merck & Co.

Bombardier said Wednesday that she and fellow researchers were given only several hours' notice before the first editorial was posted online - leaving them no opportunity to properly respond at the time.

At issue were allegations that researchers did not include the three heart attacks in the original paper; that the omission skewed the results in favour of the drug; and that data on the adverse cardiovascular events had been deleted prior to submission to the journal.

In a point-by-point response Wednesday, Bombardier and her 10 fellow academic researchers from around the world stood by their original article, saying it was "written in line with basic clinical trial principles, specifying that data must be analyzed according to plans" set out and approved before the study began.

"We stand by our response," Bombardier said in an interview. "These events (heart attacks) occurred after the cut-off date before anyone knew about the data."

Two Merck researchers, Dr. Alise Reicin and Deborah Shapiro, also defended the paper.

"We and our co-authors worked diligently to present the VIGOR data in what we believed to be a scientifically appropriate manner . . . (and) we stand firmly behind the propriety of the scientific analysis and presentation of data in the paper."

Bombardier said the heart attack data were not deleted from the manuscript - and they would not have changed researchers' conclusions about the drug's possible side-effects.

"Whether you have the additional three (heart attacks) in there or you don't have, the results are the same," she said. "And that difference is significant beforehand and it is significant after."

In fact, Bombardier said, it was the VIGOR study that first raised a red flag about the drug's effects on the cardiovascular system and spawned a slew of subsequent studies to determine whether the medication increased the incidence of heart attack and stroke and by how much.

Further research showed Vioxx indeed doubled the risk for these cardiovascular events, leaving Merck no choice but to pull the drug from the worldwide market in September 2004.

Since then, Merck has been inundated by almost 10,000 lawsuits over Vioxx. But last Friday, a federal jury in New Orleans cleared Merck of responsibility in the death of a 53-year-old Florida man who had a heart attack after taking the drug for less than a month.

The New England Journal of Medicine, which was called to give a deposition in the case regarding the VIGOR study, published its reaffirmation less than a week after the trial ended.

That has led to speculation about the timing of the journal's online release - especially since Bombardier said the research team submitted its response five weeks ago.

However, none of the NEJM editors were available for comment Wednesday.

Spokeswoman Sandra Jacobs said the journal followed guidelines set out by the International Committee of Medical Journal Editors for dealing with concerns about studies and the matter is now considered closed.

"So we're following through to set the academic record straight," Jacobs said from Waltham, Mass. "Reaffirming the expression of concern means that it will stand alongside the VIGOR article in perpetuity.

"As a practical matter, any time someone seeks the VIGOR article online, they also will see a permanent link to the expression of concern and all related materials, including the responses from the authors and the reaffirmation of the editors' concerns."

Bombardier said she and her academic co-authors will discuss whether they will take any further action on the issue.

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