When Drug Sales and Science Collide*

by

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Part I—February 2001

One early morning a young husband and wife, Jeff and Leslie, were briskly walking around their neighborhood in Chapel Hill, North Carolina, before they headed off to work.

"I can't believe how much better my stomach and arthritic knees have felt since I started taking Vioxx®," Leslie said as they finished their first mile.

"It's amazing how well it has worked, and without that awful upset stomach," said Jeff.

Jeff, too, had been reflecting on how much more energetic and upbeat Leslie had been lately, pleased that "his" company's new drug was working so well for her. Jeff had just been hired by Merck as a pharmaceutical representative (salesperson) and couldn't believe how lucky he was to have been placed on the Vioxx (chemical name, rofecoxib) account. It had been less than two years since Vioxx had been approved by the FDA and it was now considered Merck's latest wonder drug.

Vioxx is known as a specific non-steroidal anti-inflammatory drug (NSAID), which has the ability to reduce pain but without the more severe gastrointestinal side effects attributed to the non-specific NSAIDs like ibuprofen, diclofenac, nabumetone, and naproxen (brand name Aleve®). So, over a year ago, when Leslie was taking naproxen, her doctor was not surprised that Leslie had chronic stomach upset, although her arthritic symptoms had been significantly reduced.

When Jeff got to work that morning, he continued to sort through what he was given on his first day, looking for any informational material he could provide to his clients. One marketing pamphlet, called "The Cardiovascular Card," had an accompanying document (http://oversight.house.gov/features/vioxx/Tab4.pdf) explaining that drug representatives could show the card to (but not leave it with) doctors who asked questions specifically about Vioxx and its possible association with myocardial infarctions (MIs or heart attacks), CVAs (strokes or cerebral hemorrhages), or TIAs (mini-strokes). Jeff wasn't aware that Vioxx had any cardiac or circulatory side effects and read the information (see next page) with interest, thinking of Leslie even though she currently had no other medical conditions beside arthritis.

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* This case study was inspired by actual events that took place in February, 2001, concerning Merck & Co., Inc. and Vioxx which have been widely reported in mainstream media and scientific literature. However, the precise scenario presented here is a work of fiction and solely the creation of the authors. Fictional elements include the characters Jeff, Leslie, and Dr. Sara, as well as their statements, thoughts, and actions. These characters and the resulting storyline have been introduced merely as a pedagogical aid to students as they examine excerpts from actual documents and data identified throughout the case. Every effort was made to portray the scientific issues precisely and accurately. Vioxx is a registered trademark of Merck & Co., Inc. Aleve is a registered trademark of Bayer Corporation. Title image credit: photo ©Ken Hurst/Fotolia.com.

CARDIOVASCULAR EVENT PROFILE

Cardiovascular thromboembolic adverse events in OA clinical trials†,1

- The overall incidence of cardiovascular thromboembolic adverse events was assessed. This review included events pertaining to cardiac (i.e., MI, angina), central nervous (i.e., CVA, TIA), and peripheral vascular (i.e., arterial embolism) systems.
- Due to the variable duration of treatment in the studies, results are expressed as events per 100 patient-years.

Cardiovascular Thromboembolic Adverse Events per 100 Patient-Years

	Placebo N=783	**VIOXX** 12.5 mg N=1,215	**VIOXX** 25 mg N=1,614	**VIOXX** 50 mg N=526	Ibuprofen 2400 mg N=847	Diclofenac 150 mg N=590	Nabumetone 1500 mg N=128
Events**	2.9	3.2	2.6	3.3	2.6	3.1	3.9

**MI, cerebrovascular accident (CVA), transient ischemic attack (TIA), and angina

The incidence of events was similar among the groups.

*__Recommended dosing in OA:__ The recommended dose of VIOXX is 12.5 mg once daily. Some patients may receive benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Note: The above is an excerpt from a tri-fold marketing pamphlet called the "The Cardiovascular Card."
Source: http://oversight.house.gov/features/vioxx/Tab5.pdf.

Questions

1. What is the advantage of Vioxx, in terms of side effects, over the naproxen Leslie was previously taking?
2. Define and describe the purpose of a placebo and a control group in an experimental design.
3. What types of medical conditions are included as a cardiovascular thromboembolic adverse (CTA) event?
4. According to the table of data, how does the incidence of CTA events with Vioxx compare to the other drugs and the placebo?
5. What do you know about the source of these data?
6. Based on these data, what should Jeff tell his wife when he goes home?

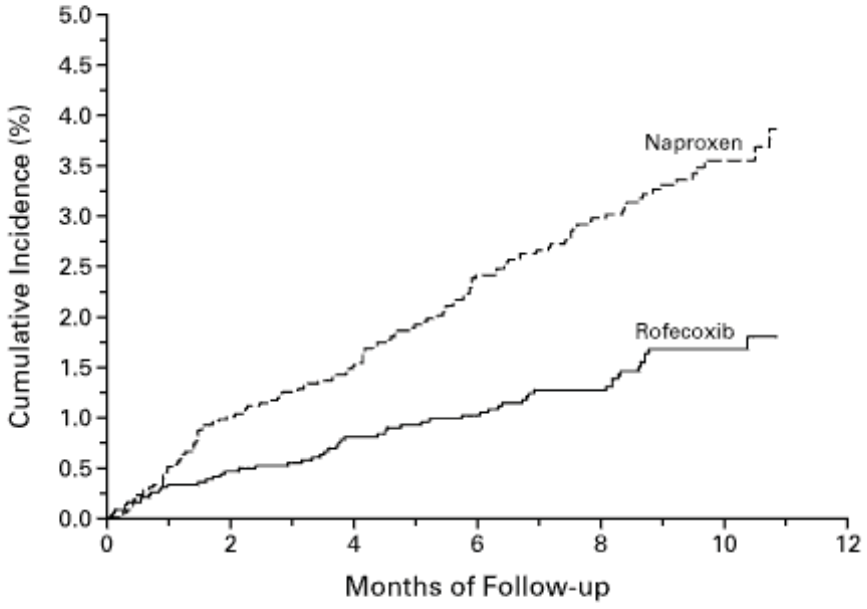
Part II—The VIGOR Study

That afternoon, Jeff made his first visit to Dr. Sara's clinic to drop off Vioxx pens and bring lunch from the local deli.

Dr. Sara said, "I'm glad that you're here. I've been so pleased with Vioxx for my arthritis patients. I finally got a chance to look at the Merck-funded publication by the VIGOR study group. These data totally agree with what I've seen in my patients! So many fewer are complaining of stomach upset or have had ulcers since I switched them to Vioxx."

The doctor pulled out the November 2000 *New England Journal of Medicine* article entitled "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis" and pointed to Figure 1. As Jeff looked it over, he wasn't surprised that the graph confirmed what he had already learned about Vioxx (rofecoxib) in his short time at Merck.

Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.



No. at Risk

Rofecoxib	4047	3641	3402	3180	2806	1073	533
Naproxen	4029	3644	3389	3163	2796	1071	513

Source: Bombardier, C., L. Laine, A. Reicin, et al. 2000. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England Journal of Medicine* 343:1520–8. Copyright ©2000 Massachusetts Medical Society. All rights reserved. Used with permission.

Questions

1. What information is on the y-axis? Express this in your own words, being sure to define "Cumulative Incidence."
2. What information is on the x-axis? Express this in your own words.
3. What do you think is a "gastrointestinal event?"
4. Suggest why these gastrointestinal event data would make Dr. Sara pleased with Vioxx.

Part III— An Inconsistency?

Dr. Sara continued: "I have one concern, though. I wasn't aware that there was a risk of heart attack for my patients on Vioxx. Look here on the fourth page of the article: 'Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent …).' Their data are statistically significant. Should I be concerned?"

Jeff was perplexed by what Dr. Sara had just said. He recalled the Cardiovascular Card he had read that morning suggesting that heart attacks and strokes were no more frequent in patients on Vioxx than those taking a placebo or non-specific NSAIDs.

Questions

1. Reexamine the table of data on the Cardiovascular Card. Can you determine the incidence of myocardial infarctions (heart attacks) with Vioxx or any of the treatments? Explain your answer.
2. The Cardiovascular Card was printed several months before the VIGOR study was published but after the study was complete. What are some possible explanations for why Merck did not directly refer to the VIGOR study on the card?
3. In the VIGOR study, with a total of about 8,000 participants, 0.1% (4 out of ~4,000 subjects) on naproxen experienced myocardial infarctions compared to 0.4% (17 out of ~4,000 subjects) on rofecoxib or Vioxx. Explain whether or not you think this is a meaningful difference.
4. It has been estimated that 80 million people worldwide took Vioxx before it was removed from the market. Predict how many of these Vioxx patients could have experienced myocardial infarctions. Does this calculation change your interpretation of whether or not this is a meaningful difference?
5. One piece of information the VIGOR study does not provide is the heart attack rate of a control group in a population similar to the one that was in this study (50+ years of age, not morbidly obese, no history of cancer, strokes or heart attacks within past 5, 2, or 1 years respectively, and no history of gastrointestinal surgery or inflammatory bowel disease, to name a few). How does this make it challenging for Jeff to interpret the meaning of the numbers?

Part IV—The Internal Bulletin

Dr. Sara then said, "I also heard that Merck reported to the FDA that 3 additional myocardial infarctions (heart attacks) occurred within 2 weeks after the study termination date. How does this change the risk of heart attack for my patients?"

Jeff was suddenly very concerned that he hadn't heard of these data. "Let me look into it and I'll get back to you tomorrow."

Back at the office, he found a memo in his inbox. As Jeff started to read the bulletin, his heart sank. "How can I work with my physician clients if I can't talk with them about published data?"

As he read the final paragraph more closely, he realized things were more serious than he had thought.

Bulletin for VIOXX®:

FDA Arthritis Advisory Committee Meeting for VIOXX®

TO:

All field personnel with responsibility for VIOXX® — Action Required
National Account Executives — Background Information
and Customer Managers (All Segments)

DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS ADVISORY COMMITTEE (ADVISORY COMMITTEE) REVIEW OF THE RESULTS OF THE VIOXX® GI OUTCOMES RESEARCH (VIGOR) STUDY. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS OUTLINED BELOW.

...

This information is provided for your background information *only* and is not to be used in discussions with physicians.

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Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patiens taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen.

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Excerpts from Bulletin for Vioxx February 9, 2001. Full document available at:
http://oversight.house.gov/features/vioxx/Tab9.pdf

Questions

1. Why do you think Jeff, as a "field personnel with responsibility for Vioxx," is prohibited from discussing the results of the VIGOR study, the same results published in the New England Journal of Medicine, or the new data provided at the bottom of the memo?
2. How is the percentage of heart attacks cited in this memo different from the published VIGOR study in the New England Journal of Medicine that Dr. Sara showed him? Give a possible explanation for the percent change in heart attacks between the memo and the published paper. Consider what Dr. Sara told Jeff.
3. Assuming 80 million people have taken Vioxx, calculate how many more people would suffer from heart attacks while on Vioxx with the percentage presented in the bulletin. Do you think this number represents a real risk to the public? Explain your answer.
4. What do you think of the data cited in the very last sentence? How could this be possible, considering the rates of nonfatal heart attacks? Is the risk of Vioxx that serious if the rate of cardiovascular mortality is no greater while on Vioxx than while on naproxen?

Part V—Conclusion

Questions

1. Considering the restrictions outlined in the Merck bulletin, express your opinion about whether or not Jeff should share the information with Dr. Sara about the increased risk of heart attacks you have just calculated. What things might Jeff need to consider?
2. Do you think Jeff should consider quitting his job at Merck? What is your reasoning?
3. Discuss what should happen next with Vioxx. Choose the perspective of Jeff, Dr. Sara, or Merck and evaluate fully.

Fast Forward	
2002	FDA asks Merck to include a warning about cardiovascular risks on the Vioxx label and package insert.
2003	Merck income estimates for Vioxx at $2.5 billion dollars.
2004	Additional cardiovascular events appear in the APPROVe study.
October 2004	Merck voluntarily pulls Vioxx from the market amid increasing safety concerns.
February 2005	Arthritis Advisory Committee and the Drug Safety and Risk Committee of the FDA vote in support of marketing Vioxx in the US (17 yes, 15 no votes) with proper labeling and contraindications for patients with heart problems.
July–August 2005	First Vioxx lawsuit trial begins in Texas and ends with the jurors awarding $253.4 million dollars to the widow of a man who suffered a fatal heart attack in 2001 after taking Vioxx.
31 May 2006	Merck admits to error in the data analysis of the APPROVe study (also published in the *New England Journal of Medicine*). Risk of damage to the heart begins sooner than claimed.
Present Day (June 2007)	Current lawsuit total stands at over 16,000 filed.