Weighing in 10 Years Later: Reflections on Contagious Off-Label Use of Phentermine and Fenfluramine

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Last summer and fall marked the 10-year anniversary of the public health warnings and the eventual withdrawal of products containing fenfluramine or dexfenfluramine. There was an explosion of prescribing of antiobesity agents in the mid-1990’s, mostly fueled by the increased prescribing of fen-phen.1 Much of this use was long-term; forty-six percent of those taking fen-phen and 33% of those taking fenfluramine or dexfenfluramine alone reported taking it for more than 12 weeks.2 Off-label use of these drugs was rampant.

Recall, however, that fenfluramine received FDA approval in 1973 for the short-term management of obesity.3 FDA approval of dexfenfluramine in 1996 for longer-term weight management therapy provided opportunities for increased exposure to fenfluramines. This dramatic change in clinical management of obesity precipitated the increased reports of incident cardiac valvulopathy, not the traditional, short-term, FDA-approved use of fenfluramines. Connolly et al.4 reported pathologic evidence of valvular plaques resembling serotonin-mediated carcinoid syndrome among cases exposed to fenfluramine-phentermine combination therapy. Following this study, the FDA reported an estimated 32.8% prevalence of valvular disease among individuals exposed to fenfluramines.2 But, 10 years later, one still wonders why was cardiac valve regurgitation a new adverse event phenomenon when fenfluramine was on the market for over twenty years?

Of equal concern was the public’s reaction to the unfolding risks of these products. On July 8, 1997, the FDA issued a public health advisory to health care professionals emphasizing the impact of fenfluramine and dexfenfluramine on users’ hearts.5 The FDA advisory stated “the FDA reminds all health care practitioners that the safety and effectiveness of the use of fenfluramine and phentermine in combination have not been established and that serious concerns about the safety of such combined use have been raised.” Despite the warnings and recommendations, many users did not discontinue use immediately. Of those individuals taking drugs containing fenfluramine or dexfenfluramine as of May 1997, it is estimated that approximately one-third stopped taking them during July and September, one-third stopped taking the pills in September and October, and the remaining one-third stopped taking the pills over the next 13 months.2 Given the extensive coverage in the media and lay press, that this proportion of users continued to take weight loss medications containing fenfluramine or dexfenfluramine months after they were removed from the market in the United States is of great concern.

The amplification of risk associated with long-term use suggests off-label use warrants safety monitoring and enforcement by FDA. Approvals for longer-term use of a particular drug such as dexfenfluramine should accompany clinical trial data regarding safety and efficacy of continuous treatment. Thus, monitoring of how medications are actually used in clinical practices post-marketing is warranted.

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The piece for this edition of Scribe focuses on the phentermine and fenfluramine story. This edition comes to you from two students in my advanced pharmacoepidemiology course, shortened significantly to meet the needs of this column. I welcome contributions which stay true to the theme of reflecting and learning about past challenges in pharmacoepidemiology.

Please forward ideas to: Kate_Lapane@brown.edu.
Looking Back, Learning Forward (continued)

A few questions remain:

Today, would the US public heed FDA warnings?

Has the scientific community learned to work in innovative ways with the FDA to investigate the safety of medications when off-label use is rampant?

Are our surveillance systems adequate to detect risks quickly when new combinations of medications are used or medications are used in ways not envisioned when approved for marketing?

With particular regard to anti-obesity agents, are manufacturers designing trials to mimic how these medications are likely to be used?

Given the increases in obesity over the past decades in the United States and across the globe, there will not be a shortage of patients seeking prescription and OTC weight loss remedies over the coming decades. It is of extreme public health importance that we strive to insure the safety of these products and their use, especially given the number of patients who currently take prescription weight loss medications and the number who may take them in the future.

References:


Do you have artistic talents or a creative spark?

In anticipation of the 25th anniversary celebration in 2009, we are pleased to announce a LOGO contest.

The winning designs will be used on the mid-year and annual t-shirts, the web, and possibly on our stationary for the 25th year.

The logo can be both text and images.

Please send your ideas and logos by April 1, 2008 to:
Susan.sacks@roche.com and Kate.Lapane@brown.edu.