Lemons for Obesity

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On 22 February 2012, the U.S. Food and Drug Administration (FDA) convened a panel for advice on a proposed antiobesity medication called “Qnexa.” Qnexa, manufactured by Vivus Inc., is a combination of phentermine, which is already approved as a diet suppressant, and topiramate, an antiseizure agent. Clinical trials demonstrated that Qnexa can lead to 10% weight loss in obese adults, but in 2010 an FDA panel recommended against approval because of safety concerns. Now, on February 22, Vivus was prepared to respond to 2 top safety worries: increased teratogenic risk for cleft lip and palate, and increased risk for cardiovascular events stemming from increases in heart rate. After reviewing documents and hearing a number of presentations, 20 FDA panelists voted in favor of approval and 2 voted against. I was 1 of the 2 (1).

My thoughts about Qnexa, and obesity medications in general, derive in part from 2 classic Nobel prize–winning publications from the 1970s. In 1970, George Akerlof wrote about the market for bad cars, otherwise known as “lemons” (2). Suppose used car buyers have reason to believe that 75% of cars are good and 25% are lemons; buyers know that some owners want to sell their cars because they’ve discovered many problems. A good car, which we’ll call “a peach,” is worth $20 000, a lemon only $5000. A prospective buyer has a big problem in being unable to distinguish peaches from lemons, whereas owners have no trustworthy way to communicate their inside knowledge. The buyer’s problem, which Akerlof referred to as information asymmetry, leads to a low offer of, say, $16 250. Owners of peaches will refuse “low-ball” offers of less than $20 000, whereas sellers of lemons will gladly accept. However, the buyer will wonder why an owner would accept a low offer for a peach, suspecting that the car is in fact a lemon. The buyer will revise his or her offer down, say, to $12 500, making owners of peaches even less willing to sell. Over time, the only cars that will sell will be lemons—peaches will be driven out of the market. Because of information asymmetry, Akerlof argued, bad products drive out good ones.

If we think about the history of obesity medications, we’ve seen plenty of lemons. Ephedra, Fen-phen, phenylpropanolamine, and sibutramine had to be withdrawn from the market because of cardiovascular toxicity. Rimonabant was approved for sale in Europe, but was never approved in the United States because of severe psychiatric side effects. At this time, Xenical is the only drug that is FDA-approved for obesity, and its use is limited by abdominal discomfort and steatorrhea. Why so many lemons? And what about Qnexa? Is it another lemon, or is it the peach we all want?

On 22 February, Vivus submitted a lengthy document that included its syntheses of cardiovascular data to the FDA panel (3). The company noted that the drug increases heart rate by a modest degree while improving other cardiovascular biomarkers, including blood pressure and highsensitivity C-reactive protein. Of 2581 patients enrolled in the company-sponsored “safety set” trials who were randomly assigned to Qnexa, 6 had myocardial infarction and 1 had a stroke, whereas among 1742 patients assigned to placebo, 1 died from an out-of-hospital cardiac arrest and 4 had strokes. On the basis of these 12 major adverse cardiovascular events, the company reported a hazard ratio of 0.84 with a confidence range of 0.26 to 2.64 (3). The company wrote, “Considering the overall absence of excess major adverse cardiovascular events in subjects in this program who received treatment with Qnexa, the lack of a direct relationship between major adverse cardiovascular events and heart rate changes, and the beneficial effects of Qnexa in models of cardiovascular risk that include heart rate, it does not appear that the small heart rate increase observed with Qnexa treatment can be associated with an increased risk for major cardiovascular events” (3).

I disagreed, arguing that it is impossible to draw any conclusions about Qnexa’s clinical cardiovascular effects based on a tiny sample of only 12 events and a confidence range that stretches from 80% protection to nearly a 3-fold increase in risk. I believe that if the public were to “buy” Qnexa after FDA approval, it would run the risk for severe, even fatal, consequences from another diet lemon. Why?

This brings me to the second classic publication from the 1970s, namely Tversky and Kahneman’s description of biases and heuristics that lead to inappropriate conclusions (4). People have an “illusion of validity,” thinking that 1 outcome is “representative” of what they’re actually interested in. In clinical research, we call this problem “excess reliance on surrogates.” We’ve seen numerous examples of failed surrogates, cases in which drugs seemed to do good things (like reduce blood sugar, increase high-density lipoprotein cholesterol, and improve left ventricular ejection fraction) yet, once rigorously tested in trials with large numbers of hard clinical events, turn out to be dangerous. We cannot assume that just because a drug reduces weight and improves some biomarkers that it will be safe, let alone beneficial.

Tversky and Kahneman also described “insensitivity to prior probability of outcomes,” in which people do not properly take into account preexisting data while attempting to interpret new data. In clinical research, we call this failure to employ “Bayesian thinking.” We know that increased heart rate may reflect adverse autonomic nervous
system effects that may increase the risk for fatal arrhythmias (5). We also know that prior obesity medications reduced weight at the price of unacceptable side effects. Taking history into account, we should be concerned about a proposed obesity medication that increases heart rate, especially considering that it may be used in tens of millions of people, many of whom are already burdened with cardiovascular risk factors.

Finally, Tversky and Kahneman described “insensitivity to sample size.” People assume that observations seen in small samples automatically translate to correct inferences about the general universe. We cannot assume that an absence of excess cardiovascular events in small trials—trials that yielded only 12 outcome events—means that we can confidently conclude that Qnexa is safe. In modern biostatistical terms, we express that uncertainty with the confidence interval.

What’s the information asymmetry? Consumers, and indeed many physicians, are not able to judge the value of a proposed obesity drug because they do not appreciate the problems with surrogates, the importance of prior probabilities, and the extreme uncertainties inherent in small numbers. Manufacturers and the FDA are aware of these problems (or at least, they should be), but they have no good way to communicate with most physicians and patients who are limited by statistical innumeracy (6–9). The result is that, absent rigorous FDA oversight, we wind up with obesity drugs that reduce weight but increase cardiovascular risk.

So what to do? We can resolve the information asymmetry by insisting on a large-scale, preapproval cardiovascular outcomes trial of Qnexa. It would be too risky to rely on postapproval surveillance or to hope that a rigorous trial could be conducted in a timely manner. If Qnexa prevents cardiovascular events, or at least doesn’t increase the risk for them, in a preapproval trial, then we will all know that we have the peach we’ve been waiting for.

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