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Slim pickings for two weight-loss drugs?

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Options are limited in America's battle of the bulge. While diet and exercise can help in the short term, they are frustratingly ineffective in the long run.

And, even the search for a magic weight-loss pill is falling short, said Drs. Steven Woloshin and Lisa Schwartz of The Dartmouth Institute for Health Policy & Clinical Practice in the Feb. 10 issue of *JAMA Internal Medicine*.

Many medications for weight loss have been proposed or are under development. The Federal Drug Administration has approved few drugs for long-term weight loss, and some are no longer marketed because of safety issues, the researchers said. In 2012, though, the FDA approved two drugs for long-term weight loss, lorcaserin hydrochloride (Belviq; Eisai Inc) and phentermine/topiramate (Qsymia; Vivus Inc).

But Dartmouth researchers question how safe these two drugs are based on the FDA approval after one-year trials?

The trials showed that randomization to either drug, in addition to a calorie-restricted diet and increased exercise, was associated with more weight loss than patients' randomization to placebos (3 percent more weight loss with lorcaserin; 7 percent more with phentermine/topiramate).

Both drugs have been associated with serious harms; both drugs' labels include warnings about memory, attention or language problems and

depression.

The trials for both drugs could not exclude important cardiovascular harms. This is why neither drug is on the market in Europe, the researchers said. The European Medicines Agency reported that it was unlikely to approve lorcaserin because of concerns about possible cancers, psychiatric disorders and heart valve problems, prompting the manufacturer to withdraw its application. The EMA explicitly rejected phentermine/topiramate twice – first in 2012 and again in 2013.

The researchers said the FDA shared many of these concerns and the agency did not approve either drug on their initial applications. On reapplication, some of the concerns were resolved but not those about serious cardiovascular harms. Nevertheless, the FDA approved the drugs and required the companies to conduct post-approval trials to assess the harms.

"The FDA's decision to approve both drugs and require post-approval than pre-approval safety trials is troubling," said Schwartz and Woloshin.

The FDA's medical reviewer's recommendation for approval says, in part, that more trials before approval would "significantly delay effective therapy," which not only reduces body weight but exerts favorable effects on blood pressure and myocardial oxygen for "patients with a serious disease condition with few treatment options."

"We disagree with the FDA's decision," the researchers said. "Although treatment options are limited, obesity is not an emergency – it is not even a disease, but rather a risk factor for disease."

"In our view, approving the drugs for marketing without more definitive evidence is an unnecessary gamble" – one that the European regulatory agency was not willing to take, the researchers said.

While the FDA's Endocrine Drug Advisory Committee expressed general agreement with the European's position on cardiovascular testing, FDA's official guidance for industry has not changed.

The required post-marketing trials should be done quickly. Unfortunately, there is currently no evidence that this is happening on schedule. None of the trial protocols have been submitted to FDA (as of December 2013). FDA does not routinely require submission of post-marketing trials prior to approval. But they should.

The researchers suggest that the FDA change the prescribing information for both drugs to be explicit about possible harm: "Because of concerns that this drug might increase cardiovascular morbidity or mortality, FDA has required a randomized trial to be completed by 2017."

"Based on the information that is currently available, the two new drugs look like slim pickings," the researchers said.

More information: To view the article in *JAMA Internal Medicine*, go to: archinte.jamanetwork.com/artic … px?articleid=1828746

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