

From Side Effect to Main Event



Weight Reduction As a Side Effect Evan David Rosen, M.D., Ph.D.

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One of the interesting things about drug trials is that you often discover that your drug does something you never expected. This is usually bad, of course, and severe side effects have derailed more than one promising new compound. But sometimes, the side effect is more interesting, and may be more promising, than the original reason you tested the drug in the first place.

This scenario is not as uncommon as you might imagine, and has played out in the diabetes world on several occasions that I am aware of. For example, sulfonylurea drugs, long the mainstay of oral diabetes drugs in this country, were originally investigated as antibiotics. Thiazolidinediones (such as Avandia™ and Actos™) were created as lipid-lowering drugs, but were found to have more potent effects on blood sugar than on cholesterol levels.

There are now two new reports on anti-obesity agents that were originally developed to treat brain disorders like epilepsy and ALS (also known as Lou Gehrig's disease). When tested for their original indications they were found to cause significant weight loss, even in non-obese patients. Recognizing that there are 60 million obese adults in the U.S. hungering for new therapies, it didn't take much prodding for the companies to decide to switch their focus to obesity. Thus, side effect becomes main event.

The first study involved the drug zonisamide (Zonegran™), already on the market for use in some forms of epilepsy. After it was discovered that zonisamide caused weight loss in addition to its intended effect on seizure activity, the company decided to fund a study (performed at Duke University) to see whether it would benefit obese patients as well. Roughly 60 people (mostly women) were treated with either zonisamide or placebo; all patients also ate a low calorie diet. At the outset of the study, the participants had a body-mass index (BMI) of around 36 (corresponding to a weight around 215 lbs.). After 16 weeks of treatment, the zonisamide group lost 6% of their body weight (about 13 lbs.), while the placebo group lost only 1% (2 lbs.). A few patients opted to stay on the treatment for 32 weeks, and zonisamide led to further weight loss, up to 10% (20 lbs.).

There were very few adverse effects seen with zonisamide (with the caveat that this was a very short trial); only fatigue was seen more frequently in the drug-treated group than in the placebo group.

It's a bit unclear how zonisamide causes weight loss, although it appears to be an appetite suppressant and to modulate the levels of some neurotransmitters in the brain known to be involved in appetite regulation.

The second trial involved the drug Ciliary Neurotrophic Factor, or CNTF. CNTF is found naturally in specific cells in the brain, and appears to help the brain recover from injury. This led a company called Regeneron to create a souped-up version of CNTF to test in patients with nerve damage due to ALS. As with zonisamide, the company was surprised to notice weight loss among those receiving CNTF. When they looked more closely at how CNTF works, however, they noted that it seems to activate the same pathways in the same parts of the brain as leptin, a hormone known to have dramatic effects on appetite. Leptin, as you may know, was the subject of quite a bit of excitement after its discovery in 1994. A recent trial of leptin's utility in treating obesity was disappointing, however. One of the primary reasons for this is that obesity seems to be associated with a state of "leptin resistance", which is to say that the brain does not respond appropriately to the very high leptin levels in most obese people. Adding more leptin on top of the high levels there just doesn't seem to give you much bang for the buck. The interesting thing about CNTF is that it seems to activate the same pathways as leptin, but it doesn't seem to be affected by obesity-induced resistance like leptin.

In the current trial, roughly 170 obese adults (again, mostly women) were treated with CNTF injections for 12 weeks. These people were a bit more obese than in the zonisamide trial, with an average BMI of 41.1 (approximately 250 lbs.). Different doses of CNTF were compared to placebo, and the results indicated that the highest doses yielded around a 9 lb. weight loss. This is frankly a disappointingly low number, but the company is pushing on with a larger Phase III trial involving 2000 patients.

One reason why CNTF may be especially interesting is that it seems to avoid the so-called "rebound effect" seen with most weight loss therapies. The rebound effect is a sharp rise in weight gain seen immediately after most therapies are discontinued. Rebound back to higher weights is seen with all approved anti-obesity drugs (phentermine, sibutramine, and orlistat), but for some reason is greatly reduced after cessation of CNTF therapy. Weight does rise, but very slowly, and many patients who had taken CNTF have kept their weight off for more than 9 months after stopping the drug. This fact alone is reason enough to pursue further investigations into CNTF, in the company's opinion. The mechanism of the effect isn't totally clear, but it does appear that most weight loss drugs induce the expression of genes whose products make you hungrier—when you stop taking the drug, those forces are left unchecked and you eat way more than you should. With CNTF, however, the expression of those genes is reduced, not elevated, so stopping the drug does not result in rebound overeating.

A brief digression: I have to say that I disagree with many of my colleagues on the overall importance of the rebound effect. We give people with hypertension drugs to reduce their blood pressure, and we are not surprised that when we stop the drugs, the blood pressure goes back up. Ditto for stopping insulin in a diabetic, or any number of other drugs used to treat chronic conditions. We do not cure these diseases with drugs, we control them. It seems to me an unfair criterion of utility to ask any different of an anti-obesity medication. Ok, now I'll get off my soapbox and get back to the subject at hand.

Another side effect turned main event in obesity therapy is also under study. Rimonabant was developed as an anti-marijuana drug; it works by blocking cannabinoid receptors in the brain that lead to the euphoric effects of smoking pot. These same cannabinoid receptors also play a role in the post-high "munchies" experienced by marijuana users, and rimonabant seems to cause weight loss in mice and humans. Larger studies to confirm the effect are underway.

I don't want to lead you to the conclusion that convenient, highly efficacious treatments for obesity are right around the corner. That would be a gross overstatement. In fact, there is a surprising paucity of new lead compounds in the pipeline. But we are learning more about the basic mechanisms of appetite control, energy expenditure, and fat cell biology all the time, and it seems likely that we will eventually learn to apply that biological know-how to the development of new compounds. Or, as with the examples above, the right drug might fall into our lap quite by accident.

References:

Kishore M. Gadde, Deborah M. Franciscy, H. Ryan Wagner, II, and K. Ranga R. Krishnan. Zonisamide for Weight Loss in Obese Adults: A Randomized Controlled Trial *Journal of the American Medical Association* 2003 289: 1820-1825.

Mark P. Ettinger, Thomas W. Littlejohn, Sherwyn L. Schwartz, Stuart R. Weiss, Harris H. McIlwain, Steven B. Heymsfield, George A. Bray, William G. Roberts, Eugene R. Heyman, Nancy Stambler, Stanley Heshka, Catherine Vicary, and Hans-Peter Guler. Recombinant Variant of Ciliary Neurotrophic Factor for Weight Loss in Obese Adults: A Randomized, Dose-Ranging Study. *Journal of the American Medical Association* 2003 289: 1826-1832.

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