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Innovations

Food and Drugs: Arena Pharmaceuticals Develops Next Generation Obesity Drug

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Large and lucrative markets could await the drug that causes significant weight loss, but developing a medication that is both safe and effective has stymied the largest of drug companies. Some new contenders are now grabbing for the brass ring by finding creative ways to make you think you are not hungry.

As researchers unravel the complicated interplay of brain, behavior, and genetics, they increasingly regard obesity not as a lack of willpower, but as a chronic disease with serious health consequences. Not only is obesity associated with higher risk for type 2 diabetes, heart disease, and certain types of cancer, but excess weight has anatomical consequences: right-sided heart failure, hip osteoarthritis, and cirrhosis of the liver. The psychological effects are brutal as well.

Overindulgence is imprinted in our DNA. We are genetically designed to hoard fat to cope with scarcity, but high-calorie food is now cheap and plentiful, and we exercise less. The CDC estimates that two thirds of American adults are overweight at a body mass index greater than 25 and 72 million Americans are obese with a BMI of 30 or more (http://www.cdc.gov/nccdphp/dnpa/obesity). Worldwide, the WHO estimates 1.6 billion adults are overweight and 400 million are obese, as developing countries adopt fast food and sedentary habits.

Losing just 5%–10% of your body weight can reduce the risk of diabetes and heart disease; such a small amount, but for many, so hard to do. A third of the people who lose weight in lifestyle modification programs gain it back in a year. Most gain back what they lost within five years, but this varies by ethnic group and exercise levels (Weiss et al., 2007).

A Few Big Buts

Annoying side effects and only modest effectiveness have meant a lukewarm reception for FDA-approved weight loss drugs such as xenical (Orlistat), which blocks fat absorption and causes an average weight loss of 2.89 kg a year but also can cause flatulence and greasy, unpredictable bowel movements. Sibutramine (Meridia) induces an average weight loss of 4.45 kg yearly via a neurotransmitter reuptake inhibitor that enhances satiety but can also lead to high blood pressure, nausea, and insomnia (Snow et al., 2005). Phentermine, a common, older, generic, amphetamine-like appetite suppressant approved for short-term use, causes an average loss of 3.6 kg over 6 months.

Merck just halted development of its cannabinoid-1 (CB1) receptor antagonist Taranabant, an appetite suppressant, as the effective dose caused anxiety, irritability, and depression. Neurological and psychiatric side effects prevented Sanofi Aventis' CB1 inhibitor rimonabant (Acomplia) entry into the European and U.S. markets. And Pfizer halted development of its weight loss compound.

According to Dr. Caroline Apovian, director of clinical research for the Obesity Research Center at Boston Medical Center, the FDA requires companies that deal with receptors that affect mood to do 5 year safety studies. Drug companies report that the investment required will not be offset by sales because the drugs are not currently covered under health insurance. (Apovian discloses she is on the advisory boards of Merck, Sanofi Aventis, and Arena Pharmaceuticals and has received study funding from companies including Orexigen, Pfizer, and Amylin.)

Apovian prescribes weight loss drugs both for their approved indications and off-label as adjuncts to encourage patients with a bit of success to get them motivated to change behavior. "The best give 10% weight loss," Apovian said. "You are not going to get the 100 pounds."

All appetite suppressants have a rebound effect. Go off them without changing behavior and the pounds come back. "If you really considered obesity to be a disease, then why would you stop the drug," Apovian asked. People who don't have a problem paying for diabetes or blood pressure drugs won't stay on their obesity drugs, according to Apovian, not because of side effects, but because they are expensive, and are not covered by health insurance. "Meridia is over $100 a month," Apovian said. "People cannot afford this month after month, to keep their 10% weight loss." On the other hand, according to Apovian, surgery to install a gastric band can provide a 17%–20% weight loss, and while some people would consider that an easy way out, making a lifestyle shift is hard.

New Contenders

San Diego-based Arena Pharmaceuticals' (http://www.arenapharm.com) oral antiobesity drug Lorcaserin (lorcaserin hydrochloride) is now in stage 3 trials. Arena's drug candidates selectively target G protein-coupled receptors (GPCRs) with and without known natural ligands (GPCRs without natural ligands are commonly referred to as "orphan"). GPCRs are proteins that are located in the cell membrane and mediate cell signaling.

The challenge is to be selective while effective. As weight regulation is controlled by multiple pathways in the brain, triggering the wrong receptor can cause psychiatric problems or heart damage. Lorcaserin targets the 5-HT_{2C} serotonin receptor in the hypothalamus, an area of the brain that mediates satiety and

metabolism. However, this receptor is similar to two others in its subclass, HT_{2A}, linked to hallucinations and HT_{2B}, associated with heart damage.

Obesity drug development is still shadowed by the debacle of Fen-phen, phentermine combined with fenfluramine or dexfenfluramine. Phentermine and fenfluramine were approved in the 1970s as individual agents for short-term use, but people used them off-label long term. In 1997, the FDA called for fenfluramine and its enantiomer dexfenfluramine to be taken off the market when Mayo Clinic researchers found heart valve damage and pulmonary hypertension in patients. Manufacturer American Home Products, now Wyeth, paid out over $21 billion in lawsuits.

According to Dominic Behan, PhD, chief scientific officer and Arena cofounder, fenfluramine was the most effective weight loss agent ever, especially in combination with phentermine. Patients lost ten percent of their body weight and more. "The problem was nonselectivity," Behan said. "Our goal, back in 2001, was to come up with a compound that was a selective HT_{2C} agonist."

In Arena's phase 2b 12 week studies of various doses, Lorcaserin at the highest dose of 20 mg caused a 3.6 kg placebo-adjusted weight loss without diet or exercise. A third of people had weight loss of 5 percent or higher. Some study subjects reported transient headache and nausea, but Lorcaserin passed a 12 month independent echocardiographic check for heart valve damage.

Lorcaserin is now in BLOOM, a double-blind, randomized, and placebo-controlled 2 year trial of 3,100+ overweight and obese patients, as well as two other 1 year phase 3 trials, BLOSSOM and BLOOM-DM for diabetes, of 3,750 overweight and obese patients. According to Behan, the weight loss caused by most drugs plateaus at 6 months or a year, but Lorcaserin offers progressive weight loss over time.

Spoiling the Treat

To La Jolla, CA, based Orexigen Therapeutics (http://www.orexigen.com), a cupcake may as well be crack cocaine. Their strategy is to ruin the pleasure of eating it. "In order to affect mechanisms that are very tightly regulated like energy balance, oftentimes a single approach may not be sufficient," said Dr. Eduardo Dunayevich, Orexigen chief medical officer. Compensatory mechanisms kick in. "A great deal of vigilance and modification of lifestyle is necessary," Dunayevich said. "Unfortunately it is difficult for people to maintain changes in life. Think about the New Year's resolutions that people make. In obesity it is compounded as there is increasing evidence that certain types of food that are very calorically rich in fat and sugar are also perceived as very rewarding."

Orexigen's lead compound Contrave combines sustained-release buproprion, a generic antidepressant also used to kick the cigarette habit, and sustained-release generic naltrexone, used in its immediate form to treat opioid addiction and alcoholism, to block the reward centers of the brain as well as receptors in the hypothalamus that regulate energy balance and metabolism.

In phase 2b trials comparing dosages, Contrave showed between 8% and 10% weight loss over 48 weeks in the 88 healthy obese people who finished the trials on Contrave, out of 171 who were started on it. Side effects included headaches, dizziness, nausea, and insomnia. Contrave is now in four separate 56 week, Phase 3 clinical trials of several thousand patients. Orexigen says that Contrave can cause progressive, sustained weight loss as well as potentially stave off symptoms of depression. Orexigen's phase 2 compound, Empatic, combines buproprion and zonasimide, an anticonvulsant.

Diet docs are watching another San Diego company, Amylin (http://www.amylin.com) (Wolfson, 2007), which is testing an injectable combination of pramlintide, a synthetic analog of amylin, a neurohormone secreted by the pancreas that regulates appetite and blood glucose, and metreleptin (methionyl recombinant leptin), a neurohormone secreted by fat cells involved in regulating metabolism and body weight. Phase 2 studies showed a weight loss of 12.7% over 24 weeks. One hundred and seventy-seven patients, averaging 205 lbs at the study start, were treated with the combo and lost an average of 25 lbs, compared with an average of 17 lbs with pramlintide alone. Side effects included transient headache and nausea.

Tesofensine, developed by Danish company NeuroSearch (http://www.neurosearch.com), achieved the best scores yet, twice the weight loss of current approved drugs, but it is still early in development. A member of the phenyltropane family and originally investigated to treat Alzheimer's and Parkinson's disease, tesofensine functions as a mixed reuptake inhibitor of certain neurotransmitters. It boosts dopamine in the reward center of the forebrain, and noradrenaline and serotonin in the hypothalamus, to raise metabolism and suppress appetite. In TIPO-1, a randomized, placebo-controlled phase 2 study of 203 obese patients (161 patients completed the study) on an energy-restricted diet, the 0.5 mg dose of tesofensine provided a placebo-adjusted weight loss of 11.3 kg in 24 weeks. Side effects included elevated blood pressure at higher doses, dry mouth, nausea, constipation, and insomnia.

I'll Have What She Is Having

It remains ambiguous as to whether short-term chemical intervention for weight loss can enable great numbers of people to change their ways, or if many will have to take drugs indefinitely. Some intriguing people are providing clues. It is just too bad nobody knows how to bottle what they've got. Graham Thomas, MS, a researcher at Brown University's Medical School, tracks a group of 6000 people who lost 30 lbs or much more and kept it off more than a year in the National Weight Control Registry (http://www.nwcr.ws/default.htm). What makes them different? They perpetually stay in bootcamp: they eat breakfast, follow a low-fat, low-calorie diet, and exercise a lot. "The most successful of these registry participants are working very hard to use basic skills, such as self monitoring, and keeping high levels of physical activity," said Thomas. "They are expending a lot of effort early on. It becomes easier after a couple of years when it becomes part of the fabric of their lives."

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