Experimental weight-loss drug cuts appetite, burns more energy

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The first clinical studies of an experimental drug have revealed that obese people who take it for 12 weeks lose weight, even at very low doses. Short-term studies also suggest that the drug, called taranabant—the second drug designed to fight obesity by blocking cannabinoid receptors in the brain—causes people to consume fewer calories and burn more, researchers report in the January issue of *Cell Metabolism*, a publication of Cell Press.

Cannabinoid receptors are responsible for the psychological effects of marijuana (Cannabis sativa), and natural "endocannabinoids" are important regulators of energy balance.

"The effects of marijuana on appetite have been known for millennia from its medicinal and recreational use," said study author Steven Heymsfield of Merck Research Laboratories. "The ingredient responsible stimulates cannabinoid receptors. When you block the cannabinoid system with an antagonist like taranabant, you suppress appetite." However, the drug, developed by Merck, also comes with an increased risk of adverse side effects at higher doses, the study shows, including mild to moderate gastrointestinal and psychiatric effects.

The first proof of concept that so-called cannabinoid 1 receptor (CB1R) inverse agonists might offer an obesity therapy came from studies of another drug, developed by Sanofi-Aventis, called rimonabant. That drug is now in use for weight loss in several European countries as an adjunct to diet and exercise but has not received FDA approval for use in the

United States.

Taranabant is a structurally novel, highly selective, potent CB1R inverse agonist, Heymsfield's team said. Preclinical studies in animals showed that it can cause weight loss at doses that block just 30 percent of cannabinoid receptors. To extend those findings to humans in the new studies, the researchers first used positron emission tomography (PET) imaging to identify a dose that would bind about 30 percent of cannabinoid receptors in the human brain. They found that 4 to 6 milligrams of taranabant was enough to achieve that goal.

A multicenter, double-blind, placebo-controlled clinical trial including 533 obese patients showed that the drug induces significant weight loss at doses ranging from 0.5 to 6 milligrams. "That was surprising," Heymsfield said. "We didn't expect weight loss at all doses."

The researchers then conducted separate food intake and energy expenditure studies in overweight and moderately obese people who took a single 4- or 12-milligram dose of taranabant. Those studies showed that people taking 12 milligrams of the drug consumed 27 percent fewer calories than those taking a placebo. People taking the drug also expended more energy while at rest and appeared to burn more fat.

The studies also found that higher doses of the drug caused two types of adverse events, Heymsfield said. These negative side effects included gastrointestinal upset, including nausea and vomiting, as well as increased irritability. Marijuana is often used to combat the nausea associated with chemotherapy drugs, Heymsfield noted, and it also tends to make people mellower. "Here, again, [these drugs] have the opposite effect."

A larger, phase III clinical trial of taranabant is now underway to further

explore its effects, Heymsfield said. “All we have here is 12 weeks; we don’t yet know what will happen at six months or a year.”

Source: Cell Press