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Weighing the Consequences of Weight-Loss Drugs

— We need more discussion of the potential harms

by Judy Butler, MS, and Adriane Fugh-Berman, MD May 12, 2023

Tirzepatide (Mounjaro), perhaps with a new brand name, will likely join semaglutide (Wegovy) by year's end as an approved weight-loss treatmentopens in a new tab or window for people with obesity or overweight and at least one weight-related medical problem. Tirzepatide is currently only approved for diabetes but is prescribed off-label for weight loss. More potent than semaglutide, which is also approved for type 2 diabetes, tirzepatide causes an average 22.5% reductionopens in a new tab or window in body-weight for people without diabetes. Tirzepatide's developer Eli Lilly will reportedly use a priority review voucher purchased for $110 millionopens in a new tab or window to shave 4 months off the approval timeline for a weight-loss indication.

Prescriptions for these incretin mimetics for weight loss -- on- or off-label -- have skyrocketed. While patients may be shedding pounds, it's far from certain whether these new drugs will actually improve health outcomes, and

we're concerned that the prevailing narrative hasn't given enough air time to the potential drawbacks.

Incretin mimetics were originally developed to treat type 2 diabetes by stimulating insulin production. When diabetics lost weight, these drugs were repurposed for weight loss. Both semaglutide and tirzepatide act as agonists for glucagon-like peptide-1 (GLP-1), a hormone that slows gastric emptying and signals the brain to decrease appetite and reduce energy intake. With the addition of an agonist for another incretin (gastric inhibitory polypeptide [GIP]), tirzepatide causes greater weight reduction (although the role of GIP is uncertainopens in a new tab or window).

The bottom line is that patients lose interest in eating, so they eat less. But incretin mimetics must be taken over a lifetime -- once the drugs are stopped, the weight returnsopens in a new tab or window. Given the adverse health consequencesopens in a new tab or window of weight cycling, any temporary benefit of weight loss could be offset by longer-term harms of weight regain when the drugs are stopped.

Weight Loss Doesn't Equal Better Health

These drugs may not improve health outcomes. In part that's because for obesity they are prescribed based only on body mass index (BMI) -- a measure solely defined by height and weight and developed using data only from white men. While a higher BMI may be associated with health risks in a population, BMI is a poor predictoropens in a new tab or window of cardiometabolic health in individuals. What's more, a little extra weight may be protective. A meta-analysisopens in a new tab or window found that, compared to normal weight, grade 1 obesity (BMI 30 to <35) was not associated with higher mortality, and overweight (BMI 25 to <30) was associated with significantly lower all-cause mortality.

Obesity is a risk factor for hypertension, hyperlipidemia, and diabetes, but is too often used as a surrogate for these conditions. Many thin people are hypertensive or diabetic, and many higher-weight people are normotensive and don't have diabetes or hypercholesterolemia.

Health outcomes can be improved without losing weight, and research supports a weight-neutral strategyopens in a new tab or window for obesity treatment. Data show that, even in the absence of weight loss, exercise training can improve most cardiometabolic risk factors associated with obesity. And increases in cardiovascular fitness and physical activity, unlike weight loss, are consistently associated with lower mortality risks.

These Drugs Come With More Than Weight Loss

GLP-1 and GLP-1/GIP receptor agonists may benefit a few highly selected patients, but given known harms -- and the potential for unknown long-term harms -- BMI alone should never be the deciding factor. Certainly no one without medical problems should be using these drugs in an effort to improve health or to improve appearance. Nausea, vomiting, and diarrhea can be severe enoughopens in a new tab or window to send patients to the hospital. These drugs also increase risksopens in a new tab or window of acute pancreatitis, gallbladder disease, kidney problems, and suicidal ideation, and may increase the risk of thyroid cancer.

Media are also reporting more adverse effects, including malnutritionopens in a new tab or window caused by inadequate food intake, hair lossopens in a new tab or window, and unusual, vivid dreamsopens in a new tab or window.

There's also concern about increased adverse effects in elders and populations of color, who were inadequately represented in clinical trials for both semaglutideopens in a new tab or window and tirzepatideopens in a new tab or window -- participants were primarily white (75%), middle-age (45 years) women (67%). Many older adultsopens in a new tab or window are

sarcopenic, and incretin mimetics cause loss of lean body mass as well as fat mass. Moderate obesity may be protective against cardiovascular risks after age 65. Questions also remain about the effect of these drugs on Black Americans, three quartersopens in a new tab or window of whom have a BMI classifying them as overweight or obese. At best, less than 8%opens in a new tab or window of trial participants were Black in the tirzepatide trial.

Consider the Messenger

Hype is common with incretin drugs, and we understand these medications can be life-changing for select patients. But there needs to be more discussion of harms, the unknown effects of lifelong use, the dearth of information on Black patients, the value of BMI as a predictor of health risks, and whether these drugs actually benefit health. Even harder to find is discussion of the robust research available that supports a weight-neutral strategy for increasing health in higher-weight patients.

Certainly our weight-obsessed culture is one reason for this limited discourse, but omitting any unappealing facts or unknowns aligns with the interest of pharmaceutical companies. A legion of conflicted individuals and organizations funded by weight-loss drug manufacturers promote a one-sided perspective and actively advocate for broad insurance coverage, especially for Medicare recipients.

Pharmaceutical company-sponsored organizations and individuals may not believe this money influences their positions, but, if their positions didn't align with the industry view, they wouldn't be receiving that funding. Doctors paid by weight-loss drugmakers are training new residentsopens in a new tab or window and medical studentsopens in a new tab or window, offering continuing medical educationopens in a new tab or window, providing interactive learning modulesopens in a new tab or window, and appearing on 60 Minutesopens in a new tab or window. A slew of obesity care and advocacy organizations lobby for insurance coverage, run awareness

campaigns, hold conventions, and offer advice for healthcare providersopens in a new tab or window. Quotes from spokespeople to the media relay industry messages without mentioning ties with industry.

While advocates may believe they are providing unbiased evidence-based information, it's woefully incomplete and misleading. Billions of dollars are likely to be spent on these drugs. A dispassionate look at what taxpayers get for that money is the only way to assess that investment. That's not going to happen when industry is pulling the strings.

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