Medical News & Perspectives

# At ObesityWeek, More Data and Questions About Semaglutide, Tirzepatide, and Retatrutide

Kate Ruder, MSJ

Antiobesity drugs were front and center at the annual ObesityWeek conference, held in Dallas, Texas, this past October.

"There was a huge focus on newer medications, their efficacy, their safety, gaps in knowledge, and what future studies are needed," said John A. Batsis, MD, an associate professor of medicine at the University of North Carolina at Chapel Hill and a member of the ObesityWeek 2023 program committee.

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New data were presented for tirzepatide, a glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. Tirzepatide, branded as Zepbound, received US regulatory approval for chronic weight management 3 weeks after the meeting. Discussions also focused on semaglutide, the GLP-1 receptor agonist marketed as Wegovy for chronic weight management. Semaglutide and tirzepatide are hormone-mimicking drugs originally approved as diabetes therapies under the names Ozempic and Mounjaro, respectively.

In interviews with *JAMA*, Batsis and other clinicians who treat patients for obesity shared what stood out for them about these and other therapies at the meeting.


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## Questions About Lifestyle Changes

In the era of highly effective drugs for weight management, the role for intensive diet and exercise changes and frequent behavioral counseling may be less clear, said John Michael Taormina, MD, an assistant professor at the University of Colorado (CU) School of Medicine.

At the meeting, researchers presented the results of a randomized clinical trial that examined tirzepatide's efficacy after an intensive lifestyle intervention that included a reduced calorie diet, 2.5 hours or more of physical activity per week, and frequent behavioral therapy.

According to the study authors, despite being a "cornerstone of obesity management," the overall effectiveness of intensive lifestyle intervention is limited because only a minority of people achieve significant weight loss and regaining weight is common. The new trial, SURMOUNT-3, was designed to see if adding the drug could help. The almost 600 participants randomized to receive tirzepatide or a placebo had already lost an average of 5% of their weight as part of a 3-month intensive lifestyle intervention. Their baseline body mass index (BMI) before the lifestyle intervention was 30 or greater or 27 or greater with at least 1 obesity-related complication besides diabetes.

After 72 weeks, people who received 10-mg or 15-mg doses of tirzepatide lost an additional 18% of their body weight on average whereas people who received a placebo regained 2.5% of their body weight.

Tirzepatide's efficacy was clear, but questions remain about how much exercise or calorie restriction is necessary with new antiobesity medications, said Taormina, who treats patients with obesity at the CU Anschutz Weight Management and Wellness Clinic.

Taormina noted that people who received tirzepatide for 88 weeks lost 26% of their body weight without any intensive lifestyle intervention in the SURMOUNT-4 trial. Those results were presented this October at the European Association for the Study of Diabetes meeting. And in the Semaglutide Treatment Effect for People with obesity (STEP) clinical trials, people who received semaglutide alongside an intensive lifestyle intervention lost only 1% more of their body weight than those who received the drug without intense diet, exercise, and counseling interventions.

"What people were talking about at the conference is, what is the role of intensive lifestyle modification anymore with these newer, more powerful medications?" said Taormina, who was not involved with the trials. "That's not an answer that we really have right now."

## Concerns About Body Composition

For Taormina, the SURMOUNT-3 findings brought up larger questions about what happens to the body during weight loss with these medications, and how clinicians should help patients manage these changes. For example, do patients who take these drugs lose healthy lean body mass? Do they develop nutritional deficiencies?

The SURMOUNT-3 trial did not report on body composition, according to Taormina. But in SURMOUNT-1, 25% of weight lost was lean body mass, similar to that reported with lifestyle-based and surgical obesity treatments. The STEP-1 trial found that total lean body mass decreased from baseline by nearly 10%; however, the proportion relative to total body mass increased by 3 percentage points.

"We also know that functionality and cardiometabolic markers improve with use of these medications, so the loss of lean mass may not necessarily lead to worsened health outcomes," Taormina wrote in an email.

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>
> **Jacinda Nicklas, MD, MPH**

"However," he added, "we worry about this particularly in older adults, who are at increased risk of sarcopenia and are not well-represented in weight loss medication clinical trials." Another concern is weight cycling with the drugs, Taormina said. In this scenario, people who have lost significant weight stop taking the medications, regain weight primarily as fat—increasing their total fat percentage—and "subsequently may have greater challenges losing weight with future attempts," he explained.

Loss of lean mass was also an important theme of the meeting for Batsis, and notable to him as a geriatrician who treats older adults for whom preservation of muscle mass, strength, and function is integral to aging well.

Batsis, who chaired and led several sessions on obesity care at the conference, said the question of body composition came up in all of them.

Instead of providing definitive answers, he and Taormina said the conference showed that clinicians are eager for more data beyond BMI, a controversial stand-alone measurement of obesity. Body composition measurements such as waist circumference or dual-energy x-ray absorptiometry (DXA) scans, should be included in clinical trials of new drugs, Taormina said, but also should be available and affordable for people currently undergoing obesity treatment.

In fact, according to an ObesityWeek abstract by Eli Lilly researchers, DXA data from a phase 2 clinical trial suggest that treatment with the investigational triple-hormone-receptor agonist retatrutide may improve body composition, at least among people with type 2 diabetes. Retatrutide targets GLP-1 and GIP, plus glucagon.

A presentation on advances in pharmacotherapy included experimental agents like bimagrumab, a monoclonal antibody that may help patients with type 2 diabetes and obesity both lose fat and increase lean mass. Taormina said in an email, "newer medications like bimagrumab are an exciting development to help mitigate lean mass loss."

Ultimately, Batsis, said, "We need to think beyond just prescribing medications. We really need a multidisciplinary strategy that requires ongoing monitoring, just like any chronic disease."

## More Effective for Women?

Jacinda Nicklas, MD, MPH, gave a talk at the conference showing that females often respond better to newer antiobesity medications than males.

"Something that we're gradually becoming more aware of over time is that GLP-1s, in general, seem to work better in females," Nicklas, an associate professor of internal medicine at CU School of Medicine who specializes in obesity and women's health, said in an interview with *JAMA*.

Nicklas did not present new research, but instead combed through past studies of GLP-1 agonists. She said sex differences haven't often been separated out in studies and that the majority of participants in the clinical trials are females.

Digging into the data from the STEP trials of semaglutide, she said females had greater weight reduction than males. The same was true in a phase 2 clinical trial of retatrutide for treatment of obesity without type 2 diabetes. Participants who received the highest dose lost an average of 24% of their body weight but females lost much more: about 29% compared with about 20% for males.

"Whether these observations are attributable to sex-dependent differences in body composition, adipose distribution, or hormonal milieu remain to be determined," authors of the retatrutide study wrote, noting that other studies of GLP-1 agonists have shown similar sex trends.

Nicklas agreed that more questions than answers remain despite early indications. It's not yet known why females might respond better to antiobesity drugs like semaglutide. And it's unknown whether females of certain ages, races or ethnicities, or baseline body weight might respond better than other females. Further research specifically examining sex differences in outcomes over time is needed, she urged.

## Coverage Issues

"One of the biggest challenges in treating obesity is that we have these great treatments, but if insurance won't pay for them and they're thousands of dollars a month for medications people take long-term, they're just not accessible for our patients," Taormina said.

The list price of Wegovy and Saxenda (the form of the older GLP-1 agonist liraglutide approved for chronic weight management) is roughly $16 000 a year. Zepbound, which is expected to become available by the end of the year, costs $12 700 annually out of pocket. Meanwhile, Medicare doesn't cover antiobesity medications and Medicaid and commercial insurance coverage varies.

Batsis said lack of access can lead to disturbing trends. For example, Medicaid may cover semaglutide in the form of Ozempic for diabetes, but not Wegovy for obesity. In sessions at ObesityWeek, he heard clinicians describe patients who tried to raise their glycated hemoglobin $A_{1c}$ level, a measure of blood glucose, to obtain a diabetes diagnosis or tried to gain more weight to reach a BMI that would qualify them for coverage.

"Let's make our health worse, so we can have access to these medications. It's so counterintuitive," Batsis said.

Batsis, Nicklas, and Taormina all agreed that new medications like Wegovy and Zepbound have the potential to change obesity treatment, but many questions remain.

"From an efficacy standpoint, we know that they work. That's the primary outcome," Batsis said. "Now, we need more real-world data to say, well, how much do they work and what's the risk-benefit?" ■

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