Semaglutide Has Disproportionate Suicidality Signal, Analysis Finds

— Reports of suicidal ideation higher when compared to other drugs in WHO database

A disproportionality analysis based on reports in a World Health Organization (WHO) database suggested a suicidal ideation signal with the GLP-1 receptor agonist semaglutide (Ozempic, Rybelsus, Wegovy).

Between 2000 and 2023, semaglutide had 45% higher odds of suicidal ideation reports compared with all other drugs in the WHO database (reporting odds ratio [ROR] 1.45, 95% CI 1.18-1.77), according to Georgios Schoretsanitis, MD, PhD, of the Zucker Hillside Hospital in Glen Oaks, New York, and colleagues.

The finding "warrants urgent clarification," the researchers wrote in *JAMA Network Open*opens in a new tab or window.

Meanwhile, liraglutide (Victoza, Saxenda) -- another GLP-1 with indications for diabetes and weight management -- didn't have this same signal (ROR 1.04, 95% CI 0.87-1.25).

The researchers found 94 reports of suicidal ideation among more than 30,000 total reports associated with semaglutide and 116 reports of suicidal ideation associated with liraglutide among more than 52,000 total reports associated with that drug.

"While our main finding was the signal of suicidal ideation related to treatment with semaglutide, we also identified a subgroup of individuals at risk of reporting suicidal ideation associated with semaglutide," Schoretsanitis told *MedPage Today*. This included patients with co-reported use of antidepressants and/or benzodiazepines with semaglutide:

- Antidepressants: ROR 4.45 (95% CI 2.52-7.86)
- Benzodiazepines: ROR 4.07 (95% CI 1.69-9.82)

Reporting was not disproportionate when excluding patients with antidepressant co-medication, but remained disproportionate when excluding those with benzodiazepine co-medication, the researchers noted.

"Based on this finding, we suggest that physicians prescribing semaglutide should inform their patients about the medication's risks and assess the psychiatric history and evaluate the mental state of patients before starting treatment with semaglutide," Schoretsanitis advised.

"A safe treatment with semaglutide should be based on a careful evaluation of risks and benefits considering, also, the potential risk of suicidal ideation," he said. "We categorically discourage off-label use of semaglutide and without any medical supervision."

Accompanying commentaryopens in a new tab or window authors Francesco Salvo, MD, PhD, of the Université de Bordeaux, and Jean-Luc Faillie, MD, PhD, of the Université de Montpellier, both in France, agreed that GLP-1 receptor agonists should be prescribed with "great caution in patients with a history of depression or suicidal attempts."

Immediate discontinuation should be considered for patients on one of these agents with new onset of depression without other apparent precipitants, Salvo and Faillie advised.

Last year's reports of suicidality and self-harm with GLP-1 agonists to the FDA and European Medicines Agency (EMA) triggered his group's investigation, Schoretsanitis said.

Several months after the first reports were received in the FDA's Adverse Event Reporting System, the agency saidopens in a new tab or window its preliminary evaluation had "not found evidence" that GLP-1 receptor agonists cause suicidal thoughts or actions, but that it "cannot definitively rule out that a small risk may exist." The agency advised healthcare professionals to monitor patients using this class of drugs to report new or worsening depression, suicidal thoughts, or any unusual changes in mood or behavior.
By April, the EMA saidopens in a new tab or window it found no evidence to support a causal link between GLP-1 receptor agonists and suicidal thoughts following a 9-month review.
"Our results extend previous analyses of the EMA and FDA databases ... especially with regards to comorbidities [and] susceptibilities of semaglutide users," said Schoretsanitis. "The WHO database, known as VigiBase, is the largest and most comprehensive pharmacovigilance database."

This was the first analysis on the topic based on VigiBase data. Using a case-control design, the researchers examined 107 unique cases of suicidal and/or self-injurious adverse drug reactions associated with semaglutide and 162 cases associated with liraglutide. The median case ages were 48 and 47 for semaglutide and liraglutide users, respectively. The majority of both groups were female (55% and 61%, respectively).

The main reason for prescription was a possible off-label use (34 patients for semaglutide and 55 for liraglutide), followed by weight management (28 and 40, respectively), and diabetes (26 and 33).

In sensitivity analyses, the researchers also found a disproportionate reporting of suicidal ideation with semaglutide compared with other glucose-lowering and weight-loss drugs, mitigating the risk of confounding by indication for diabetes and obesity:

- Metformin: ROR 3.86 (95% CI 2.91-5.12)
- SGLT2 inhibitor dapagliflozin (Farxiga): ROR 5.56 (95% CI 3.23-9.60)
- Anti-obesity drug orlistat (Xenical, Alli): ROR 4.24 (95% CI 2.69-6.69)

Schoretsanitis and co-authors pointed out that a causal link cannot be assumed between semaglutide and suicidal thoughts or actions. Other limitations included an inability to determine whether weight change or other outcomes influenced the associations. There also was limited information about off-label prescribing.

Schoretsanitis suggested future studies look at patients with a previous history of mental disorders or with comorbid mental disorders, including patients in clinical practice.

News Source:

https://www.medpagetoday.com/psychiatry/generalpsychiatry/111601