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GLP-1 Receptor Agonists and Suicidality—Caution Is Needed

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Glucagon-like peptide 1 (GLP-1) receptor agonists, such as semaglutide or liraglutide, were first marketed as a second- or third-line treatment for patients with diabetes whose illness was not entirely managed with metformin, sulfonylureas, or dipeptidyl peptidase–4 (DPP-4) inhibitors. During their clinical development, the hypothesis that they could also be active as appetite suppressants arose and thereafter was clinically studied and confirmed. Recently, semaglutide was the first-in-class to receive marketing authorization for weight loss in patients with obesity or patients with overweight and cardiovascular risk factors. Moreover, their prescription could be continued *sine die* for weight control. These drugs could thus be considered blockbuster medications, and recent data showed a relevant increase in their prescriptions, in particular among young and adolescent patients. Between 2020 and 2023, GLP-1 receptor agonists use increased by 594% in young people, particularly in women.[1] Multiple influencers used social networks to endorse the efficacy of these drugs and were in part responsible for their success or at least put social pressure on physicians to prescribe them for weight loss in young adults and adolescents. Randomized clinical trials suggested that GLP-1 receptor agonists are globally well tolerated, but with an exponential increase in their use, rare events could have a public health impact. Several safety issues have already been raised, including a possible increased risk of thyroid cancer.[2]

More recently, GLP-1 receptor agonists have been associated with a possible increased likelihood of depression and suicidality. From a general perspective, evaluating the role of appetite suppressants in depression and suicidality risk is particularly challenging because of the bidirectional association between obesity and depression: patients with obesity are at increased risk of depressive disorders, while depression increases the likelihood of obesity. Past experience suggests that this risk must be attentively evaluated to avoid drug safety crises, as happened with the worldwide withdrawal of rimonabant in 2008.

Concerning GLP-1 receptor agonists, a certain imbalance of depressive symptoms was seen in phase 2 or 3 trials without reaching statistical significance. This could be related to at least 2 reasons. First, this event is too rare to be well studied in a premarketing setting. Second, patients with a positive history of depression or suicidality were excluded from these trials to avoid unnecessary risk.

Until today, only a very recent cohort study using Market Scan data was sufficiently powerful to assess the risk of suicidality in real-life GLP-1 receptor agonist users. However, it did not detect any cases of suicidal ideation among a very large cohort of patients with obesity treated with semaglutide and did not support any increased risks of suicidal ideation with this GLP-1 receptor agonist compared with other anti-obesity (or antidiabetes) medications. Authors advocated nonetheless to pay attention when prescribing these drugs for patients with a positive history of psychiatric disorders.[3]

Aside from this study, evidence related to this possible risk comes essentially from studies conducted though pharmacovigilance databases. One study using the US Food and Drug Association pharmacovigilance database suggested that suicidal ideation and suicidal depression for semaglutide and liraglutide were more reported than expected (ie, disproportionate reporting),[4] whereas another did not detect an association with suicidality and GLP-1 receptor agonists, suggesting concomitantly to pay attention to the psychiatric status of patients with a history of neuropsychotropic drugs.[5] Contradictory results in studies based on pharmacovigilance data are quite expected. Khouri et al[6] showed a wide variability of results coming from disproportionality analyses, depending both on the method and model specifications, thus opening the door for a

selective reporting of results. The preregistration of protocols and the presentation of a set of secondary and sensitivity analyses are thus warranted to reduce, as much as possible, these biases.[6]

Through a timely and well-conducted study, Schoretsanitis et al[7] add an important piece to the very relevant safety issue related to GLP-1 receptor agonists. For the first time, they analyzed the data collected in the global World Health Organization database, using both frequentist and bayesian methods, and proposing a number of sensitivity analyses that are coherent with the principal one. Moreover, they applied a very recent guideline for increasing the quality of reporting studies in pharmacovigilance databases.[8,9] They found a signal related to semaglutide but not liraglutide, particularly pronounced in patients with coreported antidepressant use. They finally suggested the conduct of specific studies in this population. Although very rare, the reported cases of patients presenting suicidal ideation with positive dechallenge and rechallenge, ie, regression of the effect on discontinuation and reappearance of the effect on reintroduction, call for caution. They also conclude that these findings need to be further confirmed through other data sources and study designs.

In the meantime, the position of the US FDA recommending caution continues to be reasonable. Whatever the cause, depression or suicidality are rare but extremely severe events and need to be prevented and managed as much as possible. Waiting for more precise data, GPL-1 receptor agonists, and appetite suppressants in general, should be prescribed with great caution in patients with a history of depression or suicidal attempts, while in patients with new onset of depression without other apparent precipitants, immediate discontinuation of GLP-1 receptor agonists should be considered.

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