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Letter to the Editor

GLP-1 agonists for metabolic disorders in schizophrenia

Patients with schizophrenia have a 2- to 3-fold higher mortality rate compared with the general population. A high prevalence of obesity, cardiometabolic disorders, and type 2 diabetes among these patients largely explains the increased cardiovascular risk (Correll et al., 2017).

To manage these metabolic abnormalities, different strategies, including diet and lifestyle modifications, behavioral interventions, switching of antipsychotics, adjunct pharmacological treatments (e.g., metformin, statins) and bariatric surgery have been proposed (Kouidrat et al., 2015, 2017). However, these approaches may be insufficient, impractical or fail to counteract metabolic dysregulation among all patients with schizophrenia.

Glucagon-like peptide-1 receptor agonists (or GLP-1 agonists) constitute a group of drugs that mimic the effects of native GLP-1, a hormone secreted by the endocrine L-cells in the gut in response to nutrient ingestion. GLP-1 plays a crucial role in glucose metabolism and body weight control through different mechanisms of action. Indeed, GLP-1 stimulates insulin secretion in pancreatic beta cells and inhibits glucagon secretion, thereby lowering plasma glucose levels. Moreover, GLP-1 slows gastric emptying and reduces appetite and food intake (Ebdrup et al., 2012). According to the American Diabetes Association (ADA) guidelines, GLP-1 agonists are used as second-line therapy for type 2 diabetes, often in combination with metformin. In 2015, a high dose of one GLP-1 agonist (liraglutide, 3 mg once daily) was approved for the treatment of obesity.

In 2013, Ishøy et al. published the first clinical evidence supporting the use of GLP-1 agonists in the treatment of antipsychotic-induced weight gain in an obese patient with schizophrenia and dysregulated diabetes (Ishøy et al., 2013). To highlight the safety, tolerability and efficacy of GLP-1 agonists in people with schizophrenia, we conducted a narrative summary based on a literature search using Medline, PubMed and the clinical trials database (ClinicalTrials.gov) until December 2017.

To date, three completed and published clinical trials were identified (Table 1). Two have suggested that this medication (treatment was self-administered) can lead to weight loss and the improvement of glucose metabolism in schizophrenia patients compared to controls (Larsen et al., 2017; Siskind et al., 2018). However, Ishøy et al. found similar weight loss in both the exenatide and placebo groups (treatment was administered by trial personnel) ($P = .98$) (Ishøy et al., 2017b). This finding may be surprising, as previous placebo-controlled trials with GLP-1 agonists in obese diabetic, as well as obese nondiabetic, nonpsychiatric patients, have consistently reported body weight losses. In addition, factors such as motivation to achieve weight loss, diet and physical exercise could have influenced between-group differences.

The safety and tolerability of GLP-1 agonists were also investigated in all 3 studies. As expected, gastrointestinal events (e.g., nausea, vomiting, and diarrhea) were the most common adverse effects reported. Consistently, nausea tends to be mild to moderate in nature and decreases over time. In all 3 of these studies involving schizophrenia patients, no differences were found between GLP-1 agonists and placebo with respect to quality of life, daily function, and psychiatric disease severity. However, two main limitations must be highlighted. First, the effectiveness of GLP-1 agonists for schizophrenia patients remains low compared to previous and large clinical trials that evaluated GLP-1 agonists to treat patients with diabetes or obesity. Second, a trial duration of 3 months may be insufficient to reach definitive conclusions. Third, the largest barrier to accessing GLP-1 agonists is probably cost, which may be partly offset by the health benefits (reduced cardiometabolic complications). Further studies should be evaluated to make appropriate formulary/prescribing decisions.

Interestingly, beyond the positive metabolic effects of GLP-1 agonists, researchers have considered the potential neuroprotective effects of GLP-1 agonists on the brain (McIntyre et al., 2013). However, Ishøy et al. found that three-month treatment with the GLP-1 agonist exenatide, 2 mg once weekly, did not improve cognition or psychosocial function in schizophrenia spectrum patients (Ishøy et al., 2017a, 2017b). These nonsignificant results could reflect a general problem of translating cognitive-enhancing effects of GLP-1 agonists from animals to humans or be explained by factors specifically related to schizophrenia spectrum patients with obesity, such as antipsychotic treatment.

Nevertheless, an ongoing clinical trial is aiming to explore the effects of GLP-1 agonists on brain structure and cognitive function in patients with mood disorders (NCT02423824). In this trial, the primary efficacy outcome corresponds to the mean change from baseline to week 4 on executive function performance, as measured by specific cognitive and psychometric tests.

To conclude, as preliminary results, GLP-1 agonists could be a potentially effective intervention that may reduce cardiometabolic morbidity in patients with schizophrenia. These findings should be taken with caution, and further research is needed to determine whether GLP-1 agonists can be used as a preventive adjunctive treatment during the emergence of weight gain and metabolic abnormalities. Future studies will also have to explore the potential neuroprotective effects of GLP-1 agonists.

Conflicts of interest

The authors declare that there are no conflicts of interest in relation to the subject of this study.

Contributors

YK managed the literature searches and analyses. All authors contributed to and have approved the final manuscript.

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Table 1
Clinical trials assessing GLP-1 agonists in schizophrenia.

Study and design	GLP-1 agonists and duration	*N* intervention/ controls	Age intervention/ controls (years)	Baseline body weight (kg)	Body weight loss (kg) *P*-value	Significant improvement of glucose metabolism
Ishøy et al. (2017b)	Exenatide 2 mg, once weekly, subcutaneous (Administered by trial personnel) (3 months)	20/20	37.4 ± 10.7 vs 34.4 ± 10.6	118.3 ± 16	2.24 ± 3.3 vs 2.23 ± 4.4 ($P = .98$)	No
Larsen et al. (2017)	Liraglutide 1.8 mg, once daily, subcutaneous (Self-administered) (3 months)	52/51	42.1 ± 10.7 vs 43.0 ± 10.5	103.3 ± 16.1	4.7 ± 0.5 vs 0.5 ± 0.7 ($P < .001$)	Yes
Siskind et al. (2018)	Exenatide 2 mg, once weekly, subcutaneous (Self-administered) (24 weeks)	14/14	18 to 64 years	108 ± 8.8	5.29 vs 1.12 ($P = .015$)	Yes

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