

Therapeutic management of atypical antipsychotic-related metabolic dysfunctions using GLP-1 receptor agonists: A systematic review

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Abstract. Metabolic disorders (MDs) like obesity, dyslipidemia, and type 2 diabetes are more frequently observed in patients diagnosed with psychiatric disorders undergoing treatment with antipsychotics, particularly atypical agents, than in the general population. The second generation of antidiabetics (SGAD) has been associated with cardiovascular benefits in large clinical trials which represent an important advantage over first-generation agents and might be of interest in the psychiatric population where multiple risk factors for cardiovascular disease (e.g., smoking, lack of exercise, and lack of healthy diet) are common occurrences. Therefore, this systematic review focused on the evaluation of the glucagon-like peptide-1 receptor agonists (GLP1-RAs), as a representative of the SGAD, to determine whether these agents may be recommended in patients with psychiatric disorders and MDs. For analysis, three electronic databases and clinical trial registers were explored for papers published between January 2000 and November 2022. After applying the inclusion and exclusion criteria, 20 clinical and preclinical trials, therapeutic guidelines, and meta-analyses were reviewed, and clinical recommendations were formulated. The large majority of the reviewed data (nine papers) were graded 'moderate' based on the GRADE criteria. The efficacy and tolerability of liraglutide and exenatide in the management of antipsychotic-induced MDs were supported by evidence of average quality, while the results regarding other GLP-1RAs were not sufficient to formulate a recommendation for their administration in this specific population. Clozapine and olanzapine had the most negative consequences on body weight, glycemic, and lipid metabolism. Therefore, careful monitoring of metabolic

parameters is required when these are prescribed. Liraglutide and exenatide may be recommended as augmentative agents to metformin therapy, especially in patients receiving these two atypical antipsychotics, but most of the reviewed data supported the efficacy of GLP-1RAs only during the treatment administration. The two follow-up studies retrieved in the literature reported modest effects after GLP-1RA discontinuation after 1 year; therefore, long-term monitoring of metabolic parameters is required. More research is needed, and three randomized clinical trials are already ongoing, to evaluate the effects of GLP-1RAs in decreasing body weight, but also on other important metabolic variables, such as HbA1c status, fasting glucose levels, and lipid levels in patients receiving antipsychotic treatment.

Introduction

Atypical antipsychotics are currently used in clinical practice for multiple indications, primarily schizophrenia spectrum disorders (SSD) and bipolar disorders, but they may be useful adjuvants in depressive disorders, behavioral and psychological symptoms associated with neurocognitive disorders, tic disorders, and autism spectrum disorders, amongst others. These pharmacological agents are related to various metabolic adverse effects, ranging from obesity, overweight, or dyslipidemia, to impaired glucose tolerance and diabetes (1-3). Negative consequences of the antipsychotic treatment led to a worse quality of life and unfavorable functional prognosis by adding to other risk factors in a population already affected by severe long-term impairments and a high rate of somatic comorbidities (1-5). Increased risk for cardiovascular diseases and diabetes has been reported in drug-naïve patients with SSD, likely based on genetic vulnerability and negative lifestyle factors (4,6). This biological vulnerability highlights the importance of investigating the role played by antipsychotics in the onset or worsening of metabolic dysfunctions in SSD patients. Pharmacogenomic-focused research could offer insight into the selection of the antipsychotic agent with the lowest risk of adverse events in a specific case, or at least could indicate the need for earlier changes in lifestyle after the initiation of treatment in vulnerable individuals.

According to a UK national survey of 31,719 participants, a lower life expectancy was reported in association with major

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psychiatric illnesses vs. controls, with a reduction of >14 years for males, and 17 years for females (2). Smoking, diabetes, as well as obesity, are among the most well-recognized contributors to this difference in life expectancy (2,7). It is estimated that antipsychotic-induced weight gain may ultimately reduce life expectancy by 25 years (8), although it seems implausible to attribute this kind of impact only to body weight changes during treatment, as an isolated factor.

Patients diagnosed with SSD have a >2x higher mortality rate vs. controls, with increased cardiometabolic risk, which is considered the primary cause of the mortality rate in this population (9). The participation of immune reactions and neurotrophic factors in the pathogenesis of psychiatric disorders, SSD included, and in the modulation of the atypical antipsychotic effects in these patients has been explored, and targeting these variables could be of interest for improving their prognosis (10-13). Shared pathogenic cascades and biological mechanisms underlying SSD and type 2 diabetes mellitus (T2DM) were studied, and common gene functions were related to the onset of both disorders (13). A poor diet, a sedentary lifestyle, and the adverse effects of antipsychotics are mediators between SSD and diabetes, making it difficult to distinguish the contribution of environmental factors from the common biological pathways (such as molecular basis, inflammation, oxidative stress, and neuroendocrine dysfunctions) (13). An increased vulnerability to the metabolic and cardiovascular adverse events of antipsychotics has been reported in children and adolescents, in particular a trend towards rapid weight gain during treatment (14).

The pharmacological mechanisms by which atypical antipsychotics induce metabolic disorders in patients with SSD are very complex and yet insufficiently clarified. The most extensively explored pathogenic pathways of the antipsychotics in obesity and diabetes are the antagonism of serotonin 5HT_{2C}, muscarinic M₁, and histamine H₁-receptors, and dysregulations of insulin, cortisol, glucagon, cholecystokinin, adiponectin, ghrelin, leptin, orexin, prolactin, and oxytocin (15,16).

Different pharmacological and non-pharmacological therapies are recommended for the control of metabolic dysfunctions in schizophrenia-diagnosed patients who are treated with antipsychotics, especially with atypical agents. Lifestyle changes, nutritional interventions, and counseling targeting a healthier lifestyle have been explored in this population in order to mitigate the trend toward weight gain (17). The switch to a metabolic-neutral antipsychotic may represent another option, but it may pose the risk of worsening psychotic symptoms (18). Adding a range of agents with favorable metabolic profiles to the current antipsychotic regimen has been suggested; however, the problem of insufficient treatment adherence and lower tolerability by increasing the number of medications in a reputedly low-insight population could be critical (19). Metformin benefits from the highest level of recommendation for the therapy of antipsychotic-induced weight gain in patients with SSD, followed by topiramate (20,21).

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) enhance insulin secretion as a reaction to high glycemic levels and decrease the speed of gastric emptying (1). The exact mechanisms of dysfunctions of glucose metabolism induced by atypical antipsychotic administration have not been

elucidated, but an increase in hepatic glucose synthesis, a decrease in pancreatic insulin discharge, and a higher peripheral/brain insulin non-responsivity were suggested (22-24). A pharmacological effect of atypical antipsychotics, especially clozapine, was involved in the acute decrease of GLP-1 signaling, suggesting this mechanism may explain the onset of obesity and glucose metabolism dysfunction in patients with SSD (25).

To date, six GLP-1RAs have been explored in clinical trials, and the recommendations formulated by the American Diabetes Association (ADA) support the use of these medications as second-line treatment for T2DM, frequently combined with metformin, while high doses of liraglutide have been approved for the therapy of obesity by the Food and Drug Administration (FDA) (8,9). The specific clinical pharmacology features of each GLP-1RA (liraglutide, semaglutide, albiglutide, dulaglutide, lixisenatide, and exenatide) have been described in Table I.

Liraglutide increases insulin secretion in the peripheral tissues, while at the central level, it exerts its actions on neurons expressing GLP-1 receptors, which are usually located in the brainstem, hypothalamus, and forebrain, including the nucleus accumbens (26,27). It was shown that GLP-1 receptor stimulation may result in the reduction of the functioning of the reward pathway (26). This phenomenon was associated with dysfunctions in the responsivity of the reward system as a common causal factor for excessive food intake and for the pathogenesis of schizophrenia (that is, the negative symptoms) (8).

Semaglutide, which is administered once a week, was superior to placebo in overweight or obese adults, according to a meta-analysis (n=4 trials, n=3,447 participants) that was focused on the change in body weight (28). Additionally, semaglutide reduced waist circumference and body mass index (BMI) vs. placebo, increased the quality of life, and improved various cardiometabolic risk factors (28). Oral semaglutide administration also had favorable results on body weight in T2DM patients, and, according to another meta-analysis (n=11 randomized controlled trials, n=9,890 participants), this drug was superior to placebo and several active comparators (including liraglutide, empagliflozin, and sitagliptin) in reducing HbA_{1c} levels and body weight (29).

Albiglutide has a very high sequence similarity to human GLP-1, is administered subcutaneously once a week, and has a longer half-life than the native peptide hormone (24). Additionally, the positive effects of albiglutide on glycemic management in cases of insufficiently controlled T2DM have proven beneficial effects on body weight, which were preserved during long-term administration, for up to 3 years (30). Unfortunately, this medication was globally withdrawn due to economic reasons by its manufacturer, in 2018 (31).

Dulaglutide is administered subcutaneously once a week and improves HbA_{1c} levels with an efficacy superior to metformin (26). Additionally, it decreased the body weight by a similar level to or less than (depending on the dosage used) its active comparator (metformin) in T2DM patients at week 52 (32).

Lixisenatide has low sequence similarity with GLP-1 (~50%) and is administered once a day (33). BMI was

Table I. Clinical pharmacology of GLP-1Ras.

Pharmacological agent	Characteristics	Clinical reports in the general population	Observations	(Refs.)
Liraglutide	Increases insulin secretion in peripheral tissues; agonist of the GLP-1R on neurons in the CNS (brainstem, HPT, and forebrain, NAc included); highly similar analog of human GLP-1; increases insulin secretion in a glucose-dependent manner; decreases abnormally high glucagon secretion. GLP-1R stimulation may reduce the activity of the rewards pathway	Decrease in body weight, decrease in body fat mass, regulates the appetite and food intake; improves glycemic control in patients with T2DM; decreases cardiovascular mortality and morbidity	Dysfunctions in the responsiveness of the reward system were found to be a common causal factor for excessive food intake and for the pathogenesis of schizophrenia (negative symptoms). Liraglutide is administered once daily s.c. in the abdomen, thigh, or upper arm	(8,9,26,27)
Semaglutide	This is a highly similar analog of human GLP-1; decreases overall appetite and decreases the preference for high-fat foods; improves β -cell function in the pancreas, lowers the fasting and postprandial glucagon levels, and causes a minor delay of the early postprandial gastric emptying	Superior to placebo in overweight or obese adults, according to a meta-analysis (n=4 trials, n=3,447 participants) focused on the change in body weight. Semaglutide reduced WC and BMI vs. placebo at a significant level while increasing the quality of life and various cardiometabolic risk factors. Oral semaglutide administration also had favorable results on body weight in T2DM patients, and, according to another meta-analysis (n=11 randomized controlled trials, n=9,890 participants), this drug was superior to placebo and several active comparators (including liraglutide, empagliflozin, and sitagliptin) in reducing HbA1c levels and body weight (29)	Administered s.c. once weekly, in the abdomen, thigh, or upper arm	(28,29)
Albiglutide	Albiglutide has a very high sequence similarity to human GLP-1; possibly less efficient than other GLP-1RAs for decreasing HbA1c	In addition to albiglutide's positive effects on glycemic management in cases of insufficiently controlled T2DM, this drug has proven	Administered s.c. once weekly; has a longer life than the native peptide hormone. This medication was globally withdrawn due to economic reasons by its manufacturer in 2018	(30,31)

Table I. Continued.

Pharmacological agent	Characteristics	Clinical reports in the general population	Observations	(Refs.)
Dulaglutide	High homology with human GLP-1 (90%). Increases insulin release in the pancreatic β cells when the blood glucose levels are high. Decreases glucagon secretion in T2DM patients. Decreases gastric emptying	beneficial effects on body weight, which were preserved during long-term administration for up to 3 years Dulaglutide has proven its capacity to improve HbA1c levels with an efficacy superior to metformin. Also, it decreased the body weight with a magnitude of effect similar to or inferior (depending on the dosage used) to its active comparator (metformin) in T2DM patients at week 52	Administered s.c. once weekly in the abdomen, thigh, or upper arm	(32)
Lixisenatide	Has low sequence similarity with GLP-1 (~50%). Increases insulin secretion when blood glucose levels are increased. Decreases glucagon secretion. Decreases gastric emptying	BMI significantly decreased when treated with lixisenatide in obese T2DM patients (3.2 kg loss after 3.8 ± 1.6 months) in an open-label study with 104 participants. However, in trials with active comparators, lixisenatide was outperformed by exenatide immediate release and liraglutide regarding the capacity to induce weight loss	Administered once daily in the thigh, abdomen, or upper arm	(33-36)
Exenatide	Unlike the other five pharmacological agents mentioned above, exenatide has a low sequence similarity to human GLP-1 (~53%)	Has been investigated for metabolic (obesity and diabetes) management, and also non-metabolic (cognitive functioning) effects in patients with SSD). The positive influence of GLP-1RAs on cognition observed in animal studies did not translate significantly in trials with schizophrenia-diagnosed patients	Administered twice daily (the immediate-release form) or once weekly (the extended-release form) s.c. in the abdomen, thigh, or upper arm	(9,34,37,39)
Tirzepatide	This is a dual GLP-1RA and glucose-dependent insulinotropic polypeptide	Pre-clinical studies and phase I to III	Administered s.c. in the abdomen, thigh, or upper	(40,41)

Table I. Continued.

Pharmacological agent	Characteristics	Clinical reports in the general population	Observations	(Refs.)
	receptor agonist. This drug is a synthetic peptide that contains 39 amino acids and is derived from the original GIP sequence	trials demonstrated the efficacy of tirzepatide in lowering blood glucose and body weight, with a tolerability profile similar to GLP1-RAs, in T2DM patients	arm, once weekly	

BMI, body mass index; CNS, central nervous system; GLP-1R, Glucagon-like peptide-1 receptor; GLP-1RA, GLP-1R agonist; HPT, hypothalamus; NAc, nucleus accumbens; s.c., subcutaneously; T2DM, type 2 diabetes mellitus; WC, waist circumference.

significantly decreased by lixisenatide in T2DM patients who were obese (3.2 kg after 3.8±1.6 months, in an open-label study with 104 participants (34). However, in trials with active comparators, lixisenatide was outperformed by exenatide immediate release and liraglutide regarding the capacity to induce weight loss (35,36).

Exenatide is a GLP-1RA investigated for metabolic disease (obesity and diabetes management) but also non-metabolic diseases (such as cognitive functioning) effects in patients with SSD (37,38). The positive influence of GLP-1RAs on cognition observed in animal studies did not translate significantly in trials with schizophrenia-diagnosed patients (9,37). Unlike the other five pharmacological agents mentioned previously (with the exception of lixisenatide), exenatide has a low sequence similarity to human GLP-1 (~53%), and it may be administered twice daily (the immediate-release form) or once weekly (the extended-release form) (33).

A comparative analysis of the effects of GLP-1RAs in T2DM patients (34 randomized controlled trials, 24-32 weeks duration) showed that all representants of this class (except for semaglutide and albiglutide, for which no data were identified) reduced the body weight compared to placebo (39). When all GLP-1RAs were compared with each other, no significant difference between them was observed regarding weight loss (39). A higher risk for gastrointestinal adverse events was reported for all agents compared to the placebo (39).

Tirzepatide was also considered within the conceptual frame of this review as this agent is a dual GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. This drug is a synthetic peptide that contains 39 amino acids and is derived from the original GIP sequence (40). Pre-clinical studies and Phase I-III trials demonstrated the efficacy of tirzepatide in lowering blood glucose and body weight, with a tolerability profile similar to GLP1-RAs, in T2DM patients (40,41).

The primary objective of this review was to determine the efficacy of GLP-1RAs in the therapeutic management of antipsychotic treatment-associated metabolic dysfunctions. Another objective was the exploration of the tolerability of the GLP-1RAs. The third objective was to formulate clinical recommendations based on the GRADE criteria (42,43) for the use of GLP-1RAs in patients with severe mental illnesses undergoing antipsychotic treatment, who developed metabolic dysfunctions.

Methods

A systematic review focused on the short- and long-term effects of GLP-1RAs administration on weight gain in subjects who received antipsychotics was performed, based on the PRISMA guidelines (44). For identifying relevant articles, three electronic databases (PubMed, <https://pubmed.ncbi.nlm.nih.gov/>; Cochrane, <https://www.cochrane.org/>; and Clarivate/Web of Science, <https://www.webofscience.com/>) as well as repositories for clinical trials (US National Library of Medicine, www.clinicaltrials.gov; EU Clinical Trial Register, www.clinicaltrialsregister.eu; and World Health Organization International Clinical Trials Registry Platform, www.who.int/clinical-trials-registry-platform) were included. The search criteria used were: 'glucagon-like peptide-1 receptor agonists' OR 'GLP1-RA' AND 'obesity' OR 'diabetes mellitus' OR 'metabolic syndrome' OR 'dyslipidemia' AND 'antipsychotics' OR 'psychiatric disorders'. All papers published between January 2000 and November 2022 were included in the primary search.

As the investigated class of antidiabetics was launched on the market relatively recently, a more inclusive methodology was chosen, using the SPIDER algorithm (Table II), which is more appropriate when quantitative, qualitative, and mixed methods research are expected to be analyzed than the traditionally recommended PICO algorithm (45). The main inclusion criteria referred to the sample (i.e., all patients, regardless of age, were included, and preclinical studies were also allowed if an antipsychotic drug was administered), the phenomenon of interest (i.e., the effects of short and long-term GLP-1RAs administration), the study design (i.e., all types of clinical and preclinical studies, case reports, and therapeutic guidelines were explored), the evaluation (i.e., efficacy, tolerability, and safety of GLP-1RAs, assessed by structured instruments, laboratory analyses, behavioral observations, and qualitative research), and the research type (i.e., qualitative and quantitative methodology). The main exclusion criteria were: Unspecified demographic parameters of the study population or insufficient descriptors for the animal models, lack of data concerning the intervention assessed, unclear diagnoses or experimental paradigms, the exploration of other non-GLP-1RA antidiabetics in monotherapy, unspecified design of the research, and lack of pre-defined measurements for the quantitative research.

Table II. SPIDER algorithm for systematic reviews.

Dimension	Inclusion criteria	Exclusion criteria
Sample	Children, adolescents, adults, and old age patients were included. Preclinical studies using any kind of subjects were allowed. All subjects were currently receiving antipsychotics. All psychiatric diagnoses or psychiatric disorders paradigms for animal studies were included	Unspecified demographic parameters of the study population (clinical research), or lack of sufficient descriptors for the animal model used (preclinical studies). Lack of specifics regarding the antipsychotics administered, or the GLP-1RA treatment regimen. Unspecified diagnoses for clinical populations or experimental paradigms for preclinical studies
Phenomenon of interest	The effects of short- or long-term GLP-1RA administration. Combined, GLP-1RAs and other antidiabetics were allowed	Other antidiabetics, if they were used as monotherapy
Design	Preclinical studies, clinical trials, prospective or retrospective, randomized or not, controlled or not, single/double-blinded or unblinded. Case reports, systematic reviews, and meta-analyses. Therapeutic guidelines, observations, document-based research, and experts' opinions	Unspecified design of the research. Reviews or meta-analyses with pre-defined quantifiable objectives that did not present different objectives (such as not including changes in the body weight or BMI) or contained poorly defined primary outcomes
Evaluation	Efficacy, tolerability, and safety of GLP-1RAs in the pre-defined population. Structured instruments, laboratory analyses, behavioral observational methods, and also qualitative research (patients' self-reports, and questionnaires)	Lack of pre-defined measurements for the quantitative research outcomes. Qualitative research, if they did not present clear references to the safety, efficacy, or tolerability of GLP-1RAs
Research type	Qualitative, quantitative, methods	Imprecise or undefined method of research

GLP-1RA, glucagon-like peptide-insulin receptor agonist.

GRADE recommendations for evaluating the quality of evidence were applied, using six dimensions: Study design, risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias (Table IV) (46). The overall quality of evidence was analyzed for each reviewed source and then rated from 'very low' to 'high'.

Results

Study inclusion. The primary search identified 107 papers, but only 20 remained after filtering them out according to the inclusion and exclusion criteria (Fig. 1). A total of three preclinical studies, two case reports, five prospective clinical trials (seven references, as two were follow-up studies), two retrospective studies, two meta-analyses, a therapeutic guideline, and three ongoing trials were reviewed in detail (Table IV and Fig. 2). The quality of evidence for the retrieved sources was 'low' (n=9), 'moderate' (n=4), and 'high' (n=4). No quality of evidence rating could be performed for the ongoing trials, due to the paucity of data available for these studies.

Preclinical trials. In a preclinical trial, C57BL/6J mice received olanzapine and/or liraglutide or exendin-4, while the blood glucose levels were periodically determined (22). The GLP-1RAs offered complete protection for male mice against increased glycemia due to olanzapine infusion while

increasing circulating insulin (both agents) and reducing the circulating levels of glucagon (in the case of liraglutide administration) (22). In the same trial, infusion of exendin 9-39 (which acts as a GLP-1RA) and olanzapine in female mice (which did not develop hyperglycemia after acute antipsychotic administration in the first phase of the experiment) led to increases in the blood glucose levels, compared with subjects receiving only olanzapine. Additionally, glucagon levels increased, and insulin levels decreased when female mice received both the antipsychotic and the GLP-1RA vs. olanzapine alone. Therefore, it may be concluded that pharmacological targeting of GLP-1 receptors may be a useful intervention to mitigate the acute negative influence of atypical antipsychotics on glucose metabolism (22).

In rats that received atypical antipsychotics-olanzapine [2 mg/kg three times a day (t.i.d)] or clozapine (12 mg/kg t.i.d), a GLP-1RA-liraglutide (0.2 mg/kg twice a day), combinations of these agents, or inactive comparator for 6 weeks, liraglutide proved beneficial by decreasing the weight gain and adiposity produced by olanzapine in the first stage of the study (47). Liraglutide also improved clozapine-induced glucose intolerance and significantly reduced the errors made during the Novel Object Recognition Test discrimination tasks (an outcome related to cognitive functioning) related to the administration of both antipsychotics (48).

Table III. Reports included in the review and their main descriptors.

First author/s, year or trial no.	Sample	Design	Results	Research type	RoB	IoR	IoE	Imp	PB	OQE	(Refs.)
Medak <i>et al</i> , 2020	Female and male C57BL/ 6J mice (n=15-18)	Preclinical trial, OLZ+/- LRGLT or EXND4, 120 min of drug co-administration. Outcomes: glycemia, insulin, and glucagon plasma levels, serum GLP level	Both GLP1RAs were associated with complete protection for male mice against OLZ- related HG. EXND4 did not protect against increases in glucagon plasma levels	Quantitative	No	No	Yes ^a	No	No	Mod	(22)
Babic <i>et al</i> , 2018	Female Sprague- Dawley rats (n=72)	Preclinical trial, OLZ, CLZ, LRGLT, OLZ+LRGLT, CLZ+LRGLT, 6 weeks. Outcomes: cognitive performance, body weight, adiposity, and glucose tolerance	LRGLT reduced OLZ- related WG and adiposity, and improved glucose intolerance and cognitive functioning	Quantitative	No	No	Yes ^a	No	No	Mod	(47)
Lykkegaard <i>et al</i> , 2008	Female Sprague- Dawley rats (n=40)	Preclinical trial, OLZ for 28 days, followed by LRGLT or placebo for 14 days. Outcomes: food intake, body weight, subcutaneous inguinal fat, mesenteric fat, retroperitoneal fat, and glucose tolerance	LRGLT improved cumulative food intake, WG, inguinal, mesenteric, and retroperitoneal fat	Quantitative	No	No	Yes ^a	No	No	Mod	(48)
Ishøy <i>et al</i> , 2013	Female patient diagnosed with SCHZ + T2DM + obesity	Case report, CLZ + LRGLT+ metformin + insulin, 3 months and 2-year follow-up.	LRGLT led to favorable outcomes (decreased HbA1c levels, BW, and daily insulin doses).	Quantitative and qualitative	Yes ^b	No	Yes ^c	No	No	Low	(49)

Table III. Continued.

First author/s, year or trial no.	Sample	Design	Results	Research type	RoB	IoR	IoE	Imp	PB	OQE	(Refs.)
		Outcomes: HbA1c, BW, insulin doses needed daily	Positive effects persisted after 2 years								
Siskind <i>et al</i> , 2016	Male patient diagnosed with SCHZ + T2DM	Case report, CLZ + EXNTD + metformin, 6 months.	EXNTD decreased BMI and waist circumference	Quantitative and qualitative	Yes ^b	No	Yes ^c	No	No	Low	(50)
Larsen <i>et al</i> , 2017; Svensson <i>et al</i> , 2019	103 patients diagnosed with SCHZ spectrum disorders	RDBCT, OLZ/CLZ + LRGLT or placebo, 16 weeks + 1-year follow-up. Outcomes: glucose tolerance, BW, waist circumference, systolic BP, adverse events, biological parameters (such as HbA1c and C-peptide levels)	LRGLT improved the glucose tolerance vs. placebo significantly at the endpoint. BW and waist circumference also decreased more vs. placebo. Primarily gastrointestinal symptoms were reported as adverse events. After 1 year, LRGLT- treated patients in the acute phase of the trial presented poorer glycemic control but a significant BW loss and BMI decrease vs. placebo	Quantitative	No	No	No	No	No	High	(51,52)
Siskind <i>et al</i> , 2018; Siskind <i>et al</i> , 2020	28 outpatients diagnosed with SCHZ ± T2DM	OLT, randomized, controlled, 24 weeks + 12- month follow-up,	EXNTD improved primary and secondary outcomes at 6	Quantitative	Yes ^d	No	No	No	No	Low	(38,53)

Table III. Continued.

First author/s, year or trial no.	Sample	Design	Results	Research type	RoB	IoR	IoE	Imp	PB	OQE	(Refs.)
		CLZ + EXNTD.	months vs. the usual care group. After 12 months, no differences between groups in BMI and BW were observed								
Ishøy <i>et al</i> , 2017	45 patients diagnosed with SCHZ spectrum disorders +/- obesity, without DM	RCT, EXNTD vs. placebo, 12 weeks. Outcome: BW change	The weight loss did not differ between groups at week 12 but was significant vs. baseline	Quantitative	Yes ^e	No	No	No	No	Mod	(54)
NCT00845507	54 patients diagnosed with BD, MDD, SCHZ, SCHZ-AF + obesity	RDBCT, OLZ + EXNTD, 28 days. Outcomes: BW change (primary)	EXNTD was superior to placebo in the primary outcome. SAE and AE rates were higher in the EXNTD group	Quantitative	Yes ^e	No	No	No	No	Mod	(55)
Whicher <i>et al</i> , 2021	50 patients diagnosed with SCHZ, SCHZ-AF, or FEP	RDBCT, 24 weeks, LRGLT vs. Placebo. Outcomes: BW (main), BMI, waist circumference, HbA1c (secondary)	The results significantly favor LRGLT, and the GLP- 1RA improved all the secondary outcomes vs. baseline	Quantitative	Yes ^e	No	No	No	No	Mod	(56)
Perlis <i>et al</i> , 2020	46 outpatients who received AP +/- an antidepressant treatment	Retrospective chart review, 1 year, AP + GLP1Ras or other AD +/- antidepressants, Outcomes: BW, HbA1c level, waist circumference, and BMI	HbA1c level decreased in both groups, but BW decreased significantly more with the GLP1Ras	Quantitative	Yes ^f	No	No	No	No	Mod	(57)
Lee <i>et al</i> , 2021	16 patients diagnosed with SCHZ or BD +	Retrospective chart review, 16 weeks, LRGLT.	BW change was significantly superior for	Quantitative	Yes ^f	No	No	No	No	Mod	(58)

Table III. Continued.

First author/s, year or trial no.	Sample	Design	Results	Research type	RoB	IoR	IoE	Imp	PB	OQE	(Refs.)
	obesity	Outcomes: BW change (primary), waist circumference, BMI, plasma glucose levels (secondary); Aes were assessed	patients treated with LRGLT, and the secondary outcomes also improved vs. Baseline values. Nausea was the most frequently reported AE								
Siskind <i>et al</i> , 2019	164 patients diagnosed with psychotic disorders + obesity	Meta-analysis (n=3 trials), primary outcome- BW change	BW change was significantly in favor of GLP-1Ras vs. Controls. Waist circumference, BMI, glucose, and lipid metabolism-related variables were significantly lower during GLP1Ras treatment. The overall tolerability was good	Quantitative	No	No	No	No	No	High	(59)
Wang <i>et al</i> , 2021	3467 participants diagnosed with SCHZ	Network meta-analysis (n=61 trials), primary outcome-BW change	GLP1Ras were significantly superior to placebo on BW and waist circumference. The tolerability was good	Quantitative	No	No	No	No	No	High	(60)
Cooper <i>et al</i> , 2016	Patients undergoing AP treatment who present WG and metabolic imbalance	Therapeutic guideline	GLP1Ras (LRGLT, EXNTD) have a 'B' rating, similar to bariatric surgery and lorcaserin. GLP1Ras may be added to other antidiabetics in the treatment	Qualitative and quantitative	No	No	No	No	Yes ^g	Mod	(61)

Table III. Continued.

First author/s, year or trial no.	Sample	Design	Results	Research type	RoB	IoR	IoE	Imp	PB	OQE	(Refs.)
			of T2DM if BMI \geq 35 kg/m ² , or if the BMI is lower, but there is an impossibility to use insulin therapy or weight loss is strongly recommended								
NCT05333003	92 patients (expected enrollment) with SCHZ spectrum disorders + obesity + non- responsivity to metformin	RDBCT, SMGLT vs. placebo as an add-on, 32 weeks. Primary outcome: BW change during the trial	No results yet	Quantitative	Not applicable						(62)
Sailer <i>et al</i> , 2019	154 patients (expected enrollment) with SCHZ spectrum disorders	RDBCT, OLZ/ CLZ + DLGLT vs. Placebo, 24 weeks. Primary outcome: % of BW change at 24 weeks	No results yet	Quantitative							(63)
ACTRN12621 001539820	120 patients (expected enrollment) with SCHZ	RDBCT, CLZ + SMGLT vs. placebo, 24 weeks. The primary outcome: % BW change at the endpoint	No results yet	Quantitative							(64)

^aanimal study, ^bblinding and allocation concealment not applicable, ^cobservational, ^dpilot study and not blinded, ^elow number of subjects in each arm, ^fretrospective study, ^gtherapeutic guidelines do not usually include negative trials. LRGLT, liraglutide; EXND4, exendin; EXNTD, exenatide; SMGLT, semaglutide; DLGLT, dulaglutide; GLP1RAs, glucagon-like peptide-1 receptor agonists; CLZ, clozapine; OLZ, olanzapine; WG, weight gain; HG, hyperglycemia; T2DM, type 2 diabetes mellitus; SCHZ, schizophrenia; BW, body weight; BPRS, Brief Psychiatric Rating Scale; RDBCT, randomized; double-blind clinical trial; BP, blood pressure; OLT, open-label trial; RCT, randomized clinical trial; BD, bipolar disorder; MDD, major depressive disorder; SCHZ-AF, schizo-affective disorder; FEP, first episode of psychosis; SAE, serious adverse events; AE, adverse events; AP, antipsychotics; AD, antidiabetics; OGTT, oral glucose tolerance test; BMI, body mass index; RoB, risk of bias; IoR, inconsistency of results; IoE, indirectness of evidence; Imp, imprecision; PB, publication bias; OQE, overall quality of evidence; Mod, moderate.

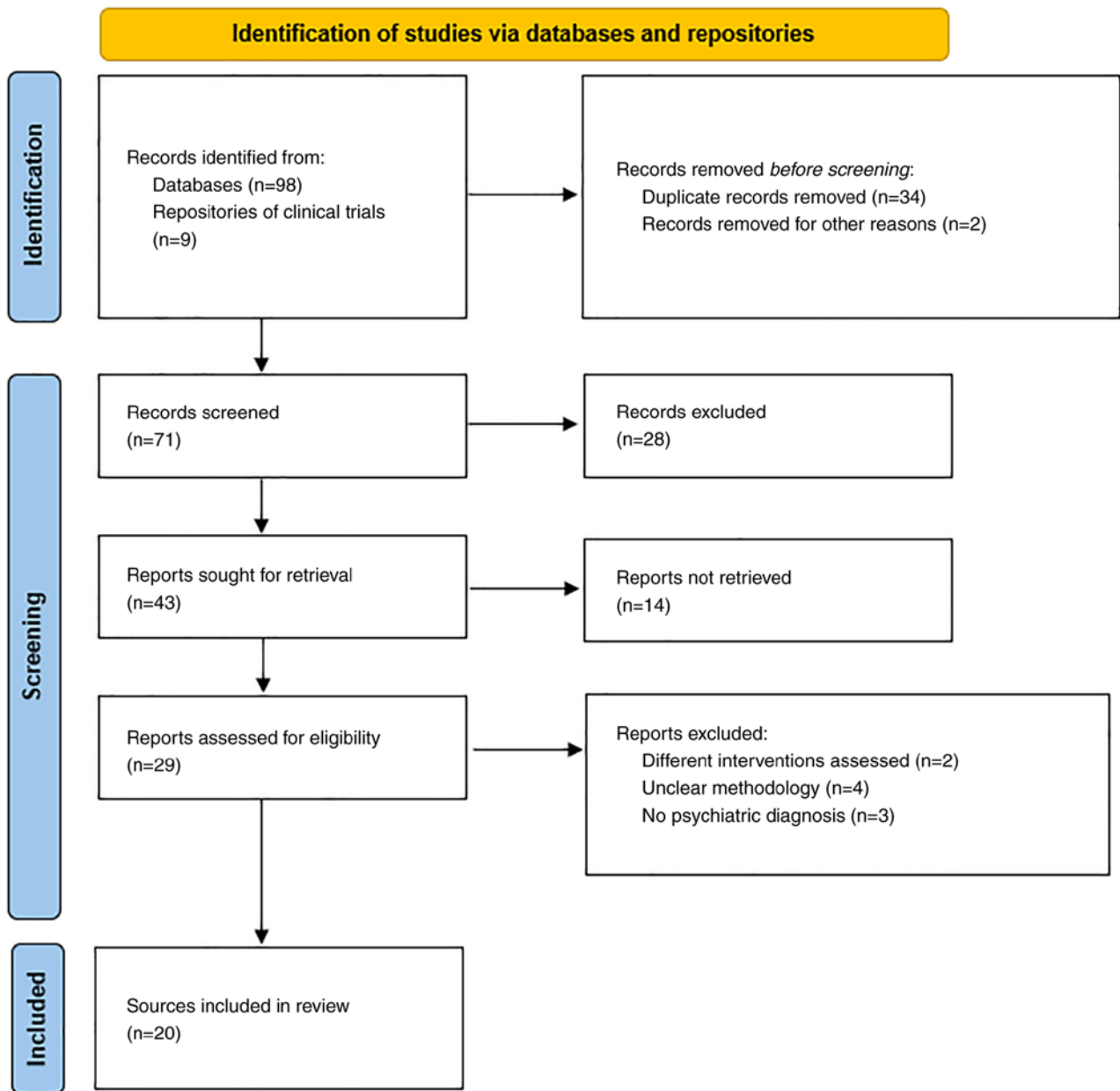


Figure 1. Results of the PRISMA-based search paradigm.

Female Sprague-Dawley rats that received subcutaneous olanzapine infusion daily or vehicle for four weeks were given after two weeks liraglutide (0.2 mg/kg) or vehicle twice daily for another 14 days (48). Olanzapine administered for 28 days led to higher cumulative food intake, increased body weight, subcutaneous inguinal fat, mesenteric fat, retroperitoneal fat, and impaired glucose tolerance, but these were reduced significantly by liraglutide administration (48).

Case reports. Liraglutide induced weight loss and lowered the HbA1c levels in a 60-year-old obese female with dysregulated T2DM diagnosed with disorganized schizophrenia and a history of drug abuse, who received treatment with clozapine (49). An initial BMI of 33.5 kg/m² and baseline HbA1c values of 10% were reported, before the addition of liraglutide 0.6 mg/day, subcutaneously, to the already prescribed metformin and insulin. The liraglutide dose

increased gradually to 1.8 mg/day, and after three months the HbA1c levels decreased to 8.9%, whilst the body weight decreased by 5.1 kg. This trend persisted up to the 2-year visit, with a bodyweight loss of 7.7 kg and a decrease in her daily need for insulin (49).

Exenatide was reported to induce weight loss of 41.5 kg after 6 months in a 43-year-old patient with schizophrenia and newly diagnosed T2DM, who was coincidentally initiated on both clozapine and the GLP-1 receptor agonist (50). This patient's initial body weight was 186.9 kg (BMI=46.3 kg/m²) and was already treated with metformin given his raised glycemic index detected 1 year before. After the initiation of exenatide, his appetite decreased, and the only reported adverse event was transient nausea, which remitted after the dose was lowered. By his last follow-up, his BMI decreased by 10 kg/m², while his waist circumference was reduced by 28 cm (from a baseline value of 160 cm) (50).

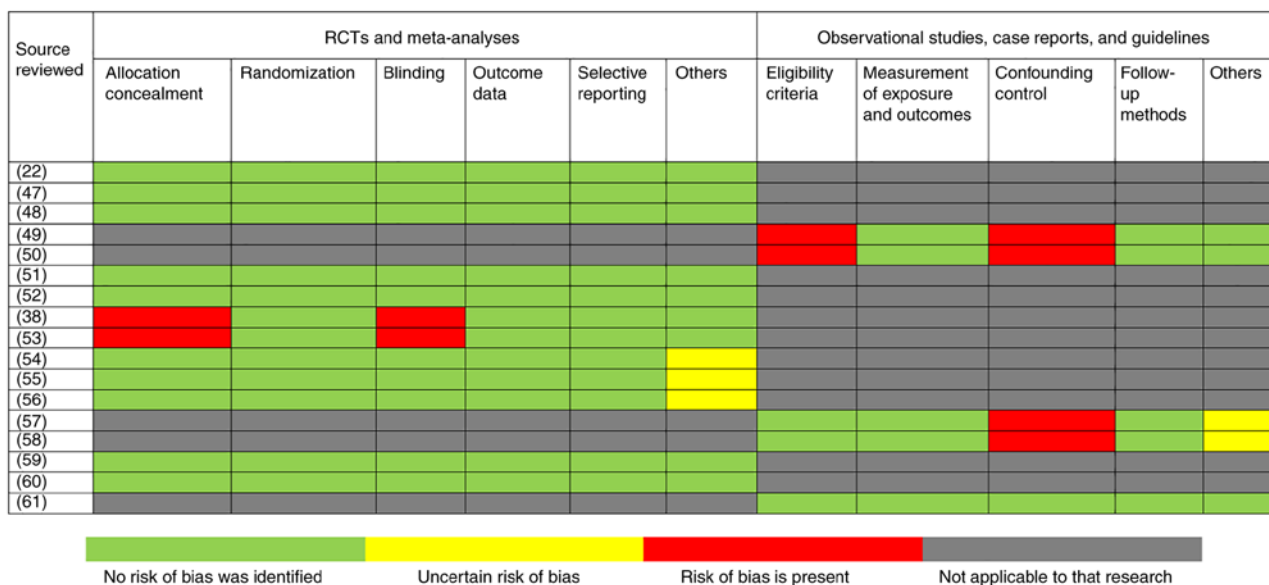


Figure 2. Risk of bias assessment. RCT, randomized controlled trial.

Clinical studies. A randomized, double-blind clinical trial enrolled 103 participants diagnosed with SSD who were being treated with olanzapine or clozapine and received liraglutide (once-daily subcutaneous injection) or placebo for 4 months (51). The primary outcome was an improvement in glucose tolerance, and this variable significantly changed in the active drug group vs. placebo, with 30 vs. 8 patients reaching normal values (64% vs. 16%) at the endpoint. The body weight decreased with liraglutide vs. placebo (-7 vs. -3.7 kg), and the waist circumference also decreased more with the GL-IRA treatment (-6 vs. -2.3 cm). Secondary outcomes, like systolic blood pressure, visceral fat, and low-density lipoprotein levels were also improved more by liraglutide than by placebo. Adverse events associated with liraglutide were primarily gastrointestinal symptoms (51). However, the liraglutide-treated patients reported better drug tolerability than patients who received placebo (51).

A total of 1 year after the last visit of this trial, the body weight increased in patients who received liraglutide in the initial phase, accompanied by increases in BMI, waist circumference, and cholesterol levels, while patients in the placebo group did report only minor changes in HDL levels (52). A comparison of the outcomes in the two groups showed that patients who initially received liraglutide were associated with poorer control of glucose metabolism. Other outcomes, such as fasting glucose, HbA1c levels, C-peptide levels, and lipids reached the baseline values 12 months after discontinuing liraglutide. Still, patients who were in the active treatment group maintained a significant loss of body weight and a reduction in BMI from baseline to the follow-up vs. placebo-receiving patients (52).

A 6 month, randomized, open-label trial evaluated the effects of exenatide on the body weight of obese patients presenting with SSD ± T2DM undergoing treatment with clozapine (n=28 outpatients, out of which 5 had T2DM) (38). A total of 6 patients treated with exenatide reached the primary outcome, which was a ≥5% weight loss compared to the initial value vs. one patient in the usual care (control)

group. Additionally, exenatide was associated with a higher body weight decrease and BMI reduction, lower levels of HbA1c, and lower fasting glucose levels. Therefore, exenatide may prove as a useful intervention in the reduction of clozapine-associated cardio-metabolic morbidity and mortality (38). The 12-month follow-up of the participants in this study explored the change in weight as the primary outcome (53). When compared to the first phase endpoint values, at 12 months, patients who formerly received exenatide had a significantly greater increase in BMI, body weight, and percentage of participants presenting ≥5% weight gain. If the 12-month follow-up values were matched to the baseline characteristics in the original trial, no differences were detected between exenatide and treatment as usual in the evolution of either BMI or body weight (53).

Another trial included 45 patients with SSD and obesity (without diabetes), undergoing treatment with antipsychotics, randomized to adjunctive treatment with exenatide (2 mg administered every week) or placebo for 12 weeks (54). Initial body weight was 118.3±16 kg and 111.7±18 kg in the active drug and placebo group, respectively, and at the endpoint, the weight loss was similar in both groups (~2.24 kg). Patients experienced significant body weight changes compared with the baseline values, but with no correlation with the type of intervention they received (54).

Another phase 4, placebo-controlled, randomized clinical trial enrolled 54 subjects diagnosed with severe psychiatric disorders and obesity, undergoing treatment with olanzapine, and explored their evolution during exenatide administration (5 µg twice daily for 28 days, and increased, if tolerated, to 10 µg twice daily after this term) (55). According to the unpublished results, retrieved from the U.S. National Library of Medicine (NLM) online registry, the primary outcome was the bodyweight change from baseline to endpoint (week 16) in favor of exenatide (-1.1 vs. +5.9 pounds), while the BMI decreased by 0.2 kg/m² (exenatide group) and increased by 1 kg/m² (placebo). The rate of serious adverse events was 8.33% in patients receiving exenatide vs. 3.33% in the placebo

Table IV. GRADE recommendations based on the reviewed papers.

Pharmacological agents	GRADE recommendations	Observations	(Refs.)
GLP-1RAs (as a pharmacological class)	C: These agents may be used as add-ons to metformin in patients diagnosed with severe mental disorders undergoing AP treatment, especially OLZ/CLZ, for the purpose of controlling BW changes C: For improvement of glucose metabolism dysfunctions (as add-ons) C: For the treatment of lipid metabolism dysfunctions (as add-ons)	Based on the favorable results of a therapeutic guideline, two meta-analyses, and one retrospective review	(57,59-61)
Liraglutide	B: As an augmentative agent to metformin for individuals diagnosed with severe mental disorders undergoing AP treatment, especially OLZ/CLZ, for the management of BW B: For the improvement of glucose metabolism dysfunctions (as an add-on). C: For the improvement of lipid metabolism dysfunctions (as an add-on)	Based on the favorable conclusions of a case report, one RCT, two meta-analyses, two retrospective chart reviews, one therapeutic guideline, and three preclinical trials	(22,47,48,56-61)
Exenatide	B: If added to metformin for patients diagnosed with severe mental disorders undergoing AP treatment, especially OLZ/CLZ, for the control of BW changes B: For the improvement of glucose metabolism dysfunctions (as an add-on) C: For the improvement of lipid metabolism dysfunctions (as an add-on)	Based on the favorable results of three RCTs, one retrospective chart review, two meta-analyses, one therapeutic guideline, and a case report	(50,53-55,57,59-61)
Semaglutide	D: Not enough data to formulate a clinical recommendation	One RCT is ongoing	(64)
Albiglutide	D: Not enough data to support a clinical recommendation		
Dulaglutide			
Lixisenatide			
Tirzepatide			

RCT, randomized clinical trial; OLZ, olanzapine; CLZ, clozapine; BW, body weight; GLP-1RA, glucagon-like peptide-1 receptor agonist.

group, while the incidence of adverse events was 58.3% vs. 36.6%, respectively (55).

In a randomized, double-blind, placebo-controlled pilot study, the effectiveness of liraglutide administration subcutaneously, once-daily injection (titrated to 3 mg/day), was compared for 6 months to placebo in 50 patients with acute or chronic psychotic disorders (56). Liraglutide had a favorable effect on the weight of the participants (-5.7±7.9 kg) compared with the placebo (no significant change). Additionally, the BMI, HbA1c levels, and waist circumference decreased in the liraglutide-treated patients (56).

A retrospective chart review included 46 outpatients who were prescribed antipsychotics and GLP-1RAs (liraglutide, exenatide, or dulaglutide) or alternative antidiabetic

agents (57). Within 1 year, both groups presented with a reduction in their HbA1c levels, but the changes in the patients' weight gain were significantly different between participants who received GLP-1 analogs (-7.07±2.62 kg compared to baseline) and controls (+1.93±1.14 kg compared to baseline). Additionally, it was noted that patients who received an antipsychotic and an antidepressant had smaller HbA1c reductions than those who did not have an associated antidepressant in the absence of a GLP-1RA, whilst patients treated with an antipsychotic and a GLP-1RA had larger HbA1c reductions vs. controls, independent of the concomitantly administered antidepressant. However, given the retrospective nature of this study, it was impossible to exclude several confounders (such as the addition

of GLP-1RAs selectively in the therapeutic regimen of individuals with a higher BMI, a lack of assessment of treatment adherence, amongst other variables) (57).

Another retrospective review included 16 patients diagnosed with obesity and schizophrenia or bipolar disorder who received treatment with liraglutide and were monitored for 16 weeks (58). The endpoint values of body weight indicated a significant effect of liraglutide (a decrease from 93.2 to 88.9 kg at the endpoint). Additionally, the waist circumference, BMI, and plasma glucose levels improved compared to the baseline. The most commonly reported adverse event was nausea (37.5% of all subjects). Responders, defined by at least 5% body weight loss, represented 50% of the 16-week treatment completers (58).

Meta-analyses. A meta-analysis (n=3 trials) evaluated the effects of exenatide and liraglutide in 164 patients diagnosed with SSD, who had a mean body weight at baseline of 105.8±20.8 kg (59). The results showed that after a mean of 16 weeks of GLP-1RAs administration, the mean body weight loss reached a value of 3.71 kg (59). The body weight change was significantly greater for GLP-1RAs vs. control, with a number-needed-to-treat value for a weight loss ≥5% of 3.8. Additionally, waist circumference, BMI, HbA1c, fasting glucose, and visceral adiposity were significantly lower during GLP-1RA treatment. Patients undergoing treatment with olanzapine or clozapine exhibited greater weight loss than those receiving other antipsychotics. The tolerability of this type of treatment was good, with nausea being more common than in the placebo group (number-needed-to-harm =3.8) (59).

A network meta-analysis compared the impact of pharmacological strategies on body weight in individuals with schizophrenia who developed antipsychotic-induced metabolic abnormalities (n=61 randomized trials, n=3,467 patients) (60). GLP-1RAs were significantly superior to placebo (weighted mean difference=-3.23), as did topiramate (-5.4), zonisamide (-3.44), metformin (-3.01), and nizatidine (-2.14) (60). The superiority of these agents was also observed in studies evaluating the BMI, and the tolerability was good, except for topiramate which was inferior to placebo, GLP-1RAs, and metformin. GLP-1RAs were superior to placebo in decreasing the waist circumference (60).

Treatment guidelines. The British Association of Psychopharmacology (BAP, 2016) guidelines on the management of antipsychotic treatment-related adverse events mention the possible use of GLP-1RAs for obesity, but the lack of a marketing authorization for this indication precludes its clear recommendation (61). The BAP rating for GLP-1RAs (such as liraglutide and exenatide) is 'B' (derived from the evidence of efficacy that exists in the general population), which places them in the same category as bariatric surgery and lorcaserin for these patients. GLP-1RAs are recommended as a component of the triple therapy; additionally, metformin and a sulfonylurea agent, for adults with T2DM who have i) a BMI of at least 35 kg/m² + a specific psychological and other medical problems related to obesity, or ii) a BMI<35 kg/m² + possible onset of significant occupational dysfunctions if insulin therapy were to be initiated, or

when weight loss would be beneficial for other concomitant diseases (61).

Trials in the pipeline. A randomized trial is expected to recruit 92 participants with SSD comorbid with obesity and non-responsive to metformin who will receive treatment with semaglutide (starting dose 0.25 mg/week and titrated up to 2 mg/week) or placebo (62). The primary outcome of this trial is weight change after 32 weeks, while the secondary outcome measures are BMI, waist circumference, oral glucose tolerance test, visceral and hepatic adiposity, fasting lipid profile, and multiple psychopathological scales, referring to the overall mental status, depressive symptoms, general functioning, cognitive performance, quality of life, nicotine dependence, and food cravings (62).

Another published study protocol envisages the enrollment of 154 participants diagnosed with SSD and newly treated with olanzapine or clozapine, who will be monitored for 24 weeks during the treatment with dulaglutide (0.75 mg/week) or placebo subcutaneously (63). The described study design is double-blind, multicenter, and randomized, and it will have as the primary outcome the mean percentage weight change at the endpoint (63).

Yet another trial protocol envisages enrollment of 120 participants diagnosed with schizophrenia who receive treatment with clozapine and who will be allocated randomly to semaglutide or placebo and monitored for 24 weeks (64). The primary variable monitored will be the change in body weight, and the secondary outcome is the risk of conversion to type 2 diabetes and/or metabolic syndrome during the trial (64).

Discussion

The impact of various GLP-1RAs on metabolic dysfunctions induced by antipsychotics was assessed quantitatively and/or qualitatively in 20 sources identified during this systematic review. To the best of our knowledge, there is little data in favor of other GLP-1RAs used in this specific population, except for liraglutide and exenatide, although isolated references to semaglutide and dulaglutide exist. According to the retrieved data, the variables related to body weight (including BMI, waist circumference, and body weight change) may be improved during treatment with GLP-1RAs (38,47,49-52,55-61). Follow-up studies (up to 1 year) are not unanimously supportive of the superiority of GLP-1RAs over placebo (52,53), while a single case report with a 2-year follow-up was more positive in this direction (48).

The favorable effect of GLP-1RAs on glucose metabolism (fasting glycemia, HbA1c, insulin, and glucagon blood levels) in subjects who received antipsychotics is supported by a large volume of clinical and preclinical data (22,38,47-50,51,56-59,61).

GLP-1RAs also have been associated with positive effects on lipid metabolism (i.e., lipids blood levels, visceral adiposity) in the reviewed papers (47,51,59,61).

Regarding the tolerability of GLP-1RAs in patients with psychiatric disorders and metabolic dysfunctions, the results are consistent with reviews that evaluated these parameters in other groups, supporting an overall good safety profile and low

incidence of adverse events, primarily gastrointestinal symptoms (including transient nausea, diarrhea, constipation, and dyspepsia) (50,51,58). For comparison, a systematic review of case reports including patients treated with GLP-1RAs (n=140 participants, treated with exenatide, liraglutide, dulaglutide, semaglutide, albiglutide, or lixisenatide) showed the most frequently reported adverse events were gastrointestinal manifestations, followed by renal, dermatologic, hepatic, immunologic, metabolic, hematologic, angioedema, neurologic, cardiovascular, and very rare psychiatric, reproductive, or generalized edema symptoms (65).

The GRADE recommendations formulated were A (high), B (moderate), C (low), or D (very low) (42,43), according to the level of confidence that the clinical use of GLP-1RAs will improve the outcome of patients with severe psychiatric disorders presenting metabolic dysfunctions related to the antipsychotic treatment.

As a limitation of the review, it must be mentioned that it includes three references to trials that are ongoing, therefore, their results are not yet available, but once known, it is possible they will modify the recommendations. Additionally, the strength of the GRADE recommendations is dependent on the quality of the reviewed body of research, and the majority of the presented sources (n=9) have been considered of moderate quality.

As strengths of the current systematic review, it included both primary and secondary reports, referring to both preclinical and clinical research. Additionally, this is the first systematic review focused on the efficacy and tolerability of GLP-1RAs in the treatment of a psychiatric population which also included a set of clinical recommendations.

Future directions of research regarding SSD patients may target finding the pharmacogenetic variables in individuals receiving antipsychotics that correlate with a higher risk for metabolic disease. In the same line of personalized medicine, exploration of the interaction between diet, physical exercise, antipsychotic treatment, and individual biological vulnerability could help in the improvement of these patients' metabolic status in the medium and long term. Head-to-head comparison trials investigating GLP-1RAs and other new-generation antidiabetics, such as inhibitors of dipeptidyl peptidase 4, or sodium-glucose transport protein 2 inhibitors may provide novel and important information regarding the specific effect of each class of agents in SSD patients. Finally, the pharmacogenetics of GLP-1RAs and other antidiabetics is certainly worth further exploration for the potential identification of sub-groups of responders and non-responders in this vulnerable population.

In conclusion, there are favorable results on a large set of metabolic variables for liraglutide and exenatide in patients with severe mental disorders, but there is enough ground to further explore the effects of semaglutide and dulaglutide in the same population. Due to the significant negative impact of metabolic dysfunctions on the quality of life, evolution of comorbid diseases, and life expectancy, second-generation antidiabetics may represent an important therapeutic resource for the management of SSD patients. The good tolerability of GLP-1RAs is essential in this population, where the high rate of treatment discontinuation due to adverse events, and the existence of poor insight and care for own health are very common.

Although the number of retrieved sources in the literature was not very high, this may be considered a consequence of the relative novelty of GLP-1RAs. It is expected that larger trials, with a longer duration of monitoring, will explore the efficacy and tolerability of GLP-1RAs both in the general population and in individuals with mental disorders.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Author's contribution

OV conceived and designed the study, collected and analyzed the data, and wrote and revised the manuscript. OV confirmed the authenticity of the raw data, and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that they have no competing interests.

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