Impact of SGLT2 inhibitors on metabolic status in patients with psychiatric disorders undergoing treatment with second-generation antipsychotics (Review)

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Abstract. Metabolic dysfunctions have been reported in patients diagnosed with severe mental illnesses who are undergoing treatment with antipsychotics, especially second-generation agents. Sodium-glucose co-transporter 2 inhibitors (SGLT2Is) and glucagon-like peptide receptor agonists are new-generation antidiabetics whose favourable effects in the treatment of diabetes mellitus in the non-psychiatric population may raise interest in their use in patients presenting with severe mental illnesses and metabolic comorbidities possibly related to the use of antipsychotics. The objectives of this review were to investigate the evidence to support the use of SGLT2Is in this population and to find the most important aspects that need to be addressed by future research. A total of one preclinical trial, two guideline-format clinical recommendations, one systematic review and one case report were found, and their conclusions were analysed. The results support the following conclusions: i) SGLT2Is may be combined with metformin in selected cases of type 2 diabetes mellitus in the context of antipsychotic treatment, as they have been associated with favourable metabolic effects; and ii) data for the recommendation of SGLT2Is as second-line treatment in patients with diabetes mellitus who are also treated with olanzapine or clozapine are supported by very limited preclinical and clinical evidence. Further high-quality, large-scale research is needed in the field of the management of metabolic dysfunctions in patients with severe psychiatric illnesses who undergo treatment with second-generation antipsychotics.

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1. Metabolic dysfunctions in patients undergoing antipsychotic treatment: General considerations

Fasting hyperglycaemia, impaired glucose tolerance, prediabetes, diabetes, obesity and metabolic syndrome are frequently diagnosed in patients with psychotic or mood disorders undergoing treatment with atypical antipsychotics (1). The prevalence of diabetes in individuals diagnosed with severe psychiatric disorders is 2- to 3-fold higher compared with that in the general population (2). Data in the literature suggest that the prevalence of diabetes increases shortly after antipsychotics are initiated and this phenomenon seems mediated by the negative influences of these medications on weight gain, insulin sensitivity and secretion alteration (2). However, the causality between schizophrenia spectrum disorders, antipsychotic use and impaired glucose metabolism is difficult to determine. Case-control studies reported alterations in fasting plasma glucose level, plasma glucose level after an oral glucose tolerance test, fasting plasma insulin level and insulin resistance in antipsychotic-naïve patients with a first episode of psychosis compared with those in the control (3). A high level of plasma triglycerides was found in patients with the first episode of psychosis, which may be another piece of evidence to support glucose dysregulation in this population, as concluded by a meta-analysis (20 case-control studies; 1,167 patients and 1,184 controls) (4). Excessive caloric intake and especially the consumption of refined grain foods and discretionary foods have been considered major contributors to weight gain in patients with the first episode of psychosis soon after the initiation of antipsychotic medication (8 months) (5). In these patients, a study found an excess of 26% in the energy balance, with a median of 1,837 kJ daily (5).

Not all antipsychotics have the same negative impact on the metabolic profile. According to a meta-analysis (48 head-to-head studies that compared second-generation

antipsychotics), olanzapine and clozapine were associated most frequently with weight gain, olanzapine led to a greater cholesterol increase than aripiprazole, risperidone or ziprasidone, and a greater increase in the glucose blood level vs. amisulpride, aripiprazole, quetiapine, risperidone and ziprasidone (6). Antipsychotics have multiple mechanisms through which they can induce metabolic disturbances, including increased appetite, sedation with secondary low energy expenditure and changes in dietary patterns, among others (Fig. 1) (6,7). Antipsychotics may significantly increase body weight and waist circumference, which leads to insulin resistance and type 2 diabetes (1). However, diabetes has been reported in patients treated with second-generation antipsychotics who did not develop obesity, raising the hypothesis of a direct effect of these psychotropics on insulin secretion (1,8,9). Antipsychotics increase appetite and caloric intake by blocking serotonergic 5-hydroxytryptamine receptor 2C (5HT2C), dopamine D2 and histaminergic H1 receptors (10). Also, the sedation related to adrenergic α1 and histaminergic H1 receptor antagonism may enhance the propensity toward weight gain by decreasing the patients' involvement in physical activity (10). An association between the affinity for muscarinic M3 receptors and the ability of antipsychotics to induce diabetes has been demonstrated (11,12). A systematic review and meta-analysis showed that several pharmacogenetic studies found that single nucleotide polymorphisms in adrenergic α2, dopaminergic D2, serotonergic 5HT2C and melanocortin-4 receptor genes were significantly associated with antipsychotic-related weight gain (13). Dysregulation of insulin, cortisol, glucagon, cholecystokinin, adiponectin, ghrelin, leptin, orexin, prolactin and oxytocin has also been reported during treatment with antipsychotic agents (14,15). The possible impairment of the mitochondrial dynamics in the pathogenesis of metabolic syndrome in patients undergoing antipsychotic treatment has been suggested, although data to support this hypothesis are still insufficient (16).

The existence of several third-generation antipsychotics, which possess partial D2/D3 receptor agonistic properties and lower affinity for other receptors, may be useful for reducing the risk of weight gain or dyslipidaemia (17,18). However, there is an intense need for more research in this field, as newer antipsychotic agents (e.g., brexanolone, cariprazine and blonanserin), with the exception of aripiprazole, have not been extensively explored for their long-term effects on metabolism.

The vast majority of the existing antipsychotics are associated with adverse metabolic effects, and switching from the currently administered agent to a metabolically more favourable one is not always possible or even recommended (19). In addition, monotherapy is rarely used in clinical practice in patients with severe mental disorders, and other pharmacological agents (mood stabilizers, antidepressants and sedatives) used as add-ons may further complicate the adverse events profile (20).

Weight loss in patients with type 2 diabetes may have important consequences to glycaemic control and potential cardiovascular complications, and it may even lead to diabetes remission in certain individuals (21). First-generation antidiabetic agents have been associated with weight gain, while newer agents, such as sodium-glucose co-transporter 2 inhibitors (SGLT2Is) and glucagon-like peptide receptor agonists (GLP-1RAs), treat obesity and diabetes simultaneously (21).

SGLT2Is are approved for treating diabetes mellitus due to their properties of reducing plasma glucose levels by inhibiting glucose and sodium reabsorption in the proximal tubules of the nephrons, an effect that leads to glucosuria (22). Body weight and adiposity may decrease as a consequence of the administration of these pharmacological agents, and the HbA1c, blood glucose and blood pressure values may also improve during this treatment due to natriuresis, glucosuria and negative caloric imbalance in patients with diabetes (1,22). In clinical trials (randomized, controlled and real-world studies), patients treated with SGLT2Is reported weight loss of 1-3 kg (23). Also, SGLT2I administration was associated with benefits in cardiovascular functioning within 6 months of therapy initiation, and also with improvements in renal function in patients with type 2 diabetes (23). SGLT2Is have few adverse effects and a lower degree of pharmacodynamic/pharmacokinetic interactions, but they must be cautiously administered in patients with severe renal or hepatic impairment (24).

SGLT2Is have been combined with other agents involved in decreasing weight gain (e.g. GLP-1RAs), which possess different mechanisms of action, to increase the probability of weight loss (22). These associations are needed, as SGLT2I administration may trigger compensatory mechanisms, which negatively impact weight loss (e.g. hyperphagia) (23). The clinical and pharmacological properties of SGLT2Is are presented in Table I.

Empagliflozin is a potent, highly selective SGLT2I that is administered orally once daily, with a low risk of hypoglycaemia, and can be administered either as monotherapy or as an add-on to other antidiabetic agents (25). Empagliflozin induces modest reductions in body weight and blood pressure, and it has cardioprotective and renoprotective properties independent of its glycaemic control effects (25).

Canagliflozin is administered orally once daily in the treatment of type 2 diabetes, and it can reduce glycaemic levels in adults, including those of older age and/or presenting with higher cardiovascular risk (26). Canagliflozin reduces cardiovascular risk and may be associated with renal benefits in patients with type 2 diabetes (26). The overall tolerability of this agent was good in clinical trials, with a low risk of hypoglycaemia and the most frequently reported adverse effects being genital/urinary tract infections and increased urination (26).

Dapagliflozin is a highly potent, reversible and selective SGLT2I administered orally once daily, either as monotherapy or add-on to other antihyperglycemic medications for patients with type 2 diabetes (27). This agent produced effective glycaemic control and reduced body weight and blood pressure, while also decreasing the rate of cardiovascular death or hospitalization for heart failure (27). The tolerability was good in clinical trials, with a low risk of hypoglycaemia, diabetic ketoacidosis and genital infections, which were more common with dapagliflozin than with the placebo (27).

Ertugliflozin significantly reduced HbA1c, fasting plasma glucose, body weight and blood pressure levels compared with a placebo and other hypoglycaemic agents (28). No significant difference in the rate of adverse events, serious adverse events,

Increased appetite and caloric intake

- Antagonism of serotonergic 5HT2C receptors
- Dopamine D2 receptor antagonism
- Histaminergic H1 receptor antagonism

Sedation

- Adrenergic α1 receptor antagonism
- Histaminergic H1 receptor antagonism

Changes in dietary patterns

Decreased fasting plasma insulin and reduced insulin secretion in response to glucose

- Muscarinic M3 antagonism

Presumed direct effect on insulin secretion

Dysregulation of other hormones

- Cortisol
- Glucagon
- CCK
- Adiponectin
- Ghrelin
- Leptin
- Orexin
- Prolactin
- Oxytocin

Presumed impairment of mitochondrial dynamics

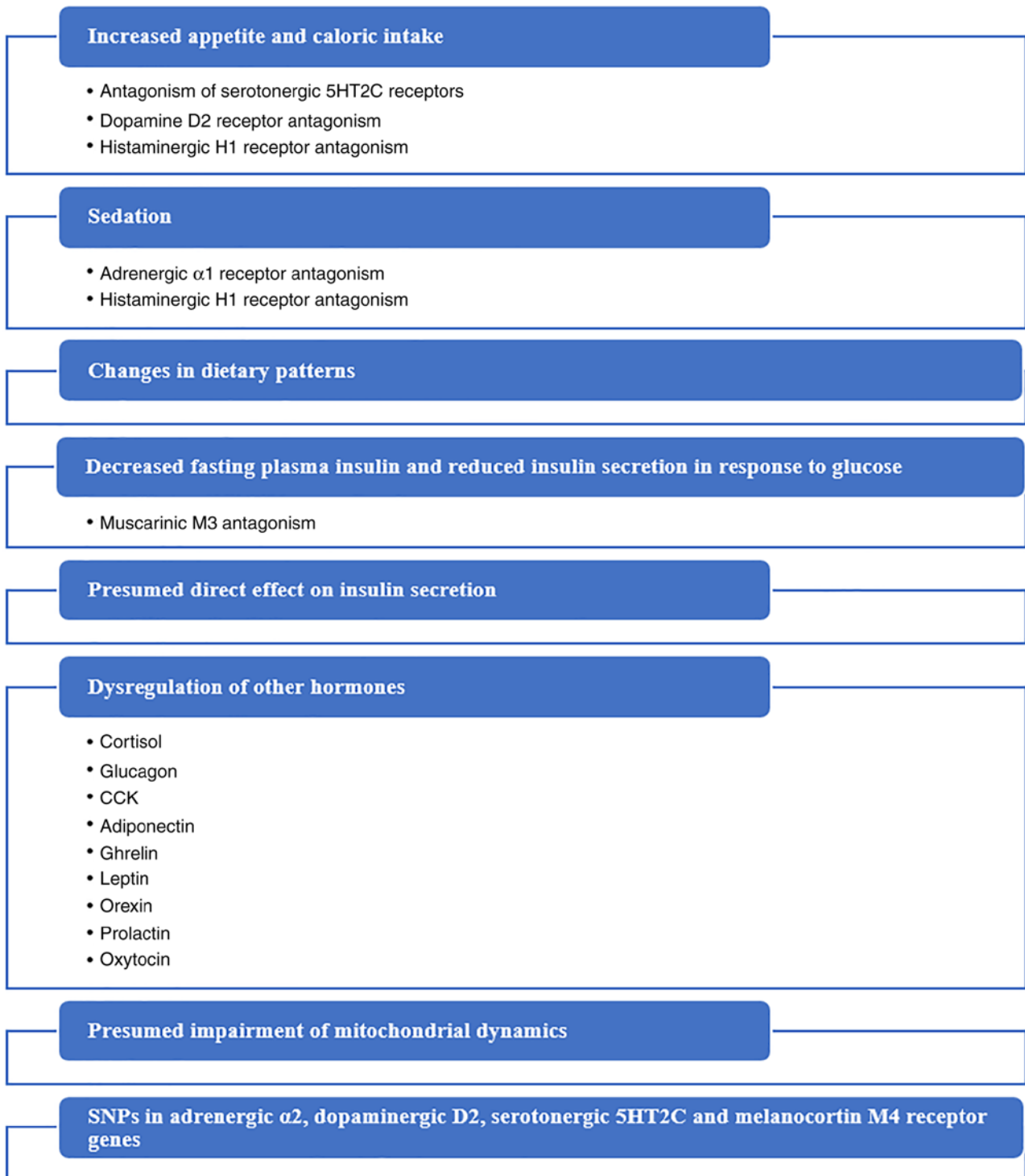**SNPs in adrenergic α2, dopaminergic D2, serotonergic 5HT2C and melanocortin M4 receptor genes**

Figure 1. Pathogenetic mechanisms of metabolic syndrome in patients undergoing treatment with second-generation antipsychotic agents (6-16). 5HT2C, 5-hydroxytryptamine receptor 2C; CCK, cholecystokinin; SNP, single nucleotide polymorphism.

deaths or discontinuations due to adverse events was recorded between the active drug and placebo (28).

SGLT2Is reduced weight and waist circumference in overweight or obese patients without diabetes compared with those in the control group (other drugs or placebo), according to a systematic review (13 studies) (29). The mean body weight loss due to SGLT2Is in this population was -1.62 kg compared with that in the placebo group, and the BMI decreased by -0.47 kg/m^2, which was superior to the placebo, according to a meta-analysis (5 clinical trials) (30). The mean reduction of the waist circumference due to SGLT2Is vs. placebo was 1.29 cm, which was not statistically significant (30).

2. Objectives and methods

The main objective of this review was to investigate the evidence that may support SGLT2Is as a potentially useful intervention in patients diagnosed with severe mental illnesses

Table I. Characteristics of the SGLT2Is.

Pharmacological agent	Pharmacological properties	Clinical particularities	Observations	(Refs.)
Empagliflozin	↑Potency, ↑selectivity for SGLT2, ↑bioavailability (>86%), Tmax=1.5 h	Low risk of hypoglycaemia, modest reductions of BW and BP, cardioprotective and renoprotective properties	Monotherapy or add-on to other ADM. Administered orally once daily	(25)
Canagliflozin	↓Selectivity for SGLT2 compared to other SGLT2Is, ↓bioavailability (65%), Tmax=1-2 h	Low risk of hypoglycaemia. ↓Glycaemic levels in adults and older patients +/-higher cardiovascular risk. Reduces cardiovascular risk and may lead to renal benefits in patients with type 2 diabetes mellitus. Adverse events: Genital/urinary tract infections, ↑urination	Administered orally once daily. Monotherapy or add-on to other ADM	(26)
Dapagliflozin	↑Potency, reversible, selective agent, ↑bioavailability (78%), Tmax=1-1.5 h	Effective glycaemic control, ↓BW, ↓BP, ↓the rate of cardiovascular death, ↓hospitalization due to heart failure. Low risk of hypoglycaemia/diabetic ketoacidosis. ↑Risk of genital infections	Administered orally once daily. Monotherapy or add-on to other ADM	(27)
Ertugliflozin	↑selectivity for SGLT2, ↑bioavailability(~100%), Tmax=1 h	↓HbA1c, ↓fasting plasma glucose, ↓BW, ↓BP. Good tolerability in clinical trials	Administered orally once daily. Monotherapy or add-on to other ADM	(28)

ADM, antidiabetic agents; BW, body weight; BP, blood pressure; SGLT2, sodium-glucose transport protein 2; SGLT2Is, sodium-glucose co-transporter 2 inhibitors; Tmax, time to peak drug concentration; ↑, higher; ↓, lower.

who are undergoing therapy with atypical antipsychotics and present with metabolic dysfunctions.

A secondary objective was to find the most important aspects that need to be addressed by future research in the field of therapeutic management in patients treated with atypical antipsychotics and comorbid metabolic dysfunctions.

A narrative literature review was initiated to comply with the two aforementioned objectives. The major electronic databases (PubMed, https://pubmed.ncbi.nlm.nih.gov/; Cochrane, https://www.cochrane.org/; CINAHL, https://www.ebsco.com/; EMBASE, https://www.embase.com/; and Clarivate/Web of Science, https://www.webofscience.com/) were searched using the words 'sodium-glucose co-transporter 2 inhibitors' AND 'atypical antipsychotics' OR 'second-generation antipsychotics' AND 'obesity' OR 'diabetes mellitus' OR 'metabolic syndrome'. All studies published between January 2000 and June 2022 were included in the primary analysis. Clinical trials, irrespective of their methodology (open-label, randomized, controlled, single-blind and double-blind), case reports and case series, preclinical studies, systematic reviews and meta-analyses, clinical guidelines, good practices and expert consensus recommendations were included. Studies with imprecise methodology (e.g., unspecified duration of the intervention, undefined setting and unstructured methods of outcome measurement) were excluded from the analysis. In addition, sources that did not explore the efficacy and/or

tolerability of the SGLT2Is (either as monotherapy or add-on) were excluded. Reports on patients without psychiatric disorders or on subjects without metabolic syndrome possibly related to the administration of antipsychotic agents were not included in the final stage of the review.

3. Results

Out of the 170 references initially found, only five corresponded to the main objective of the present review (Fig. 2). A total of one preclinical trial, two guideline-format clinical recommendations, one systematic review and one case report were found, and their conclusions are reported in this section (Table II). The other 165 papers did not refer to psychiatric conditions or atypical antipsychotic-associated metabolic dysfunctions (n=90), were duplicates (n=52) or did not report on well-defined variables regarding the tolerability and/or efficacy of the SGLT2Is (n=23).

Preclinical studies. In the reported preclinical study, researchers evaluated the effects of empagliflozin on body weight gain induced by olanzapine administration in female and male Wistar rats (31). Olanzapine induced a sustained increase in body weight in this population, while the subsequent treatment with empagliflozin attenuated the antipsychotic-induced weight gain only in female rats (31).

Table II. Main results of the reviewed studies.

First author, year	Methodology	Results	Observations	(Refs.)
Ashraf et al, 2021	Wistar rats, the empagliflozin effect on olanzapine-induced body weight increase was observed	SGLT2I reduced the weight gain determined by olanzapine	This preclinical study supports the SGLT2I efficacy in mitigating the effects of olanzapine on weight gain	(31)
Cooper et al, 2016	Therapeutic guidelines for the management of metabolic disturbances	Metformin + an SGLT-2 inhibitor may be appropriate as an intensification approach if HbA1c remains ≥6.5% after 3-6 months	SGLT2Is are recommended as an add-on to metformin in selected cases of type 2 diabetes mellitus	(32)
Lally et al, 2018	Expert consensus for the treatment of patients with severe mental disorders and type 2 diabetes	SGLT2Is may be used in combination with metformin if HbA1c target values cannot be obtained with metformin monotherapy after 3 months	SGLT2Is, GLP1RAs and dipeptidyl-peptidase-4 inhibitors are second-line therapy for these dually diagnosed patients	(33)
Cernea et al, 2020	A systematic review (14 randomized controlled trials)	SGLT2Is and GLP1RAs are second-line therapy, and they may be used as add-ons in patients with diabetes and comorbid conditions	The support for SGLT2Is is still not very solid	(1)
Barbosa and Fernandes, 2021	Case report, 45-year-old overweight patient, treated with clozapine	Metformin was initiated, but insulin, exenatide and empagliflozin were also added. Clozapine was discontinued	SGLT2Is may be added for the control of glycaemic dysfunction induced by clozapine	(37)

SGLT2I, sodium-glucose cotransporter 2 inhibitor; GLP1RAs, glucagon-like peptide receptor agonists.

Clinical guidelines and expert consensus. British Association of Psychopharmacology guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment, published in 2016, formulates the following therapeutic algorithm for patients with type 2 diabetes: i) First-stage intervention includes educational, lifestyle and dietary measures; ii) if HbA1c remains >6.5% after 3-6 months drug therapy should be offered; iii) metformin should be the first-line medication, but if it is not tolerated or it is contraindicated, then a dipeptidyl-peptidase-4 (DPP-4) inhibitor, or pioglitazone, or a sulfonylurea treatment will be initiated; and iv) the first intensification of drug treatment includes combinations of DPP-4 inhibitor + metformin, metformin + pioglitazone or metformin + sulfonylurea, but metformin + an SGLT-2I may be appropriate (32). It may be observed that SGLT-2Is are recommended in selected cases of type 2 diabetes in the context of antipsychotic treatment, but only as an add-on to metformin (32).

Based on an expert consensus, in the management of hyperglycaemia in patients diagnosed with severe mental disorders and type 2 diabetes, SGLT2Is, as well as GLP-1RAs, dipeptidyl-peptidase-4 inhibitors (DPP-4Is), pioglitazone, insulin and sulfonylureas, may be used in combination with metformin if the HbA1c target value cannot be reached after 3 months of monotherapy with metformin, administered at the maximum tolerated doses (33). Agents with a low risk of hypoglycaemia and with weight loss properties, such as SGLT2Is, GLP-1RAs and DPP-4Is, are the preferred options for second-line therapy in patients with severe mental disorders (33).

Data from systematic reviews. A systematic review (14 randomized controlled trials with patients treated with second-generation antipsychotics) found metformin to be the most efficient first-line therapy for individuals with diabetes mellitus and co-morbid conditions, while the GLP-1RAs and SGLT-2 inhibitors were supported by evidence as add-on therapies (1). Both GLP-1RAs and SGLT2Is favourably influenced glucose metabolism and BMI in general in these patients, but the support for the use of SGLT2Is is not yet very solid (1). Using these new-generation antidiabetics offers additional benefits such as weight control, cardiovascular and renal protection, and a low risk of hypoglycaemia (1).

Metformin is also an option for patients with prediabetes, especially if additional conditions, such as obesity, exist (1). The mechanisms by which metformin improves antipsychotic-induced metabolic dysfunctions remain unclear, but preclinical studies support the hypothesis of attenuation of hepatic insulin resistance during olanzapine administration (1,34). Moreover, the anorectic effects of metformin
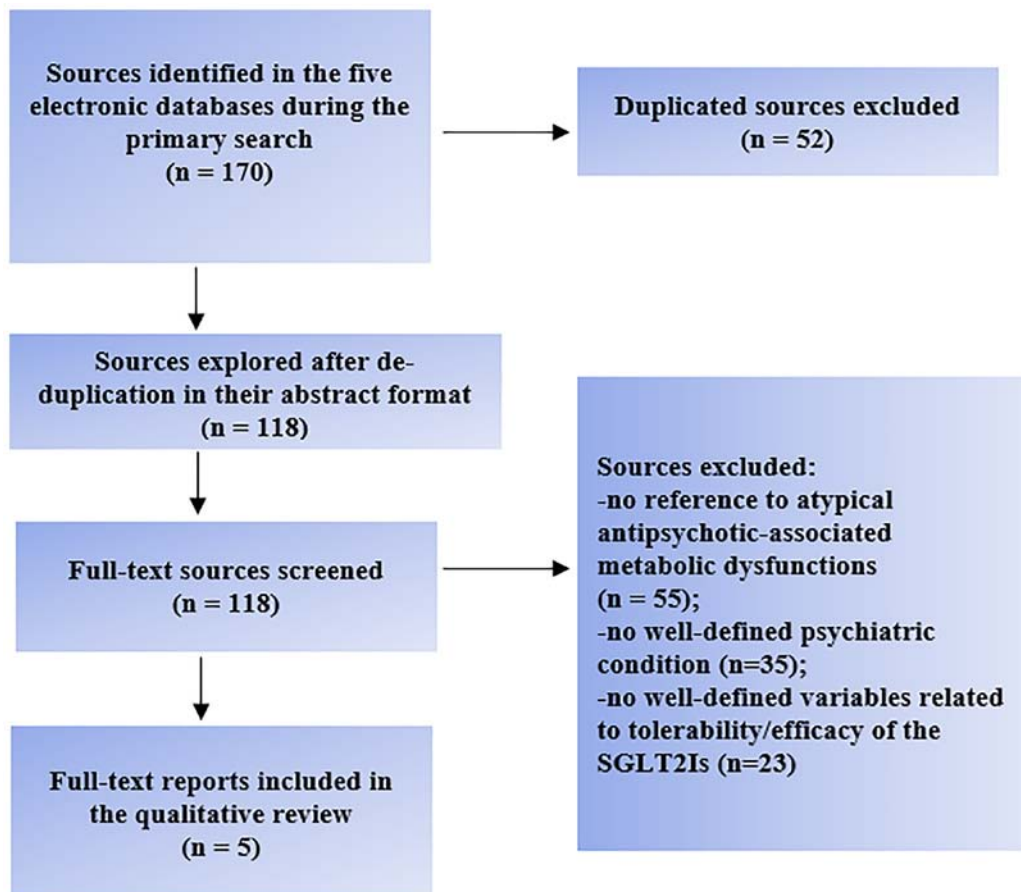
Figure 2. Results of the screening and selection process. SGLT2I, sodium-glucose co-transporter 2 inhibitor.

could mitigate the increased appetite induced by antipsychotics (1,35). Kidney function monitoring is indicated during metformin administration, as it can be safely used only if the glomerular filtration rate is >30 ml/min/1.73 m² (1,36).

The same systematic review showed that the prognosis of lifestyle-based strategies for treating diabetes or prediabetes in this population was modest (1). Also, if prediabetes or diabetes appears, switching from the current antipsychotic to another with an improved metabolic profile, is a very useful strategy, but the risk of worsening psychiatric outcomes should be anticipated and monitored carefully (1).

Case reports. In a 45-year-old overweight female patient diagnosed with Parkinson's disease who received clozapine for refractory dyskinesia and a history of gestational diabetes, the acute onset of a glycaemic dysfunction (blood glucose, 505 mg/dl; reference range, <99 mg/dl; HbA1c, 12.4%; reference range, <5.7%) was observed (37). Metformin was started and clozapine was discontinued, but the glycemia could not be controlled until insulin was added, together with exenatide and empagliflozin (37).

4. Conclusions and clinical observations

Atypical antipsychotic-associated weight gain and metabolic disorders are clinical challenges that may reduce therapeutic adherence, health-related quality of life and life expectancy in patients with severe mental illnesses (38,39).

Early interventions focused on nutritional counselling, an increase in physical exercise and the use of adequate antipsychotic treatment have been suggested for patients with schizophrenia spectrum disorders, starting from the first episode of psychosis to chronic forms of disorders (4). Changing the currently administered antipsychotic to a metabolically less harmful agent has also been suggested as a measure to improve the prognosis of patients with both severe mental disorders and diabetes mellitus, obesity or dyslipidaemia (39,40). Adding metformin has also been associated with favourable results on the metabolic parameters in this population, and other add-on therapeutic agents, such as amantadine, topiramate and orlistat, have been explored, with various results (39,40). However, an optimum strategy is still missing, as all the previously listed options are associated with significant risks, from the possibility of psychotic symptoms worsening in the case of antipsychotic switching, to adding new adverse events in the case of using other pharmacological agents for controlling metabolic dysfunctions.

In this context, newer antidiabetics, such as SGLT2Is, may represent a therapeutic option in patients undergoing antipsychotic treatment, and their favourable effects on blood pressure and serum lipids (41) may be useful in these patients. These newer agents are not without adverse effects, and more trials are required to determine their effect on macrovascular outcomes (41). Based on the current literature review, it can be concluded that SGLT2Is may be added to

metformin in selected cases of type 2 diabetes mellitus in the context of antipsychotic treatment, as suggested by a clinical guideline and an expert consensus; a case report and a systematic review also support this strategy (1,32,33,37). Evidence to support the administration of SGLT2Is as second-line treatment in patients with diabetes mellitus who are also treated with olanzapine or clozapine is derived from very limited preclinical (31) and clinical data (37). The advantages of SGLTI2s, i.e., the low risk of hypoglycaemia and the associated weight loss properties, may recommend these agents, along with GLP-1RAs and DPP-4Is, as preferred options for second-line therapy in patients with severe mental disorders (33).

Regarding the secondary objective of this review, further domains of interest for the clinical research that may help improve the health and related functional outcomes in patients with severe mental illnesses and metabolic pathology are as follows: i) The identification of prognosis factors that may predict a favourable response to SGLT2I add-on in patients with a dual diagnosis (severe mental disorders and metabolic dysfunctions) undergoing treatment with second-generation antipsychotics; ii) randomized clinical trials to help find positive effects and adverse events during long-term treatment with SGLT2Is; iii) comparative studies with different new generation antidiabetic agents (e.g. GLP1-RAs); iv) identification of possible interactions between specific second-generation antipsychotics and SGLT2Is; and v) identification of potential pharmacogenetic determinants of SGLT2Is responsiveness.

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Authors' contributions

OV is responsible for the collection, processing and presentation of the data within the review. OV has read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and informed consent

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that they have no competing interests.

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