



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
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ARTICLE TITLE	SGLT2i NEUROPROTECTIVE PROPERTIES IN DEPRESSION, AUTISM SPECTRUM DISORDER AND EPILEPSY
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DOI	https://doi.org/10.31435/ijitss.3(51).2026.6321
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RECEIVED	19 July 2026
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ACCEPTED	08 September 2026
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PUBLISHED	21 September 2026
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SGLT2i NEUROPROTECTIVE PROPERTIES IN DEPRESSION, AUTISM SPECTRUM DISORDER AND EPILEPSY

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ABSTRACT

SGLT2i (sodium-glucose cotransporter 2 inhibitors) are a class of medications widely used in the treatment of diabetic, cardiology and nephrology conditions. Beyond cardioprotection and nephroprotection there are reports that SGLT2i demonstrate additional neuroprotective properties.

This article focuses on the clinical features of central nervous system disorders including epilepsy, autism spectrum disorder and major depression. We also describe current approach to their therapy and discuss possible treatment options placing the main emphasis on the SGLT2 inhibitors and their potential neuroprotective properties.

Methods and materials: A qualitative synthesis of the data focusing on SGLT2i neuroprotective properties in central nervous system was performed. This literature review of SGLT2i effect on major depression, autism spectrum disorder and epilepsy included recent publications, primarily from the past 10 years, and was conducted from January 2026 to July 2026 using the PubMed database.

A systematic search was performed using specific keywords and medical subject headings (MeSH terms) related to SGLT2i, depression, autism spectrum disorder and epilepsy. The primary search terms included: “diabetes mellitus”, “SGLT2i”, “depression”, “autism spectrum disorder”, “epilepsy”, “flosins”, and “neuroprotection”. The criteria for inclusion of articles were as follows: published before July 2026, written in English, peer-reviewed original research articles. Exclusion criteria included publications not available in full text, articles in languages other than English. Editorials, commentaries, and conference abstracts without full data were also excluded. Titles and abstracts of the retrieved articles were screened to determine eligibility based on the inclusion and exclusion criteria.

Aim of the study: In this literature review, we aim to provide an integrated overview of neuroprotective properties of SGLT2i and assess their current perspectives in treatment of central nervous system disorders including depression, autism spectrum disorder and epilepsy.

KEYWORDS

SGLT2i, Neuroprotection, Depression, Autism Spectrum Disorder, Epilepsy

CITATION

Zajac, D., Darasz, D., Jucha, J., Ochońska, I., Dziewięcka, O., Ziębka, W., Żołyński, M. K., Kaczorek, M., Machnik, K., & Łobaziewicz, M. (2026). SGLT2i neuroprotective properties in depression, autism spectrum disorder and epilepsy. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.6321](https://doi.org/10.31435/ijitss.3(51).2026.6321)

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Introduction:

In diabetes mellitus type 2 (T2DM) patients, sodium-glucose cotransporter 2 inhibitors (SGLT2i) are often co-administered with other hypoglycemic medications, such as metformin, insulin or DDP-4i (dipeptidyl peptidase-4 inhibitors). Based on the existing data, drug interactions between SGLT2i and DDP-4i are not clinically significant [1]. However, dual therapy consisting of SGLT2i (especially Empagliflozin), and insulin or insulin secretagogues may increase the risk of hypoglycemia. Co-administration of SGLT2i with other diuretics such as thiazides have a potential risk of causing volume depletion [2]. They should be used with caution in people who are at risk of dehydration, such as older adults or people with certain medical conditions. It should be especially considered in individuals with dementia or other form of cognitive impairment.

Dapagliflozin, Ertugliflozin and Ipragliflozin have not been reported to inhibit or induce CYP450 enzymes [1]. Kalgutkar et al. mentioned that ertugliflozin exhibited no relevant, reversible or time dependent inhibitory effects against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 activities, whereby CYP3A4/3A5 were the principal enzymes responsible in Ertugliflozin biotransformation (Kalgutkar et al. 2011). Thus, other drugs could hypothetically disturb the SGLT metabolism by CYP3A4. CYP3A4 presence in central nervous system have been demonstrated, what could affect the pharmacokinetics of SGLT2i used for any purpose within the brain, especially in some individuals with increased CYP450 expression (Ghosh et al. 2011). However, the significance of this phenomenon remains unknown.

The entire class of SGLT2 inhibitors are contraindicated in patients with an eGFR less than 30 ml/min/1.73m². Some SGLT2i such as Empagliflozin, Dapagliflozin and Canagliflozin should not be

administered to patients with persistent eGFR less than 45 ml/min/1.73m² and they should be discontinued from the treatment if eGFR drops below that threshold. Moreover, the threshold for Ertugliflozin was set at an eGFR of 60 ml/min/1.73m² [3]. Severe kidney impairment may increase the risk of ketoacidosis.

Many clinical studies have been conducted on SGLT2i and their potential side effects. Their occurrence is more frequent with the given factors: more than 75 years of age, glomerular filtration rate (GFR) less than 60 mL/min/1.73m² and use of loop diuretics [4].

Recent meta-analyses have shown that SGLT2i increased risk of urinary tract infections (UTIs) and concludes that this risk depends on the duration of use – longer use of SGLT2i promotes the progression of UTIs [5]. The increased risk of genital and fungal infections with the use of flozins was also confirmed in these studies. However, the earlier association of SGLT2i with progression of acute kidney injury (AKI) has been rejected, as it turned out that flozins contribute to reducing the risk of developing AKI and have a nephroprotective effect on kidneys [5], [6].

There have also been reported cases of SGLT2i-related diabetic ketoacidosis (DKA) incidents. However, the incidences were very low (< 0.2% in Canagliflozin studies [7]) and DKA is more likely in patients with insulin-deficient diabetes: mostly type 1 diabetes mellitus (T1DM) but also rarely with type 2 [2], [7], [8], [9]. Triggering factors which may lead to DKA include insulin omission, dose reduction, dehydration, extensive exercise, low carbohydrate diet and excessive alcohol intake [8]. Potential mechanism of SGLT2i leading to DKA may be hyperglucagonemia caused by decrease in blood glucose [6], [7].

SGLT2i main physiological action is lowering blood glucose levels by increasing urinary glucose excretion. The risk of hypoglycemia is low when SGLT2i are used in monotherapy. However, when combined with other hypoglycemic drugs such as sulfonylureas or insulin, the risk may be increased so to avoid hypoglycemia dosage of insulin or other blood glucose lowering drugs should be decreased [6], [10]. It is worth mentioning that in patients with T2DM SGLT2i monotherapy lowers HbA1c by 0.79% and combined with other hypoglycemic agents by 0.61% [10], [11]. In the neurological field hypoglycemic potential of SGLT2i combined with mentioned drugs is considered particularly dangerous for central nervous system. Severe or repeated episodes of hypoglycemia can lead to damage in the central nervous system and other organs. The brain is especially sensitive to low blood glucose because it relies on its constant supply for energy production. When blood glucose levels drop too low, it results in neuroglycopenia with following symptoms such as confusion, difficulty speaking, seizures, and loss of consciousness. Long-term complications of hypoglycemia can include neurological problems such as difficulty with memory, concentration, and coordination. In severe cases, hypoglycemia can lead to coma or death. It is important to carefully monitor blood glucose levels and take steps to prevent hypoglycemia, especially in individuals with diabetes who are taking insulin with other blood glucose-lowering medications. The potential negative effects on the nervous system should always be reflected when considering the use of SGLT2i in the management of neurological diseases.

SGLT2 inhibitors have been shown to influence lipid metabolism by elevation both LDL-C and HDL-C and reduction in triglycerides [12]. Many studies, including EMPA-REG OUTCOME trial, have stated that Empagliflozin seems to increase the levels of LDL cholesterol by decreasing its clearance from blood circulation [3], [12]. In clinical studies of Canagliflozin there has been defined possibility for hypersensitivity and hyperkalemia incidents when drugs that have an impact on potassium excretion are used alongside Canagliflozin [2]. Hypotension, impact on bone metabolism (dysregulated calcium and phosphate homeostasis) and increased risk of fractures and limb amputation are possible yet not investigated well enough side effects, because many studies show different outcomes [6].

Animal studies have shown an increased risk of renal defects during SGLT2i treatment in renal development periods of fetus which corresponds to 2nd and 3rd trimesters of human pregnancy and due to insufficient data and inability to determine risks for birth defects and miscarriage, SGLT2i are not recommended in pregnant women. However, they should be considered to use only if the potential benefits justify the risk to the fetus [2]. There have been cases of euglycemic DKA in pregnant women with diabetes mellitus during SGLT2i treatment [9].

1. Epilepsy.

Worldwide epilepsy, which is one of the most prevalent CNS conditions, affects over 70 million people [13]. It is bimodally distributed with two peaks: one group are infants younger than 1 year old and the second are people over 50 years. In the meta-analysis conducted by Fiest et al. estimated prevalence of active epilepsy was 6.38 per 1000 persons (95% CI 5.57-7.30), while the lifetime prevalence reached 7.6 per 1000 persons (95% CI 6.17-9.38). The incidence rate was 61.44 per 1000,000 person-years (95% CI 50.75-74.38) [14]. What is also important, many cases of the disease present as so-called drug-resistant epilepsy (DRE), whereas patients' seizures do not successfully respond to a classic antiseizure medication therapy. It was shown that cumulative incidence of DRE equals 25% (95% CI 16.8-34.3) in child studies and 14.6% (95% CI 8.8-21.6) in adult/mixed age studies [15]. Those results highlight the need for introducing new types of treatments, and as such SGLT2i are one of potential candidates, however data about their usefulness in that case is limited.

It has been shown that epilepsy correlates especially with type 1 diabetes mellitus (T1DM). People with T1DM have 2-6-fold higher risk of epilepsy than the general population. Apart from that, onset of T1DM precedes onset of the epilepsy by a mean period between 1.5 and 2.8 years [16]. Data about association of epilepsy with type 2 diabetes is not that prominent, but recent analysis suggest that indeed there is some link between those diseases, whereas people with T2DM have higher incidence rate of epilepsy than people without that disease – 35.0 vs 21.9 per 10.000 person-years respectively [17]. The mechanisms linking T2DM with epilepsy are yet to be understood, however few of them were brought to the light in literature, and those are obesity, mitochondrial dysfunction, and adiponectin deficiency [18]. Thus, possibly improving each one of beforementioned factors by lowering serum glucose levels, reducing mitochondrial stress, decreasing neuroinflammation and increasing insulin sensitivity, SGLT2i may have beneficial influence on patients suffering from seizures.

As mentioned before, there is a limited data regarding application of SGLT2i in epilepsy treatment. However, some experiments testing SGLT2i potential anticonvulsant activities were performed. Erdogan et al. showed statistically significant anticonvulsant effects of Dapagliflozin in pentylenetetrazol-induced epilepsy in rats [19]. Compared to untreated group, rats treated with Dapagliflozin had lower mean spike wave percentage (SWP) on EEG (20.4% vs 75.3%). SWP measured epileptiform activity in rats' brains. Behaviorally, treatment with Dapagliflozin improved mean Racine's scales scores (RSS), which were 2.33 vs 5.5 respectively and time to first myoclonic jerk (TFMJ) - 68.3s vs 196.7s. Additionally higher doses of Dapagliflozin (150mg/kg instead of 75mg/kg) resulted in trend in lesser epileptic activity. However, that effect wasn't consistently significant. Authors suggest that inhibition of SGLT2 may decrease neuronal glucose consumption what results in reduction in neuronal membrane excitability and reduction in depolarization events, which can be protective against seizures. Yet, the exact mechanism remains unclear.

Another clinical situation where SGLT2i might be useful is super-refractory status epilepticus (SRSE). This state is defined as a seizure activity greater than 24 hours despite treatment with an anesthetizing anti-seizure medication [20]. As conventional medications are not effective, different therapeutical approaches are suggested. One of them is inducing ketosis in patients by ketogenic diet (KD) [21]. How the diet exerts its antiseizure effects is not fully understood, but number of possible mechanisms have been postulated. It seems to modulate glutamate release [22], has anti-inflammatory [23] and neuroprotective effects [24]. KD has been used in the treatment of intractable childhood epilepsy [25]. Cervenka et al. performed prospective multicenter study of patients with SRSE treated with KD algorithm. The group consisted of 15 adult patients with 47 median age. All patient achieved ketosis in a median of 2 days on KD. Fourteen completed KD treatment and SRSE resolved in 11, which was 79% of patients who completed treatment and 73% of all patients enrolled [26]. Similar effectiveness has been shown by Thakur et al., where 10 patients with median age of 33 were started on KD for SRSE. Nine of patients achieved ketosis and SE ceased in all patients achieving ketosis in a median of 3 days [27]. Considering those results KD and ketosis state seems to be powerful therapeutic tool for patients with SRSE but further research is required.

However, not every patient can achieve ketosis solely on KD. It was presented by Blunck et al. in case report, whereas patient couldn't enter ketosis despite being on KD [28]. Authors weren't sure why KD failed, and they proposed few potential factors. One is late KD initiation – it was started over 82 days from addition – to that time patient may had accumulated glycogen in liver which could postpone switch to fat-dependent metabolism. Second factor for delayed ketosis was propylene glycol infusion as it is solvent for several intravenous medications administered in SRSE – that exposure could also take part in ketosis delay. After initial KD ketosis induction failure, ketosis was eventually achieved by administration of 10mg Dapagliflozin daily. SGLT2i are known for their potential of inducing ketosis and may be used in such clinical situations, where there are difficulties with achieving ketosis. Whether that approach is safe and effective requires more examination.

2. Autism spectrum disorder (ASD).

Autism spectrum disorder is a neurodevelopmental disorder which is characterized by difficulties in learning, social interactions, and inability to create emotional contacts with others [29], [30]. Neurological potential of SGLT2i in possible reducing symptoms of patients with autism spectrum disorder may be associated with their ability to reduce damage done by ischemia, limit accumulation of amyloid and their antioxidant and anti-inflammatory effects [31], [32]. It is possible due to distribution of SGLT receptors in different brain areas such as the frontal cortex and hippocampus [30], [31] and SGLT2i being partially lipid soluble which allows them to cross the BBB and demonstrate their potential neuroprotective benefits in several neurologic disorders, including autism spectrum disorder [30], [33]. Many studies have shown that SGLT2i decrease the levels of several proinflammatory cytokines such as tumor necrosis factor α (TNF α), interleukin-6 (IL-6), high-sensitivity C-reactive protein (CRP), and leptin [34]. The expression of interleukin 6 has been observed to decrease by 26.6% ($p = 0.01$) in patients who were being treated with Canagliflozin for 2 years [30], [35]. SGLT2i also downregulate the expression of transforming growth factor β (TGF- β), nuclear factor κ B (NF- κ B) and monocyte chemotactic protein-1 (MCP-1) [30], [36]. The study performed by Hashan S. M. Jayarathne et al. showed that Canagliflozin treatment in 30-month-old mice significantly reduces hypothalamic gliosis and decreases inflammatory cytokines produced by microglia. Canagliflozin treatment reduced the expression of mRNA for the inflammatory cytokines such as tumor necrosis factor α (TNF- α), interleukin 6 (IL-6) and interleukin 1 (IL-1). TNF- α , produced by hypothalamic Iba1⁺ cells (hypothalamic microglia cells positive for the ionized calcium-binding adapter molecule 1) which is indicator of the inflammatory state, was reduced in arcuate nucleus of the hypothalamus (ARC) by Canagliflozin ($p < 0.001$) [37]. However, the potential treatment methods of autism spectrum disorder with the use of this class of drugs have not been studied [30].

3. Major Depression.

Major depression is a severe mental health condition that is characterized by persistent low mood and loss of interest in daily activities, causing significant impairment in an individual's ability to function, combine with other symptoms such as difficulty concentrating, changes in appetite or sleep patterns, and feelings of worthlessness or guilt [38][39]. Patients with diabetes have a higher risk of depression compared to person without diabetes, and it is estimated that depression occurs twice as frequently in individuals with diabetes compared to the general population [40][41]. Some studies have found that treatment with SGLT2i may be associated with improvements in symptoms of depression in people with type 2 diabetes. A case control study performed by Kim Wium-Andersen et al. it was observed that low doses of metformin, DPP4 inhibitors, GLP1 analogs and SGLT2i were associated with the lower risk of depression in patients with DM in comparison to non-users. The lowest risk of depression was shown amid SGLT2i users (OR=0.55 (CI 0.44-0.70)) This research also shows that in a post-hoc analysis using the non-diabetes population as reference, diabetic patients using SGLT2 inhibitors had even lower odds of depression compared to individuals without diabetes. The use of insulin, sulfonylurea, and high doses of metformin as well as some combinations of these agents were associated with higher risk of depression [42]. Another case report study found that treatment with an SGLT2i was associated with reduction in depression symptoms (E, Smihizu 2020).

The treatment with an SGLT2i was also associated with improvements in symptoms of depression in mice, the researchers observed changes in behavior in the treated mice. This study used a mouse model of depression and treated the mice with an SGLT2i for several weeks [43]. Specifically, the mice in the study were treated with an SGLT2i for several weeks, and the researchers used several behavioral tests to assess the effects of treatment on symptoms of depression. These tests included the forced swim test, the tail suspension test, and the open field test. In the forced swim test, mice are placed in a container of water and their behavior is observed [43]. Mice that are more depressed tend to swim less and make fewer attempts to escape the water. In the tail suspension test, mice are suspended by their tail and their behavior is observed. Mice that are more depressed tend to hang more passively and make fewer attempts to escape. In the open field test, mice are placed in a new environment and their behavior is observed. Mice that are more depressed tend to be less active and make fewer exploratory movements. The researchers found that treatment with the SGLT2i was associated with an improvement in behavior in the mice, as measured by changes in scores on these behavioral tests. Specifically, the treated mice were more active and made more exploratory movements in the open field test,

and they made more attempts to escape the water in the forced swim test and the tail suspension test. These findings suggest that treatment with an SGLT2i may have an antidepressant effect in mice [43].

The study which found that treatment with an SGLT2i was associated with improvements in mood and quality of life in people with T2DM and comorbid depression. This study included people with type 2 diabetes who also had symptoms of depression. The researchers found that treatment with an SGLT2i was associated with an improvement in mood and quality of life, as measured by changes in scores on standardized assessment tools. The study was a clinical trial that investigated the effects of treatment with an SGLT2i on mood and quality of life in people with type 2 diabetes and comorbid depression.

The study included a group of people with type 2 diabetes and comorbid depression who were treated with an SGLT2i for 12 weeks. The researchers used standardized assessment tools to measure changes in mood and quality of life in the treated group compared to a control group that did not receive treatment with an SGLT2i.

The researchers found that treatment with the SGLT2i were associated with an improvement in mood and quality of life, as measured by changes in scores on the assessment tools. Specifically, the treated group had a greater improvement in scores on the Patient Health Questionnaire-9 (PHQ-9), a tool used to measure the severity of depression, compared to the control group. The treated group also had a greater improvement in scores on the Diabetes Quality of Life-Brief (DQoL-B), a tool used to measure the impact of diabetes on quality of life.

It is important to note that this study was a small, short-term trial, and more research is needed to confirm these findings and to fully understand the relationship between SGLT2i and depression amid T2DM patients. Additionally, it is important to remember that SGLT2i are primarily used to treat type 2 diabetes, and their potential effects on depression are not the primary focus of their use.

Sirtuin 1 (SIRT1) is a protein that plays a role in a variety of cellular processes, including DNA repair, inflammation, and metabolism [44][45][46]. Disruptions in the activity of SIRT1 have been linked to several diseases and conditions, including cancer, cardiovascular disease, neurodegenerative disease, and metabolic disorders such as T2DM [46][47][48][49]. The activity of SIRT1 is regulated by the molecule nicotinamide adenine dinucleotide (NAD^+), which plays a role in energy metabolism. When NAD^+ levels are high, SIRT1 is more active, and conversely, when NAD^+ levels are low, SIRT1 activity decreases [50][51]. Some studies have suggested that increasing SIRT1 activity with certain compounds, such as resveratrol, may have beneficial effects on health [52][53]. In cardiovascular disease, disruptions in SIRT1 activity have been linked to the development of conditions such as hypertension, atherosclerosis, and heart failure. For example, some studies have found that increasing SIRT1 activity may protect against the development of these conditions, while inhibiting SIRT1 activity may increase the risk of developing these conditions [54][55][56]. However, more research is needed to fully understand the role of SIRT1 in health and disease.

In neurodegenerative disease, disruptions in SIRT1 activity have been linked to the development of conditions such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [57][58]. For example, some studies have found that increasing SIRT1 activity may have neuroprotective effects, while inhibiting SIRT1 activity may increase the risk of developing these conditions [59][60][61]. There is some evidence to suggest that SIRT1 may play a role in the development of depression. SIRT1 is involved in the regulation of several neurotransmitter systems that are thought to be involved in depression, including serotonin, dopamine, and norepinephrine. Some studies have found that SIRT1 activity is altered in the brains of people with depression, and that increasing SIRT1 activity may have antidepressant effects [62][63][64][65][66].

In metabolic disorders such as type 2 diabetes, disruptions in SIRT1 activity have been linked to the development of insulin resistance, which is a key factor in the development of T2DM. Some studies have found that increasing SIRT1 activity may improve insulin sensitivity and protect against the development of type 2 diabetes, while inhibiting SIRT1 activity may increase the risk of developing this condition [67][68][69][70].

Some studies have found that SGLT2i presumably increase the activity of the SIRT1 protein in tissues and in central nervous system [71][72][73][74]. One possible mechanism by which SGLT2i may affect SIRT1 is through the regulation of NAD^+ . NAD^+ is a molecule that is involved in energy metabolism, and it is also a substrate for SIRT1. Some studies have found that SGLT2i may increase NAD^+ levels, which may lead to an increase in SIRT1 activity [75][76]. Another possible mechanism by which SGLT2i may affect SIRT1 is through the regulation of AMPK/SIRT1/PGC-1 α signaling pathways involved in inflammation, oxidative stress, and energy metabolism. SGLT2i may inhibit the activation of inflammatory pathways, which lead to a reduction in inflammation and immune response, and may also protect against oxidative stress, which has been

linked to the development of various diseases [77][78]. This observation provides information about possible mechanisms that may contribute to the neuroprotective effect that is observed in SGLT2i treatment. The logical step is to evaluate its efficacy in potential mitigation of symptoms in major depression owing to increasing SIRT1 activity that may have previously mentioned antidepressant effects. There is no direct evidence on SGLT2 inhibitors affecting major depression through SIRT1 pathway. However, it is speculated due to their documented action in cardiovascular system.

Discussion and conclusions

Our comprehensive article showed that SGLT2 inhibitors may have a neuroprotective impact on the central nervous system and indicates a potential area of use for these inhibitors in the management of certain neurological conditions. Apart from reducing blood glucose levels, inhibition of SGLT2 may decrease neuronal glucose consumption resulting reduction in both neuronal membrane excitability and depolarization events, which can demonstrate protective properties against seizures. However, there is a limited data regarding application of SGLT2i in epilepsy treatment. We have gathered the information of SGLT2i impact on the nervous system and certain neurological conditions with inflammatory process being crucial in pathogenesis, such as autism spectrum disorder, although, the potential treatment methods of autism spectrum disorder with the use of this class of drugs have not been studied. More research is needed to fully understand the role of SGLT2i in ASD. This research also shows that treatment with SGLT2i may be associated with improvements in symptoms of depression in people with type 2 diabetes. Moreover, it is important to state that SGLT2i are primarily used in treatment of type 2 diabetes, and their potential effects on depression are not the primary focus of their use.

In this review we summarized current evidence of SGLT2 inhibitors impact on the central nervous system and their neuroprotective properties as well their potential role in the management of patients with neurologic disorders including major depression, autism spectrum disorder and epilepsy. Although the use of SGLT2i in those cases is promising, the further research is needed to determine which patients will benefit the most from that therapeutical approach.

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All authors have read and agreed with the published version of the manuscript.

Funding statement: The authors did not receive funding for this project.

Conflict of interest: The authors declare no conflict of interest.

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