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REVIEW

Sodium-Glucose Cotransporter-2 Inhibitors in Mood Disorders: A Narrative Review of Mechanisms, Evidence, and Challenges

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Abstract: Mood disorders, including major depressive disorder and bipolar disorder, are frequently comorbid with metabolic syndrome, contributing to greater illness severity and poorer outcomes. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i), a novel class of anti-diabetic agents, not only improve glycemic control but have also shown potential neuroprotective and cognitive benefits. This narrative review summarizes preclinical and clinical evidence on the application of SGLT-2i in mood disorders, with emphasis on their multifaceted mechanisms, including metabolic modulation, anti-inflammatory and antioxidant effects, mitochondrial protection, autophagy regulation, and enhancement of neurotrophic signaling. But it is also notable that current evidence remains limited and heterogeneous. Most clinical data derive from observational studies in diabetic populations and evidence supporting therapeutic effects in patients with established mood disorders is still preliminary. Other important limitations include the scarcity of disorder-specific randomized controlled trials, uncertainty regarding long-term safety in psychiatric populations, and potential interactions with psychotropic medications. Collectively, SGLT-2i may represent a mechanistically relevant and clinically exploratory approach at the interface of metabolic and psychiatric disorders, though further high-quality studies are required to establish their efficacy and safety in mood disorder populations.

Keywords: SGLT-2 inhibitors, major depressive disorder, bipolar disorder, metabolic syndrome, neuroinflammation, neuroplasticity

Mood Disorder and Metabolic Syndrome

Mood disorders are a group of psychiatric diseases characterized primarily by significant and persistent disturbances in affect or mood, with major clusters including major depressive disorder (MDD) and bipolar disorder (BD). The 12-month prevalence of depressive disorder is estimated to be around 6% globally, with a lifetime risk of 15–18%.[1] The lifetime prevalence of bipolar I disorder worldwide is approximately 0.6%, while bipolar II disorder has a slightly higher prevalence, ranging from 0.4% to 1%.[2] Both conditions are strongly associated with reduced quality of life and increased mortality risk. Specifically, depression ranked 13th leading cause of disability-adjusted life years (DALYs) in 2019 and 2nd as a cause of years lived with disability (YLDs) globally.[3] Bipolar disorder is associated with a potential reduction in life expectancy of approximately 10–20 years.[2] Among the excess mortality observed in patients with severe mental illnesses, including MDD and BD, about 60% is attributable to comorbid physical diseases, particularly cardiovascular conditions,[4] indicating the possible relation between mood disorders and metabolic disorders.

Metabolic syndrome (MetS) directly increases the risk of cardiovascular disease, type 2 diabetes mellitus (T2DM), and all-cause mortality. Various criteria have been proposed for the clinical diagnosis of MetS.[5–7] Though varying across organizations, they typically represent a cluster of interrelated conditions including abdominal obesity, insulin resistance or hyperglycemia, dyslipidemia, and hypertension.[8]

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Consistent with the elevated risk of cardiovascular mortality, patients with mood disorders show a significantly increased comorbidity rate with MetS, approximately 31.3% and 31.7% for MDD and BD, respectively.[4] Conversely, individuals with metabolic disorders also exhibit a heightened risk of mood disorders. For instance, the prevalence of MDD in patients with T2DM is 14.5%, significantly higher than in the general population (OR = 1.73).[9] These observations suggest a potential shared biological foundation between the two conditions.

This comorbidity exacerbates the severity of mood disorders and alters the disease course. The presence of MetS in older adults with depression is associated with greater symptom severity and chronicity.[10] In BD, metabolic risk factors have been associated with poor treatment response, chronic course of illness, increased risk of rapid cycling, and worse global functioning.[11] Both metabolic dysfunction and mood disorders are also independently associated with cognitive deficits,[12] with each component of MetS negatively affecting cognitive performance.[13] The most pronounced impairments manifest in working memory, followed by attention, executive function/processing speed, global cognition, verbal memory, and visual memory.[12]

Taken together, these findings suggest that the metabolic burden associated with mood disorders is not merely a comorbidity but an important factor that may worsen prognosis and complicate treatment. In this context, current antidepressants and mood stabilizers remain limited by incomplete response, relapse, residual cognitive symptoms, and, in some cases, adverse metabolic effects. Therefore, it may be a new direction to improve the prognosis of mood disorders by exploring treatment strategies from the perspective of metabolic mechanisms. Several metabolic modulating agents like lipid-lowering agents and anti-diabetic drugs, including statins, thiazolidinediones, glucagon-like Peptide 1 (GLP-1) agonists, and metformin, have been evaluated for the treatment of mood disorders.[14–16]

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i), as an emerging class of anti-diabetic agents, act through inhibiting SGLT-2 receptors in the proximal renal tubules, thereby reducing blood glucose levels by preventing glucose reabsorption from the urine and inducing a negative energy balance.[17] They may be of particular interest because they exhibited the most significant association with the reduction of depression onset in diabetic patients among many agents including GLP-1 agonists and metformin.[18–20] Moreover, these agents have demonstrated therapeutic benefits across multiple organs, with robust clinical evidence supporting their efficacy in cardiovascular and renal diseases through mechanisms including ketogenesis which might also benefit in mood disorders, anti-oxidation and anti-inflammation, and increasing evidence suggesting their potential neuroprotective and cognitive improvement benefits in neurological conditions such as Alzheimer's disease.[21–24]

Overall, the rationale for examining SGLT-2 inhibitors in mood disorders rests on three considerations: the shared pathophysiological basis of metabolic and affective dysregulation, the persistent unmet therapeutic needs in mood disorders, and the possibility that SGLT-2i may offer a distinct translational profile among metabolic-modulating agents. Within this metabolic–psychiatric framework, SGLT-2i warrant discussion as a mechanistically relevant but still clinically preliminary approach in mood disorders. This review will summarize the established preclinical and clinical evidence regarding the potential effects of SGLT-2i in mood disorders, and then outline their underlying mechanisms targeting the frequent comorbidity of metabolic dysfunction in mood disorders, exploring their future clinical applications.

SGLT-2 and SGLT-2i

SGLT-2 belongs to a group of sodium-dependent symporters that mediate the transport of various substances.[25] SGLT-2 itself is a glucose transporter that functions against a concentration gradient, transporting one Na^+ and one D-glucose molecule, which is thought to be responsible for 80%–97% of renal glucose reabsorption.[26]

SGLT-2 is predominantly located on the apical membrane of the brush border in renal proximal tubule cells, with emerging research revealing that SGLT-2 may also be expressed in tissues beyond the kidney. Notably, the brain depends heavily on glucose as its primary energy source, demanding glucose to cross several barriers linked with tight junctions via transporter proteins.[27] In vivo PET imaging in rats with Me-4-FDG revealed widespread functional expression of SGLTs in the brain, including hippocampal pyramidal neurons, cerebellar Purkinje cells, the frontal cortex, caudate-putamen, amygdala, parietal cortex, and hypothalamic paraventricular nucleus.[28] Among SGLTs, though SGLT-2 expression in the brain is lower than SGLT-1, co-expression of SGLT-1 and SGLT-2 has been reported in several CNS regions.[29] Human SGLT-2 mRNA has been detected in the cerebellum.[25] Evidence from animal models suggests that SGLT-2 may localize in the brain microvasculature of the blood–brain barrier (BBB),[30] the choroid plexus and ependymal cells facing the CSF,[31] as well as in the hypothalamus, amygdala, periaqueductal gray (PAG), and the nucleus tractus solitarius (NTS) involved in autonomic control,[32] such distribution patterns

indicate that SGLT-2 may participate in the regulation of learning, food intake, energy, and glucose homeostasis, central cardiovascular and autonomic functions,[33] supporting the rationale for their potential involvement in metabolic and neuropsychiatric diseases.

SGLT-2i has become a cornerstone in the treatment of T2DM. Widely approved agents nowadays include empagliflozin, dapagliflozin, and canagliflozin. These agents differ in their pharmacokinetic profiles and selectivity. While none is absolutely selective for SGLT-2, empagliflozin exhibits the highest selectivity (SGLT-2/SGLT-1 about 2500), followed by dapagliflozin (about 1200), and canagliflozin (about 250).[34]

Beyond glycemic control, accumulating evidence suggests broader therapeutic potential for SGLT-2i. Notably, due to their lipophilicity, SGLT-2i are capable of crossing the BBB and exert direct effects on the CNS. Among them, empagliflozin shows the highest brain-to-serum area under the curve (AUC) ratio at 0.5, compared to 0.3 for dapagliflozin and canagliflozin.[35] Such property supports their potential utility in the treatment of neuropsychiatric disorders. Their potential role in mood disorder treatment will be reviewed in the following section.

Application of SGLT-2i in Mood Disorders

Evidence from Preclinical Animal Models

The accumulating animal experimental data have demonstrated the role SGLT-2i might play in the treatment of mood disorders. As anti-diabetic agents, SGLT-2i exert regulatory effects on diabetes-induced depressive behaviors in diabetic animal models. In DM rats, systemic or local administration of dapagliflozin directly acts on the LHb, suppressing its neuronal activity thereby producing anti-depressant effects.[36] High-dose empagliflozin (10 mg/kg) daily oral administration alleviates depressive-like behaviors induced by olfactory bulbectomy in DM rats, which could be attributed to its antioxidant and brain-derived neurotrophic factors (BDNF) modulating properties.[37]

The anti-depressant potential of SGLT-2i has also been demonstrated across various depression-related animal models. In rats subjected to chronic unpredictable stress (CUS), all the mentioned SGLT-2i have been found effective to reverse the resulting pathological changes in the hippocampus, such as upregulated inflammatory and oxidative markers, as well as improve behavioral performance, indicated by shortened immobility in tail suspension and forced swim tests and normalized sucrose preference.[38–40] In mice exposed to single-prolonged stress (SPS), dapagliflozin treatment reversed depressive-like behaviors and normalized SPS-induced increases *Crh, Bax, Il1b*, and *Bdnf* mRNA levels in brain, as well as corticosterone level in serum.[41] As noted above, endocrine dysregulation can promote depression development. Ovariectomized rats exhibit depressive-like behaviors which could be reduced by empagliflozin, likely through regulation BDNF and AMPK pathways.[42] Which is also suggested in reserpine-induced depressive animals.[43] These actions ultimately improve hippocampal neuroplasticity and restore the balance of monoamines, autophagy, and inflammation, contributing to the reversal of behavioral, biochemical, and histopathological alterations associated with depression.[43]

Recent studies have also explored the effects of SGLT-2i on BD. In a rat model of mania-like behavior induced by paradoxical sleep deprivation (PSD), dapagliflozin is found to alleviate those behaviors accompanied by enhanced autophagic clearance in the hippocampus and promoted GABAergic transmission.[44]

The studies investigating the effects of SGLT-2i on mood disorders are listed in Table 1. And the verified molecular pathways of SGLT-2i in mood disorders are summarized in Figure 1.

Cognitive impairment is a key feature of mood disorders and is often exacerbated by comorbid metabolic conditions. SGLT-2i has been shown to be useful in cognition improvement manifested in diabetes-associated cognitive impairment. Empagliflozin reduces cortical thinning, amyloid plaque burden, microglial activation, and oxidative stress, improving memory performance possibly through modulating neuroinflammation and neurotrophic factors.[45–47] But these findings are indirect with respect to mood disorders and should be interpreted as supportive mechanistic evidence rather than disorder-specific therapeutic data.

Clinical Evidence of SGLT-2i in Mood Disorders

While the growing animal studies have demonstrated the therapeutic potential and mechanisms of SGLT-2i for mood disorders, it's important to note that the doses used in these experiments are typically much higher than clinical doses, and

Table 1 Summary of Evidence for SGLT-2i in Animal Models Related to Mood Disorders

Author	SGLT-2i	Animal Models	Mechanisms
Muhammad et al[38]	Dapagliflozin 1 mg/kg/d p.o.	Rats exposed to CUS expressing depressive-like behavior	Anti-inflammation Improve neuroplasticity
Khedr et al[40]	Canagliflozin 20 mg/kg/d p.o.	Rats exposed to CUMS expressing depressive-like behavior	Anti-inflammation Activate autophagy Reduce TRY/KYN Regulate HPA axis
Dong et al[36]	Dapagliflozin 1 mg/kg/d ig. or 500 ng/mL LHb microinjected	HFD-induced diabetic rats expressing depressive-like behavior	Enhance GABAergic transmission
Borikar et al[37]	Empagliflozin 5 or10 mg/kg/d p.o.	Streptozotocin- induced diabetic rats with OBX-induced depression	Anti-oxidation Improve neuroplasticity
Muhammad et al[43]	Empagliflozin 10 mg/kg/d p.o.	Rats exposed to reserpine expressing depressive-like behavior	Anti-inflammation Anti-Oxidation Activate autophagy Improve neuroplasticity
Fathy et al[42]	Empagliflozin 10 mg/kg/d p.o.	Female rats subjected to ovariectomy expressing depressive-like behavior	Anti-inflammation Improve neuroplasticity
Saleh et al[44]	Dapagliflozin 1 mg/kg/d p.o.	Mice exposed to PSD with mania-like behavior	Activate autophagy Enhance GABAergic transmission Anti-inflammation
Ali et al[39]	Empagliflozin 10 mg/kg/d p.o.	Rats exposed to CUMS expressing depressive-like behavior	Anti-inflammation Anti-oxidation Anti-apoptosis Relieve insulin resistance
Amawi et al[41]	Dapagliflozin 1 mg/kg/d p.o.	Mice exposed to SPS with depressive-like behavior	Regulate HPA axis Anti-apoptosis Anti-inflammation

Abbreviations: LHb, lateral habenula; CUS, chronic unpredictable stress; CUMS, chronic unpredictable mild stress; HFD, high-fat diet; OBX, olfactory bulbectomy; PSD, paradoxical sleep deprivation; SPS, single-prolonged stress; TRY/KYN, tryptophan/kynurenine; HPA-axis, Hypothalamic–pituitary–adrenal axis; GABA, G-protein-coupled γ-aminobutyric acid.

the metabolic profiles of animal models differ significantly from those of human patients. Therefore, additional clinical data are required before SGLT-2i can be formally adopted for mood disorder treatment.

Since SGLT-2i are primarily used as anti-diabetic medications, most related clinical studies were conducted in diabetic populations. A retrospective study from Taiwan, China, showed that patients with T2DM treated with SGLT-2i have a significantly reduced risk of developing psychiatric disorders (HR=0.80, 95% CI: 0.72–0.88).[48] Focusing on mood disorders, a retrospective cohort study published in 2019 has already found that among multiple anti-diabetic drugs, SGLT-2i was associated with a significantly lower risk of developing depression in diabetic patients (OR=0.09, 95% CI: 0.01–0.63) but was limited by the small number of T2DM patients with comorbid depression receiving SGLT-2i.[49] Subsequent clinical studies with larger sample sizes provide more reliable results. A nested case–control study finds that several anti-diabetic agents are related to reduced risk of depression onset in diabetic patients, among which SGLT-2i exhibits the most significant association (OR=0.55, 95% CI: 0.44–0.70).[18] Two other large cohort studies report similar findings.[19,20]

Another case–control study further investigates the broader neuropsychiatric effects of SGLT-2i in diabetic patients. Diabetic patients have significantly higher PHQ-9 scores than healthy controls, but among the diabetic cohort, it's significantly lowered through the treatment of SGLT-2i compared to sulfonylureas.[50] Similar favoring effects are also observed in inflammatory biomarker levels, cognitive function tests, and quality of life (QoL) scores.[50]

There is also evidence supporting the role of SGLT-2i for clinical symptoms of mood disorders, including cognitive defects. A recent meta-analysis assesses the relationship between anti-diabetic drugs and cognitive impairment in T2DM patients and reveals that, those taking SGLT-2i have a significantly reduced risk of dementia (OR=0.75, 95% CI: 0.64–0.87), which is the most robust among all anti-diabetic drugs studied.[51]

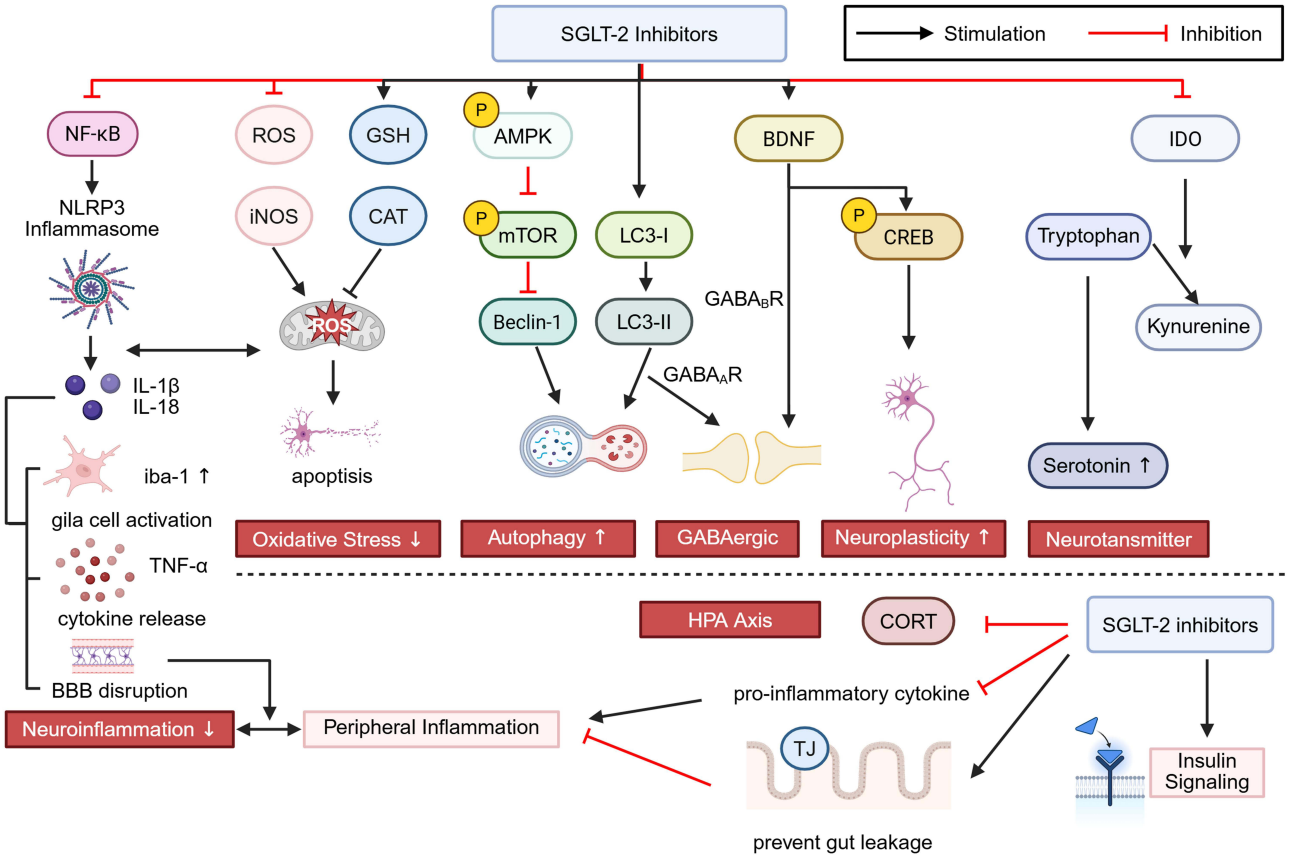

Figure 1 Proposed neurobiological mechanisms underlying the potential benefits of SGLT-2 inhibitors in mood disorder animal models. SGLT-2 inhibitors modulate multiple pathways implicated in mood disorders. These converging mechanisms help restore cellular homeostasis and ultimately improve mood-related behaviors, as validated in preclinical models. Upward arrows indicate relative increases or enhancement, whereas downward arrows indicate relative decreases or inhibition in the indicated molecules, pathways, or biological effects.

Abbreviations: SGLT-2, Sodium-glucose cotransporter-2; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL-1β/IL-18, Interleukin-1 beta/Interleukin-18; TNF-α, Tumor necrosis factor-alpha; BBB, Blood–brain barrier; ROS, Reactive oxygen species; iNOS, Inducible nitric oxide synthase; GSH, Glutathione; CAT, Catalase; AMPK, AMP-activated protein kinase; mTOR, Mammalian target of rapamycin; LC3-I/LC3-II, Microtubule-associated protein 1A/1B-light chain 3 isoforms I and II; BDNF, Brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; IDO, Indoleamine 2,3-dioxygenase; GABA$_A$/GABA$_B$ R, Gamma-aminobutyric acid A/B receptor; HPA axis, Hypothalamic–pituitary–adrenal axis; CORT, Cortisol; TJ, Tight junction.

While these population-based studies provide encouraging evidence for the beneficial psychiatric effects of SGLT-2i, they primarily focus on comorbidity risk in diabetic populations, which are not designed to evaluate their therapeutic efficacy in individuals already diagnosed with mood disorders. Two recent studies have attempted to amend this gap. A randomized controlled trial in MDD patients with baseline HDRS scores ≥17 shows that those receiving citalopram plus 10 mg empagliflozin have a greater reduction in HDRS scores than the placebo group, suggesting a potential therapeutic effect of empagliflozin in MDD.[52] Another cohort study focuses on patients diagnosed with BD and suggests that SGLT-2i may have a neutral to potentially protective effect on suicide-related outcome compared to DPP-4 (IR = 0.17 vs. 0.26 per 100 person-years; IRD = −0.09; 95% CI: −0.16–0.02).[53]

However, not all studies report consistent findings. A cross-sectional study finds no statistically significant difference in depressive symptom severity between diabetic patients using and not using SGLT-2i.[54] This study underscores the need for further research to clarify the effects of SGLT-2i on mental health.

The clinical studies concerning SGLT-2i and mood disorders are summarized in Table 2.

Mechanisms Linking Mood and Metabolic Disorders

SGLT-2i exert potential therapeutic effects on mood disorders through multiple mechanisms. To better understand their multi-target effects, we first explore the various pathways involved in the comorbidity between metabolic disorders and

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Table 2 Summary of the Clinical Studies Evaluating the Effects of SGLT-2 Inhibitors on Mood Disorders

Author	Study Type	Data Source/Site	Population and Outcomes	Key Findings
Akimoto et al[49]	Retrospective cohort study	Nihon University School of Medicine (NUSM) Clinical Data Warehouse (CDW)	Patients aged above 20 diagnosed with T2DM at least 30 days with (N=1979) and without (N=38235) depression.	SGLT-2i decreased the risk of depression (AOR: 0.09; 95% CI: 0.01–0.63; P = 0.0153), but only 1 patient with T2DM and depression had taken SGLT-2i.
Wium-Andersen et al[18]	Cohort and nested case-control study	Six National Danish registries	Patients with T2DM (N=116699) and matched group without diabetes. Outcome is the diagnosis of depression.	Use of SGLT2i in diabetic patients was associated with the lowest odds of depression (OR = 0.55; 95% CI: 0.44–0.70), and lower odds compared to those without diabetes (OR = 0.77; 95% CI: 0.61–0.98)
Mui et al[19]	Retrospective cohort study	Clinical Data Analysis and Reporting System (CDARS), Hong Kong	T2DM patients over 18 years old using SGLT2i (N = 19,381) or DPP4i matched, followed up until new-onset depression or death.	Compared to DPP4i, SGLT2i use was associated with significantly lower incidence of new onset depression both before (HR: 0.42; 95% CI: 0.36–0.49; P < 0.0001) and after matching (HR: 0.35; 95% CI: 0.30–0.41; P < 0.0001).
Hu et al[48]	Retrospective cohort study	National Health Insurance Research Database (NHIRD), Taiwan	Patients with diabetes, taking SGLT2i (N=336140) matched with non-users. Incidence of psychiatric disorders including BD was measured.	SGLT2i reduce psychiatric disease (IR = 1.26 vs. 1.75; aHR = 0.80; 95% CI: 0.72–0.88; p < 0.001), but not significant for BD alone (aHR = 0.83; 95% CI: 0.69–1.00).
Zandifar et al[52]	Randomized Controlled Trial	Imam Ali Hospital, Alborz, Iran	MDD outpatients (HDRS > = 17), randomly divided into two groups receiving placebo (N = 45) or empagliflozin (10 mg/d) (N = 45) combined with citalopram (40 mg/d), evaluated with HDRS in week 4/8.	The average of HDRS in empagliflozin recipients (27.4 ± 3.8 to 7.0 ± 1.1) was significantly lower than the placebo group (28.4 ± 3.8 to 13.4 ± 3.4).
Ganz et al[54]	Retrospective cohort study	National Health and Nutrition Examination Survey (NHANES)	23575 participants in total. 7862 had T2DM, among which 68 were on SGLT2i. Depression status was assessed by PHQ-9.	Diabetic patients on SGLT2i did not show significant difference in PHQ-9 score compared to non-users (−0.769675; 95% CI: −1.6177–0.0724; p = 0.0732).
Chen et al[20]	Retrospective cohort study	TriNetX US Collaborative Network	T2DM patients (N =359787) receiving monotherapy of metformin, GLP-1RA, DPP-4i, SGLT-2i (N = 31,785). Outcomes included incident depression and all-cause mortality, assessed after 1,3,5 years.	GLP-1 RA showed higher depression risk than SGLT-2i (HR = 1.33; 95% CI: 1.16–1.53); SGLT-2i showed lower risk than DPP-4i (HR = 0.62; 95% CI: 0.55–0.71); higher risk than metformin in year 3 (HR = 1.30; 95% CI: 1.01–1.37) but not in year 1 and 5.
Chang et al[53]	Retrospective cohort study	TriNetX US Collaborative Network	BD patients receiving psychiatric treatment initiated SGLT-2i or DPP-4i (N = 1711 each). Outcomes included suicide-related events and all-cause mortality.	In BD patients with T2DM, SGLT-2i showed significantly lower risk of suicide-related events (IR = 0.17 vs. 0.26 per 100 person-years; IRD = −0.09; 95% CI: −0.16–0.02; p = 0.0154) and all-cause mortality (HR = 0.594; 95% CI: 0.451–0.783; p < 0.001) compared to DPP-4i.
Majid et al[50]	Case-control study	Outpatient Department of Medicine and Diabetes Unit, Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi, India	166 participants divided into three groups: healthy controls (N = 55), SGLT2i-treated T2DM patients (N = 57), and SUs-treated T2DM patients (N = 54). Cognitive function (MoCA), depression (PHQ-9), serum neuroinflammatory and metabolic biomarkers were measured.	PHQ-9 scores were significantly higher in SUs group (8.2 ± 1.67) than SGLT2i group (6.5 ± 3.8), both higher than healthy controls (3.4 ± 1.2) (p < 0.001). MoCA scores were significantly lower in both SGLT2i (22.51 ± 4.2) and SUs (20.03 ± 2.04) groups compared to healthy control (29.38 ± 1.04) (p < 0.001). Neuroinflammatory markers (HMGB1, IL-1β, TNFα, IL-6, ADAM-10, and TLR4) and metabolic markers (mTOR) were higher in T2DM groups compared to healthy controls.

mood disorders. Several hypotheses linking these two disorders have been proposed, like genetic and environmental factors, psychotropic medications, and moreover, the interconnected framework including inflammatory processes, hypothalamic–pituitary–adrenal (HPA) axis, oxidative stress, neuroplasticity, and gut microbiota.[55]

Genetic Factors

The causal links between depression and metabolic traits have been verified by Mendelian randomization studies: fat mass is a causal risk factor for depression,[56] while depression demonstrates a significant causal effect on T2DM and 36.5% of the effect was mediated by BMI.[57] Specifically, Amare et al identify 24 candidate pleiotropic genes and important biological pathways that are likely to be shared with mood and metabolic disorders through meta-GWAS analysis.[58]

Environmental Influences

Unhealthy lifestyles such as smoking, excessive alcohol consumption, poor sleep hygiene, physical inactivity, and unhealthy nutritional patterns are highly prevalent among MDD/BD patients, and the limited access to quality healthcare services further exacerbates this risk of pathophysiological disturbances and developing MetS.[59–61] Considering the prevalence of unhealthy behaviors among patients with psychiatric disorders and its substantial influence on MetS, it is likely that adverse habits contribute remarkably to this comorbidity.[55] Intriguingly, it is suggested that novel environmental inputs, including artificial light at night and sustained refined sugar intake, may aggravate the metabolic and circadian dysregulation, driving the BD development.[62]

Effects of Psychotropic Medications

Psychotropic medications, particularly antipsychotics, further elevate the risk of metabolic disturbances like obesity, dyslipidemia, and diabetes in these patients.[63] Individuals treated with any single antipsychotic agent, especially olanzapine, commonly used in mood disorders treatment, have a higher risk of developing MetS compared to those who received none.[4] The prevalence of T2DM significantly increased in those treated with antipsychotics except for aripiprazole and amisulpride compared to non-users.[64] Most psychotropic medications also contribute to weight gain through mechanisms involving increased appetite, higher caloric intake, and delayed satiety signaling.[65] The effect of mood stabilizers on weight gain in BD patients is also significant, with a reported 77% patients experiencing an average weight gain of 4–6.3 kg.[65,66] Anti-depressants, particularly those with high affinity for norepinephrine re-uptake transporters, serotonergic 5-HT2C receptors, and histamine H1 receptors, also contribute to the increased risk of new onset diabetes, especially in high doses and long-term treatment.[65]

However, it is important to note that even after adjusting for lifestyle covariates, the association between metabolic disorders and psychiatric illnesses persists,[67] and is also observed in patients receiving diverse treatment regimens and extends even to those who remained untreated.[68] These findings suggest that additional pathophysiological mechanisms inherent to psychiatric disorders themselves contribute to the development of metabolic disorders.

Inflammation and Oxidative Stress

CNS inflammation would affect synaptic plasticity, neurogenesis, and emotional behavior.[69] It is well recognized that a high-fat diet (HFD) related to inflammation of the hypothalamus as well as mitochondrial dysfunction and insulin resistance in the hippocampus, induces cognitive or affective dysfunction.[70–72] Obesity is a pro-inflammatory state, with adipose tissue functioning as an endocrine organ capable of secreting pro-inflammatory cytokines and hormones such as leptin.[55] An immune cell will further infiltrate into metabolic tissues, promoting insulin resistance and exacerbating systemic glucose metabolism dysregulation, thereby propagating the vicious cycle of inflammation.[73] In conclusion, inflammation associated with mood disorders predisposes individuals to metabolic dysregulation; metabolic dysfunction perpetuates inflammation, establishing a vicious cycle that reinforcing both metabolic and psychiatric pathology.

Disturbance of the HPA Axis

The HPA axis plays a key role in the body's adaptation to environmental stress. Its hyperactivation is a hallmark of MDD, contributing to emotional and cognitive dysfunction and stress-related abnormalities through its effects on neurotransmitters, neuroplasticity, and inflammatory responses, especially in the amygdala and hippocampus.[74] The resulting chronic elevation of cortisol promotes visceral fat accumulation and insulin resistance through the activation of lipoprotein lipase and inhibition of lipid mobilization, thereby increasing the risk of MetS, obesity, and diabetes.[55]

Neuroplasticity and Neurotrophic Factors

Neuroplasticity helps encode experiences and adapt to stimuli. Its mechanisms, mediated by regulators like BDNF and mammalian target of rapamycin (mTOR), encompass neurogenesis, programmed cell death, and activity-dependent synaptic plasticity.[75] The development of mood disorders is closely related to neuroplasticity, and some antidepressants could regulate it to take their effect.[76] Neuroplasticity is also affected in obesity. The magnitudes of long-term potentiation and long-term depression were lower at the hippocampus of obese mice.[77] Application of mTOR inhibitor rapamycin in HFD-induced metabolic dysregulated and depressed mice could ameliorate both disorders,[78] implicating the role of neuroplasticity between mood and metabolic disorders.

Gut Microbiota

The gut microbiota has been proven to be related to MDD and BD, through the bidirectional gut-brain axis based on metabolic, endocrine, neural, and immunological pathways.[79] Meanwhile, gut microbiota and its metabolites may act directly or indirectly on the brain via vagal stimulation and food reward signals to regulate metabolism, body homeostasis, and energy balance, thus contributing to obesity.[80]

Summary of Comorbid Mechanisms

To sum up, the interaction between mood disorders and metabolic disorders is bidirectional and involves multiple interrelated factors, as shown in Figure 2, suggesting that medications targeting metabolic dysfunction may also help mood disorders treatment. Moreover, considering the adverse effects of antipsychotic medications, combination therapy to alleviate patients' metabolic burden could be beneficial. Against this background, SGLT-2i, whose effects target those overlapping pathways, has attracted growing attention for its potential neuropsychiatric benefits, which will be discussed in the following section.

Mechanical Basis for Neuropsychiatric Benefits of SGLT-2i

Given the various overlapping mechanisms between mood and metabolic disorders, SGLT-2i may confer neuropsychiatric benefits through different biological pathways. This section outlines the major mechanistic domains through which SGLT-2i may modulate mood and cognitive function.

Metabolism

As an anti-diabetic medication, SGLT-2i effectively lower blood glucose levels and reduce insulin resistance, while concurrently improving lipid metabolism and promoting weight loss.[81] These metabolic benefits alleviate peripheral metabolic burden, potentially mitigating mood disorder through previously described mechanisms shared between metabolic and mood disorders. However, except for such indirect metabolic effects, SGLT-2i directly regulates various metabolic pathways like ketogenesis, mTOR and central insulin signaling pathways also benefits multiple neuropathological processes.

Ketogenesis

SGLT-2i induces mild ketosis via a mechanism often described as an "accelerated starvation state".[82] During prolonged fasting when glycogen stores are depleted, the liver converts fatty acids into ketone bodies to serve as an alternative fuel.[82] SGLT-2i induce a similar metabolic state by promoting renal glucose excretion in the absence of fasting, leading to metabolic adaptations including enhanced lipolysis and ketogenesis, mediated through AMPK activation and mTOR inhibition.[82,83]

Ketone bodies, especially β-hydroxybutyrate (BHB), are a more efficient energy substrates that improve tissue energy metabolism.[84] Given the brain's high energy demand, it may particularly benefit from such metabolic effects. Ketos also manifested neuroprotective, antioxidant, and neurotransmitter-regulatory effects in the brain.[85] Specifically, BHB could function as a histone deacetylase inhibitor, leading to transcriptional activation of genes responsible for oxidative stress defense and metabolic homeostasis.[86] It also modulates the activation of NLRP3 inflammasome and other inflammatory pathways, thereby suppressing inflammatory responses.[87] Ketogenic diet has been associated with changes in monoamine neurotransmitters, including dopamine, noradrenaline, and serotonin in epilepsy, and also inhibits glutamate decarboxylase, thus stimulating GABA synthesis.[85] Clinically, multiple randomized trials have already confirmed that the ketogenic diet does

improve depressive mood, but its poor adherence and limited serum ketone maintenance pose challenges that SGLT-2i may help overcome pharmacologically, making them promising agents in mood disorder treatment.[88]

Restoring the Rhythm of mTOR Activity

mTOR is another target of SGLT-2i concerning metabolism,[83] which integrates extracellular and intracellular signals to regulate cell homeostasis and metabolism,[89] thus acting as a potential link between metabolic diseases and cognitive impairment in psychiatric disorders.[27] Under conditions where sufficient insulin and amino acids are available, mTORC1 complex is activated and suppresses autophagy, whereas nutrient deprivation inhibits mTORC1, restoring autophagic and lysosomal activity to release amino acids into circulation.[90] However, in patients with metabolic diseases exhibiting insulin resistance, chronically elevated circulating amino acids sustain mTORC1 activation and impair autophagy.[91] By promoting continuous glucose excretion, SGLT-2i helps re-establish normal circadian dynamics of mTOR activity—promoting anabolic activity during the day and catabolic activity at night[91]—thereby maintaining metabolic balance, mitigating inflammation, and ultimately contributing to improvements in cognitive function and mood regulation.

In addition to its role in metabolic regulation, mTOR regulates multiple neural processes, including autophagy-dependent neuronal survival, axonal regeneration and sprouting, neurogenesis and differentiation, myelination and oligodendrocyte maturation, as well as synaptic activity regulation downstream of NMDA receptor.[92] Several of these mechanisms are also implicated in the modulatory effects of SGLT-2i in neuropsychiatric disorders.

Ameliorating Brain Insulin Resistance

The brain is an insulin-sensitive tissue and is also exposed to the deleterious effects of insulin resistance. Brain insulin resistance disrupts neuronal energy metabolism, aggravates oxidative stress, and promotes neuroinflammation.[93] The resulted abnormal neuronal activities are considered a critical factor underlying AD, MDD/BD, and the accompanying cognitive deterioration.[94–97]

SGLT-2i have been shown to enhance peripheral insulin sensitivity via enhanced fat utilization and browning, M2 macrophage polarization,[98] and mTOR pathway modulation.[95] Similarly in CNS, SGLT-2i enhances brain insulin signaling and improves hippocampal-dependent learning, memory, and cognitive functions in T2DM-AD mouse.[99] Dapagliflozin increases the expression of insulin receptor and improves hippocampal insulin signaling, rescuing the HFD-induced cognitive impairment.[72,100] As for humans, empagliflozin ameliorates insulin resistance in the hypothalamus, mediating the decrease in fasting glucose and liver fat.[101] However, another study in HFD-fed female mice found that such improvement is only peripheral.[102] More studies are needed to further validate the influence of SGLT-2i on central insulin signaling.

Inflammation

Elevated peripheral inflammatory markers in mood disorder patients may disrupt the blood–brain barrier, promoting neuroinflammation and microglial activation, as observed in both MDD and BD patients.[103–105] These changes, observed in brain regions involved in reward and cognition, are associated with neuronal network disruption, synaptic dysfunction, and altered neurotransmission, including the kynurenine pathway, glutamate, and dopaminergic signaling.[105,106]

Firstly, SGLT-2i mitigates inflammation through the regulation of metabolic dysfunction, as shown in conditions such as myocardial infarction and renal diseases.[107] SGLT-2i also induce the polarization of macrophages toward M2 phenotype through multiple pathways,[107,108] and suppress NLRP3 inflamamsome.[109,110] Systemic inflammatory reduction is the result of these anti-inflammatory responses, supported by preclinical studies and population-based RCTs, which demonstrate that SGLT-2i significantly reduces multiple inflammatory as well as metabolic markers.[111–114] Alleviation of peripheral inflammation mitigates BBB disruption, thus indirectly slowing the progression of neuronal damage.

Moreover, SGLT-2i could directly alleviate neuroinflammation. The regulation of microglia by SGLT-2i may represent a critical mechanism underlying their therapeutic effects in mood disorders. In vitro studies have shown that empagliflozin reduced the expression of inflammatory mediators in LPS-activated rat primary microglia, which might be mediated by NHE-1 and by the inhibition of the ERK1/2 and NFκB pathways.[115] In vivo, SGLT-2i are reported to reduce microglial activation and promote a shift in microglial to the anti-inflammatory M2 phenotype in the LPS-induced rat neuroinflammation model, as

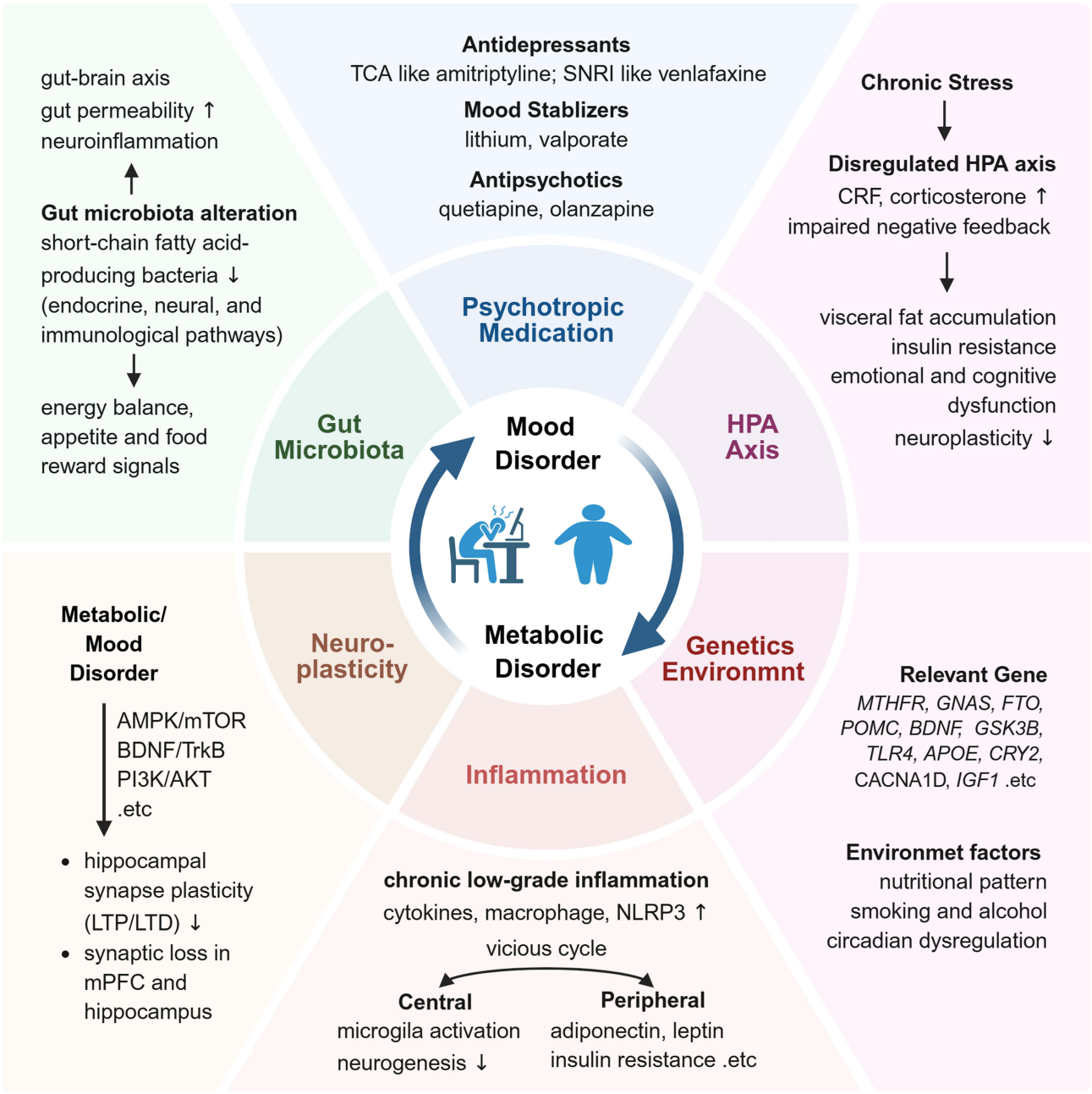

Figure 2 Mechanisms contributing to the bidirectional influence of mood disorders and metabolic disorders. Multiple interacting pathways contribute to the close relationship between mood and metabolic disturbances. Together, these mechanisms form a vicious cycle linking emotional and cognitive dysfunction with metabolic dysregulation. Upward arrows indicate relative increases or enhancement, whereas downward arrows indicate relative decreases or inhibition in the indicated molecules, pathways, or biological effects.

Abbreviations: HPA axis, Hypothalamic–pituitary–adrenal axis; CRF, Corticotropin-releasing factor; AMPK, AMP-activated protein kinase; mTOR, Mammalian target of rapamycin; BDNF, Brain-derived neurotrophic factor; TrkB, Tropomyosin receptor kinase B; PI3K/AKT, Phosphoinositide 3-kinase / protein kinase B; LTP / LTD, Long-term potentiation/Long-term depression; mPFC, Medial prefrontal cortex; NLRP3, NOD-like receptor thermal protein domain associated protein 3; MTHFR, Methylenetetrahydrofolate reductase; GNAS, Guanine nucleotide-binding protein G(s) subunit alpha; FTO, Fat mass and obesity-associated protein; POMC, Pro-opiomelanocortin; GSK3B, Glycogen synthase kinase 3 beta; TLR4, Toll-like receptor 4; APOE, Apolipoprotein E; CRY2, Cryptochrome circadian regulator 2; CACNA1D, Calcium voltage-gated channel subunit alpha1 D; IGF1, Insulin-like growth factor 1.

well as inhibit NLRP3 inflammasome expression by disrupting the pTau-CX3C1 interaction.[33,116] Inhibition of NLRP3 inflammasome activation and its downstream signaling also serves as a key therapeutic target of CNS-related pathologies,[117] through which SGLT-2i exert their neuroprotective effects, as shown in CUS-induced depressed rats,[32] as well as other various

animal models, including Aluminium Chloride-induced AD rats,[118] rotenone-intoxicated rats with Parkinson disease (PD)[119] and methotrexate-induced cognitive impairment rats.[120]

Mitochondrial Function and Cell Homeostasis

Mitochondria act as the hub of energy metabolism and autophagy, essential for maintaining neuronal homeostasis. Mitochondrial dysfunction has emerged as a key etiological factor in mood disorders, manifesting through: (i) structural abnormalities in morphology and distribution, (ii) impaired energy metabolism process with reduced ATP production and enhanced anaerobic glycolysis, and (iii) compromised quality control due to dysregulated biogenesis and mitophagy clearance pathways.[121,122] Oxidative stress and autophagy, both closely linked to mitochondrial function, contribute greatly to the pathogenesis of mood disorders and metabolic disorders. The ability of SGLT-2i to modulate these processes may contribute to its therapeutic effects for mood disorders.

Anti-Oxidative Properties of SGLT-2i

The brain is highly vulnerable to oxidative stress due to its high metabolic rate, lipid content, and limited antioxidant defenses.[121] Excessive ROS disrupts cellular communication, induces lipid and protein peroxidation, and triggers neuronal apoptosis via Ca^{2+} overload.[123] Elevated oxidative stress is consistently observed in mood disorders, correlates with disease severity, and some treating medications like fluoxetine, citalopram, lithium, and valproate may exert benefits by modulating redox balance.[124–127]

SGLT-2i reduces oxidative stress through multiple mechanisms: direct improvement of mitochondrial function, downregulation of oxidative enzymes, and enhancement of antioxidant systems.[128] Indirect effects include improving glycemic control, alleviating insulin resistance, modifying hemodynamics, and ameliorating renin-angiotensin system (RAS) activation.[128] By suppressing inflammatory pathways, SGLT-2i further reduce oxidative stress.[129] Additionally, ketone bodies promoted by SGLT-2i can serve as antioxidants and support mitochondrial function.[82,88]

Many preclinical studies have confirmed such antioxidative and neuroprotective effects, including CUS-induced depressive rats in which empagliflozin reversed the increased oxidative markers.[33] In vitro studies reveal that empagliflozin mitigates dendritic and spine alterations induced by hydrogen peroxide in primary neurons and inhibits neuronal ferroptosis induced by oxygen–glucose deprivation/reoxygenation.[130,131] In rotenone-induced PD rat models, both empagliflozin and dapagliflozin are able to reverse the elevated oxidative stress through AMPK/SIRT-1/PGC-1α pathway or DJ-1/Nrf2 pathway.[132,133]

SGLT-2i Modulates Autophagy

Dysregulated autophagy is observed in both mood disorders and neurodegenerative diseases characterized by abnormal protein aggregation, like AD.[134,135] Recent studies demonstrate that acute stress activates, while chronic stress suppresses autophagy in the lateral habenula (LHb), and the latter is associated with maladaptation to chronic stress.[136] Several antidepressants and mood stabilizers have been shown to modulate autophagy, including fluoxetine, sertraline, paroxetine, desvenlafaxine, lithium, and valproate.[137]

But it's noteworthy that both excessive and insufficient autophagy have been implicated in neurological disorders, with some depression-like animal models exhibiting increased autophagic markers.[137] AKT1/mTOR has been found to be reduced in BD patients during depressive episodes,[138] and is also compromised in the prefrontal cortex of MDD patients during postmortem studies.[139] But the anti-depressant effect of mTOR inhibitor rapamycin has also been reported in animal models.[140]

SGLT-2i can modulate autophagy through both mTOR-dependent and independent mechanisms, as verified in heart and kidneys,[89] and also animal models of mood disorders. Empagliflozin reverses the depressive behaviors and hinders autophagy in the hippocampus of depressed rats induced by reserpine through AMPK/mTOR/Beclin1/LC3B machinery.[37] Canagliflozin also modulates TYR/KYN and AMPK/mTOR autophagic signaling in rats subjected to chronic unpredictable mild stress.[34] In manic mouse models, dapagliflozin influences autophagic flux and ameliorates mania-like behaviour.[38] Similar regulation of the autophagy pathway is also found in AD rat models,[141] rotenone-lesioned rats,[119] vigabatrin-induced neurotoxicity,[142] and PD rats.[143] But the exact effects of SGLT-2i on autophagy and thus mood disorders need further clarification.

Brain-Derived Neurotrophic Factor

Neurotrophic factors, particularly BDNF, are important targets of SGLT-2i. BDNF plays a critical role in neuronal survival and growth, acting as a mitogenic and chemotactic factor that promotes the proliferation, migration, and maturation of neural progenitor cells, ultimately contributing to synaptic transmission and plasticity, especially in hippocampus.[144] BDNF also exerts neuroprotective effects through the suppression of apoptosis, oxidation, and autophagy.[145]

Decreased serum levels of mature BDNF (m-BDNF) are consistently observed in MDD patients, while pro-BDNF remains unchanged.[146] In BD patients, the reduction is more pronounced, and the m-BDNF/pro-BDNF ratio differs significantly from MDD, potentially serving as a discriminatory biomarker between the two disorders.[147] BDNF mediates the effects of many anti-depressants like ketamine, which triggers BDNF release via AMPA receptor activation, enhances BDNF synthesis by inhibiting eEF2K, and promotes BDNF-TrkB binding, ultimately activating mTOR and stimulating synaptogenesis.[76]

BDNF contributes greatly to the interaction between SGLT-2i and psychiatric disorders, and acts synergically with other mechanisms listed above. The verified anti-depressant mechanisms of SGLT-2i in various studies involve BDNF/CREB signaling, highlighting its significance in mood disorder treatment.[31,32,35–37] Besides, SGLT-2i have also manifested their benefits in AD cognitive impairment by increasing BDNF,[148–150] with similar effects observed in other neuropsychiatric conditions like PD and epilepsies.[132,151,152]

Additional Effects

Beyond mood disorders, other pathways have also been implicated in the therapeutic effects of SGLT-2i in a range of neurological and neurodegenerative conditions, including AD, PD, HD, and metabolic-related cognitive impairment. Although some mechanisms have not yet been directly validated in mood disorders, they provide important insights for understanding the potential intersections between SGLT-2i and mood pathology.

Cholinergic Modulation

SGLT-2i has also been found to possess potential acetylcholinesterase (AChE) inhibitory property in AD.[153] Animal studies have shown that SGLT-2i can improve memory deficits in scopolamine-induced amnesia rat models by dampening AChE activity and increasing monoamine neurotransmitter levels.[154]

Cerebrovascular Protection

The neurovascular unit (NVU), composed of neurons, glial cells, vascular cells, the extracellular matrix, and the functional coupling of these diverse components, is crucial for maintaining CNS homeostasis.[155] Damage to both micro- and macro-vascular structures can lead to NVU dysfunction and neurovascular remodeling, which play critical parts in the onset and progression of neurodegenerative diseases and cognitive impairment.[156] Empagliflozin has been shown to ameliorate microvascular damage and NVU remodeling caused by diabetes[157] and also enhance endothelial cell function through various mechanisms, thus hindering the progression of atherosclerotic disease.[158]

Summary

Evidence suggests that the neuroprotective effects of SGLT-2i arise from a convergence of multiple mechanisms summarized in Figure 3. SGLT-2i attenuates systemic inflammation and oxidative stress, thereby reducing harmful signaling to the central nervous system. And by improving metabolic status through ketogenesis, regulation of mTOR activity, and restoration of insulin sensitivity, these agents benefit the CNS. Within the brain, SGLT-2i enhances mitochondrial bioenergetics, restores autophagy balance, and suppresses neuroinflammation through inhibition of microglial activation and inflammasome pathways. In addition, SGLT-2i upregulates BDNF, promotes synaptic plasticity, supporting neuronal resilience. Collectively, these mechanisms interact under the treatment of SGLT-2i, providing a plausible biological basis for the observed improvements in affective and cognitive symptoms. This multifaceted mode of action highlights the potential of SGLT-2i as a bridge between metabolic regulation and neuropsychiatric benefits.

Overall, the mechanistic rationale linking SGLT-2 inhibitors to mood disorders remains biologically plausible but it should also be interpreted with caution. Much of the available evidence is derived from animal studies, in vitro experiments, or disease models not specific to mood disorders. So accordingly, the pathways discussed above should be regarded primarily as

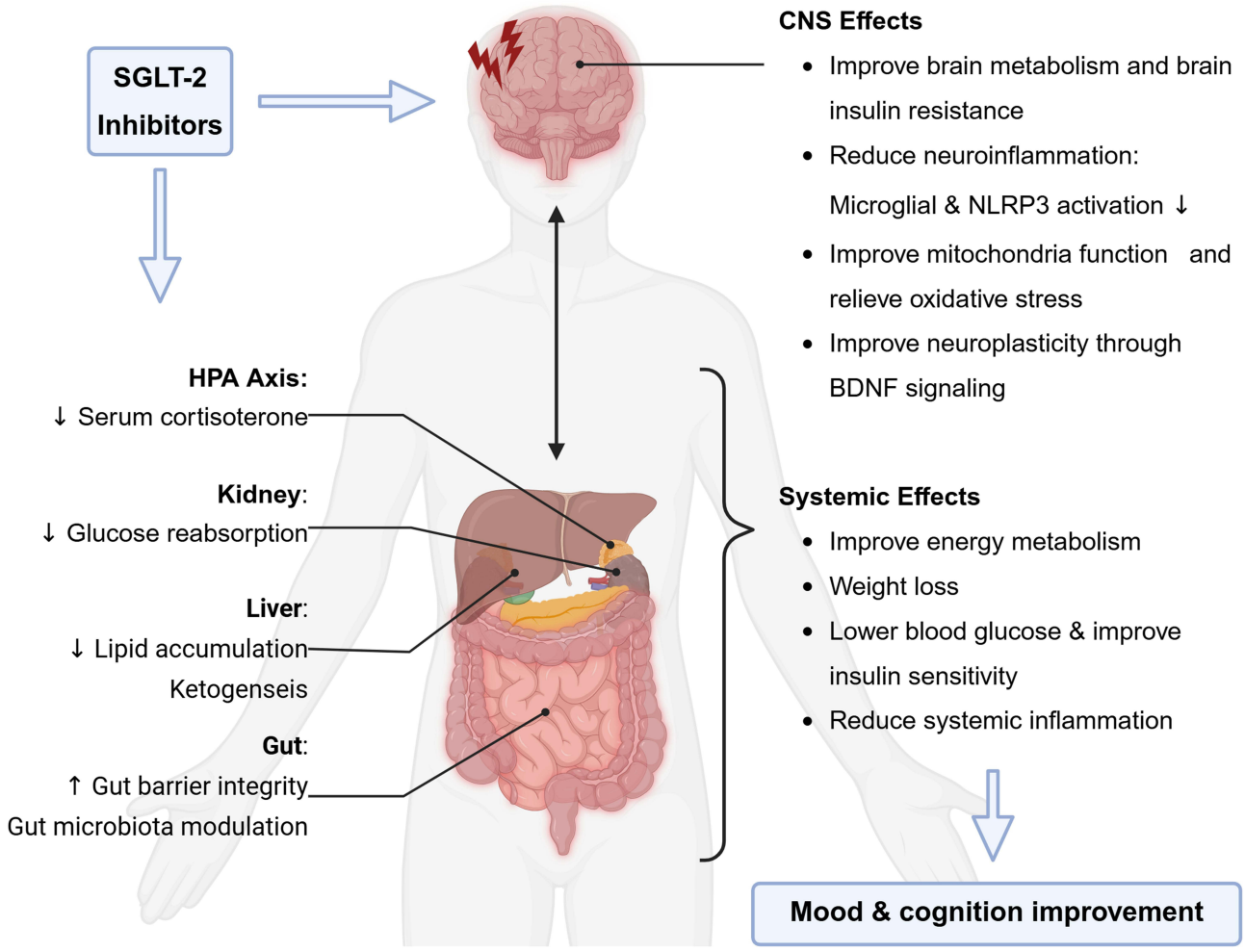

Figure 3 Proposed mechanisms of SGLT-2 inhibitors in mood disorders. SGLT-2 inhibitors exert benefits to psychological disorders through multifaceted mechanisms, both directly in the brain, and indirectly peripherally. Collectively, SGLT-2 inhibitors contribute to mood and cognitive improvements. Upward arrows indicate relative increases or enhancement, whereas downward arrows indicate relative decreases or inhibition in the indicated molecules, pathways, or biological effects.
Abbreviations: SGLT-2, Sodium-glucose cotransporter-2; HPA axis, Hypothalamic–pituitary–adrenal axis; NLRP3, NOD-like receptor thermal protein domain associated protein 3; BDNF, Brain-derived neurotrophic factor.

proposed or potentially relevant mechanisms rather than established therapeutic mechanisms in mood disorders. Further translational studies are needed to clarify which of these effects are reproducible in human populations and whether they are sufficient to translate into meaningful psychiatric benefit.

Potential and Challenges of SGLT-2i in Mood Disorders

Initially developed for T2DM, SGLT-2 inhibitors are gaining more recognition for their pleiotropic effects that may benefit mood regulation. Preliminary data from animal and population studies suggest a multifaceted framework of its biological mechanism, though translation to clinical use in mood disorders is still constrained by insufficient evidence and several practical challenges.

Safety Considerations of SGLT-2i in Mood Disorder Treatment

The application of SGLT-2i in patients with mood disorders calls for the consideration of potential side effects and complex interactions with existing psychotropic medications. Known adverse effects include common genitourinary infections, volume depletion-related events including orthostatic hypotension and hypovolemia, acute kidney injury, bone fractures, euglycemic or hyperglycemic diabetic ketoacidosis, elevated low-density lipoprotein and cholesterol, lower-

https://doi.org/10.2147/NDT.S599108

limb amputation, and even malignancy.[20,159,160] Several clinical cases have also presented the potential negative outcomes when SGLT-2i are combined with commonly used antipsychotics or mood stabilizers.

For instance, empagliflozin could be associated with valproate toxicity when used in combination, likely due to changes in drug distribution related to weight loss.[161] Co-administration of lithium and empagliflozin may result in serum lithium concentrations, possibly through increased renal excretion by inhibiting proximal tubular reabsorption of lithium-glucose co-transport.[162] These cases highlight the need for careful consideration of potential direct or indirect interactions between SGLT-2i and psychotropic medications when applied to mood disorders. Dose adjustments and close monitoring of serum drug concentration are required to ensure safety and efficacy in such combined treatment regimens.

Direction of Future Research

Despite the growing interest in SGLT-2i as potential therapeutic agents for mood disorders, current evidence remains preliminary and fragmented, warranting further validation across multiple research levels.

At the basic research level, although studies have indicated low-level expression of SGLT-2 in the central nervous system,[24–26] its functional activity and regulatory pathways in the brain remain poorly characterized. Meanwhile, current investigations on SGLT-2i in mood disorders primarily employ CUS-induced depression-like models, with scarce research involving manic or phase-switching models.

Clinically, existing evidence mainly derives from secondary analyses or retrospective observational studies in T2DM patients, limiting causal inference. The absence of controlled trials in normoglycemic populations makes it difficult to distinguish mood improvements resulting from direct effects of SGLT-2i and those driven by glycemic normalization. Importantly, while some findings support a reduced risk of depression or cognitive impairment onset, evidence for the reversal of established symptoms remains insufficient. To date, only a small number of clinical trials have investigated the long-term effects of SGLT-2i use, so questions remain regarding the durability of therapeutic efficacy,[163] particularly in psychiatric populations where long-term safety and interactions with psychotropic medications are important. Given the marked clinical heterogeneity observed in patients with mood disorders, individual responses to SGLT-2i are likely to vary. Stratified studies are essential to delineate patient subgroups most likely to benefit from this type of medication.

More trials are needed to validate this hypothesis, with two already underway (NCT05757791, NCT05792540). In summary, while current findings are limited in scope and quality, SGLT-2 inhibitors represent a promising class of metabolic modulators with potential pleiotropic neuropsychiatric benefits. Future mechanistic studies integrating neuroimaging, multi-omics, and immune-metabolic profiling are needed to bridge translational gaps and identifying predictive biomarkers for precise therapy. Future clinical research should prioritize well-characterized patient subgroups, especially individuals with mood disorders and coexisting metabolic dysfunction, to identify the patient populations and biological pathways most relevant to future clinical application. In addition to broad diagnostic categories, studies should also consider stratification by illness stage, symptom profile, cognitive impairment, and exposure to metabolically adverse psychotropic medications, as these factors may influence both treatment response and tolerability. Moreover, well-designed RCTs are needed to clarify whether SGLT-2i improves core mood symptoms, cognition, and functioning, and whether such effects are independent of improvements in metabolic status. At the same time, longer-term studies should evaluate safety and feasibility in psychiatric populations, including side effects and potential interactions with commonly used psychotropic agents.

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Disclosure

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References

1. Malhi GS, Mann JJ. Depression. *Lancet*. 2018;392(10161):2299–2312. doi:10.1016/S0140-6736(18)31948-2
2. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841–1856. doi:10.1016/S0140-6736(20)31544-0
3. Collaborators GMD. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. 2022;9(2):137–150.
4. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry*. 2015;14 (3):339–347. doi:10.1002/wps.20252
5. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention. *Circulation*. 2009;120(16):1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644
6. Alberti KG, Zimmet P, Shaw J, Group IDFETFC. The metabolic syndrome--a new worldwide definition. *Lancet*. 2005;366(9491):1059–1062. doi:10.1016/S0140-6736(05)67402-8
7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735–2752. doi:10.1161/CIRCULATIONAHA.105.169404
8. Neeland IJ, Lim S, Tchernof A, et al. Metabolic syndrome. *Nat Rev Dis Primers*. 2024;10(1):77. doi:10.1038/s41572-024-00563-5
9. Yoshimura R, Watanabe C. Comorbidity of Major Depression and Type 2 Diabetes Mellitus: epidemiology, Pathophysiology, and Treatment Approaches. *J UOEH*. 2025;47(2):95–103. doi:10.7888/juoeh.47.95
10. Mulvahill JS, Nicol GE, Dixon D, et al. Effect of Metabolic Syndrome on Late-Life Depression: associations with Disease Severity and Treatment Resistance. *J Am Geriatr Soc*. 2017;65(12):2651–2658. doi:10.1111/jgs.15129
11. Gimenez-Palomo A, Gomes-da-Costa S, Dodd S, et al. Does metabolic syndrome or its component factors alter the course of bipolar disorder? A systematic review. *Neurosci Biobehav Rev*. 2022;132:142–153. doi:10.1016/j.neubiorev.2021.11.026
12. Maksyutynska K, Stogios N, Prasad F, et al. Neurocognitive correlates of metabolic dysregulation in individuals with mood disorders: a systematic review and meta-analysis. *Psychol Med*. 2024;54(7):1245–1271. doi:10.1017/S0033291724000345
13. Palacio NP, Valencia JG, Upegüi CDV, Jaramillo CL. Pathophysiological relationships between cognitive deficit in bipolar affective disorder and metabolic syndrome. *Revista Colombiana Psiquiatría*. 2024;53(3):376–384. doi:10.1016/j.rcpeng.2024.10.002
14. Jones BDM, Farooqui S, Kloiber S, Husain MO, Mulsant BH, Husain MI. Targeting Metabolic Dysfunction for the Treatment of Mood Disorders: review of the Evidence. *Life*. 2021;11(8):819. doi:10.3390/life11080819
15. Sepanjnia K, Modabbernia A, Ashrafi M, Modabbernia MJ, Akhondzadeh S. Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. *Neuropsychopharmacology*. 2012;37(9):2093–2100. doi:10.1038/npp.2012.58
16. Gougol A, Zareh-Mohammadi N, Raheb S, et al. Simvastatin as an adjuvant therapy to fluoxetine in patients with moderate to severe major depression: a double-blind placebo-controlled trial. *J Psychopharmacol*. 2015;29(5):575–581. doi:10.1177/0269881115578160
17. Chao EC, Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. *Nat Rev Drug Discov*. 2010;9(7):551–559. doi:10.1038/nrd3180
18. Wium-Andersen IK, Osler M, Jorgensen MB, Rungby J, Wium-Andersen MK. Diabetes, antidiabetic medications and risk of depression - A population-based cohort and nested case-control study. *Psychoneuroendocrinology*. 2022;140:105715. doi:10.1016/j.psyneuen.2022.105715
19. Mui JV, Li L, Chou OHI, et al. Comparing sodium-glucose cotransporter 2 inhibitors and dipeptidyl peptidase-4 inhibitors on new-onset depression: a propensity score-matched study in Hong Kong. *Acta Diabetol*. 2023;60(7):917–927. doi:10.1007/s00592-023-02063-6
20. Chen IC, Pai YW, Lin JF, et al. Association of antidiabetic medications with depression risk and All-Cause mortality in type 2 Diabetes: a TriNetX-Based cohort study. *Diabet Res Clin Pract*. 2025;223:112167. doi:10.1016/j.diabres.2025.112167
21. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373 (22):2117–2128. doi:10.1056/NEJMoa1504720
22. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377 (7):644–657. doi:10.1056/NEJMoa1611925
23. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380 (24):2295–2306. doi:10.1056/NEJMoa1811744
24. Wicinski M, Wodkiewicz E, Gorski K, Walczak M, Malinowski B. Perspective of SGLT2 Inhibition in Treatment of Conditions Connected to Neuronal Loss: focus on Alzheimer's Disease and Ischemia-Related Brain Injury. *Pharmaceuticals*. 2020;13(11):379. doi:10.3390/ph13110379
25. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev*. 2011;91(2):733–794. doi:10.1152/physrev.00055.2009
26. Perry RJ, Shulman GI. Sodium-glucose cotransporter-2 inhibitors: understanding the mechanisms for therapeutic promise and persisting risks. *J Biol Chem*. 2020;295(42):14379–14390. doi:10.1074/jbc.REV120.008387
27. Koepsell H. Glucose transporters in brain in health and disease. *Pflugers Arch*. 2020;472(9):1299–1343. doi:10.1007/s00424-020-02441-x
28. Yu AS, Hirayama BA, Timbol G, et al. Regional distribution of SGLT activity in rat brain in vivo. *Am J Physiol Cell Physiol*. 2013;304(3): C240–7. doi:10.1152/ajpcell.00317.2012
29. Rizzo MR, Di Meo I, Polito R, et al. Cognitive impairment and type 2 diabetes mellitus: focus of SGLT2 inhibitors treatment. *Pharmacol Res*. 2022;176:106062. doi:10.1016/j.phrs.2022.106062
30. Enerson BE, Drewes LR. The rat blood—brain barrier transcriptome. *J Cereb Blood Flow Metab*. 2006;26(7):959–973. doi:10.1038/sj.jcbfm.9600249
31. Chiba Y, Sugiyama Y, Nishi N, Nonaka W, Murakami R, Ueno M. Sodium/glucose cotransporter 2 is expressed in choroid plexus epithelial cells and ependymal cells in human and mouse brains. *Neuropathology*. 2020;40(5):482–491. doi:10.1111/neup.12665

32. Nguyen T, Wen S, Gong M, et al. Dapagliflozin Activates Neurons in the Central Nervous System and Regulates Cardiovascular Activity by Inhibiting SGLT-2 in Mice. *Diabetes Metab Syndr Obes*. 2020;13:2781–2799. doi:10.2147/DMSO.S258593
33. Pawlos A, Broncel M, Wozniak E, Gorzelak-Pabis P. Neuroprotective Effect of SGLT2 Inhibitors. *Molecules*. 2021;26(23):7213. doi:10.3390/molecules26237213
34. Cinti F, Moffa S, Impronta F, et al. Spotlight on ertugliflozin and its potential in the treatment of type 2 diabetes: evidence to date. *Drug Des Devel Ther*. 2017;11:2905–2919. doi:10.2147/DDDT.S114932
35. Tahara A, Takasu T, Yokono M, Imamura M, Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. *J Pharmacol Sci*. 2016;130(3):159–169. doi:10.1016/j.jphs.2016.02.003
36. Dong D, Liu X, Ma L, et al. Dapagliflozin inhibits the activity of lateral habenula to alleviate diabetes mellitus-induced depressive-like behavior. *Exp Neurol*. 2023;366:114448. doi:10.1016/j.expneurol.2023.114448
37. Borikar SP, Chitode GV, Tapre DN, Lokwani DK, Jain SP. Empagliflozin ameliorates olfactory bulbectomy-induced depression by mitigating oxidative stress and possible involvement of brain derived neurotrophic factor in diabetic rats. *Int J Neurosci*. 2025;135(12):1502–1518. doi:10.1080/00207454.2024.2414270
38. Muhammad RN, Ahmed LA, Abdul Salam RM, Ahmed KA, Attia AS. Crosstalk among NLRP3 inflammasome, ETBR signaling, and miRNAs in stress-induced depression-like behavior: a modulatory role for SGLT2 inhibitors. *Neurotherapeutics*. 2021;18(4):2664–2681. doi:10.1007/s13311-021-01140-4
39. Ali MA, Michel HE, Menze ET, Tadros MG, Wahdan SA. The potential neuroprotective effect of empagliflozin against depressive-like behavior induced by chronic unpredictable mild stress in rats: involvement of NLRP3 inflammasome. *Eur J Pharmacol*. 2025;998:177525. doi:10.1016/j.ejphar.2025.177525
40. Khedr LH, Eladawy RM, Nassar NN, Saad MAE. Canagliflozin attenuates chronic unpredictable mild stress induced neuroinflammation via modulating AMPK/mTOR autophagic signaling. *Neuropharmacology*. 2023;223:109293. doi:10.1016/j.neuropharm.2022.109293
41. Amawi H, Makhlouf T, Hammad AM, et al. Sodium-glucose cotransporter-2 inhibitor, dapagliflozin, reverses depressive-like behavior in a mouse model of post-traumatic stress disorder. *Brain Res Bull*. 2025;228:111414. doi:10.1016/j.brainresbull.2025.111414
42. Fathy N, Labib MA, Essam RM, El-Boghdady NA. The Interplay between MiR-134/BDNF and LKB1/AMPK/SIRT1 Accentuates the Antidepressant Efficacy of Empagliflozin in Ovariectomized Rats. *ACS Chem Neurosci*. 2024;15(20):3692–3703.
43. Muhammad RN, Albahairy MA, Abd El Fattah MA, Ibrahim WW. Empagliflozin-activated AMPK elicits neuroprotective properties in reserpine-induced depression via regulating dynamics of hippocampal autophagy/inflammation and PKCzeta-mediated neurogenesis. *Psychopharmacology (Berl)*. 2024;241(12):2565–2584. doi:10.1007/s00213-024-06663-0
44. Saleh NK, Farrag SM, El-Yamany MF, Kamel AS. Exploring Dapagliflozin's Influence on Autophagic Flux in Mania-like Behaviour: insights from the LKB1/AMPK/LC3 Pathway in a Mouse Model. *J Neuroimmune Pharmacol*. 2025;20(1):57. doi:10.1007/s11481-025-10218-1
45. Lin B, Koibuchi N, Hasegawa Y, et al. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc Diabetol*. 2014;13(1):148. doi:10.1186/s12933-014-0148-1
46. Piatkowska-Chmiel I, Herbet M, Gawronska-Grzywacz M, Pawlowski K, Ostrowska-Lesko M, Dudka J. Molecular and neural roles of sodium-glucose cotransporter 2 inhibitors in alleviating neurocognitive impairment in diabetic mice. *Psychopharmacology (Berl)*. 2023;240(4):983–1000. doi:10.1007/s00213-023-06341-7
47. Yaribeygi H, Hemmati MA, Nasimi F, Pakdel R, Jamialahmadi T, Sahebkar A. Empagliflozin alleviates diabetes-induced cognitive impairments by lowering nicotinamide adenine dinucleotide phosphate oxidase-4 expression and potentiating the antioxidant defense system in brain tissue of diabetic rats. *Behav Brain Res*. 2024;460:114830. doi:10.1016/j.bbr.2023.114830
48. Hu WS, Lin CL. Psychiatric disorders in patients with type 2 diabetes mellitus on sodium-glucose cotransporter-2 inhibitors-a nationwide retrospective cohort study. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;397(1):575–581. doi:10.1007/s00210-023-02623-1
49. Akimoto H, Tezuka K, Nishida Y, Nakayama T, Takahashi Y, Asai S. Association between use of oral hypoglycemic agents in Japanese patients with type 2 diabetes mellitus and risk of depression: a retrospective cohort study. *Pharmacol Res Perspect*. 2019;7(6):e00536. doi:10.1002/prp2.536
50. Majid H, Islam SU, Kohli S. Neuroinflammation and metabolic dysregulation as predictors of cognitive impairment, depression, and quality of life in type 2 diabetes mellitus patients on SGLT2 inhibitors and sulfonylureas. *Inflammopharmacology*. 2025;2025:1–10.
51. Li Z, Lin C, Cai X, Lv F, Yang W, Ji L. Anti-diabetic agents and the risks of dementia in patients with type 2 diabetes: a systematic review and network meta-analysis of observational studies and randomized controlled trials. *Alzheimers Res Ther*. 2024;16(1):272. doi:10.1186/s13195-024-01645-y
52. Zandifar A, Panahi M, Badrfam R, Qorbani M. Efficacy of empagliflozin as adjunctive therapy to citalopram in major depressive disorder: a randomized double-blind, placebo-controlled clinical trial. *BMC Psychiatry*. 2024;24(1):163. doi:10.1186/s12888-024-05627-0
53. Chang E-W, Huang J-Y, Lo S-C, Huang C-N, Yang Y-S, Kornelius E. Association between SGLT-2 inhibitors and suicide risk in type 2 diabetes and bipolar: a real-world cohort study. *Front Pharmacol*. 2025;16:1601118. doi:10.3389/fphar.2025.1601118
54. Ganz M, Schrier R, Yomtov N, et al. Investigating the Influence of Antidiabetic Medications and Psychosocial Factors. *Cureus*. 2024;16(5):e60270. doi:10.7759/cureus.60270
55. Penninx B, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. *Dialogues Clin Neurosci*. 2018;20(1):63–73. doi:10.31887/DCNS.2018.20.1/bpenninx
56. Speed MS, Jefsen OH, Børglum AD, Speed D, Østergaard SD. Investigating the association between body fat and depression via Mendelian randomization. *Transl Psychiatry*. 2019;9(1):184. doi:10.1038/s41398-019-0516-4
57. Maina JG, Balkhiyarova Z, Nouwen A, et al. Bidirectional Mendelian randomization and multiphenotype GWAS show causality and shared pathophysiology between depression and type 2 diabetes. *Diabetes Care*. 2023;46(9):1707–1714. doi:10.2337/dc22-2373
58. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry*. 2017;7(1):e1007–e1007. doi:10.1038/tp.2016.261
59. M DEH, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52–77. doi:10.1002/j.2051-5545.2011.tb00014.x
60. Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. *Lancet Psychiatry*. 2015;2(5):452–464. doi:10.1016/S2215-0366(15)00115-7

61. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;74:277–286. doi:10.1016/j.neubiorev.2016.07.003
62. Campbell IH, Frye MA, Campbell H. Metabolic plasticity: an evolutionary perspective on metabolic and circadian dysregulation in bipolar disorder. *Mol Psychiatry*. 2025;30(11):5600–5612. doi:10.1038/s41380-025-03123-9
63. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*. 2015;14(2):119–136. doi:10.1002/wps.20204
64. Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry*. 2016;15(2):166–174. doi:10.1002/wps.20309
65. Mazereel V, Detraux J, Vancampfort D, van Winkel R, De Hert M. Impact of Psychotropic Medication Effects on Obesity and the Metabolic Syndrome in People With Serious Mental Illness. *Front Endocrinol*. 2020;11:573479. doi:10.3389/fendo.2020.573479
66. McIntyre RS, McElroy SL, Eudicone JM, Forbes RA, Carlson BX, Baker RA. A 52-week, double-blind evaluation of the metabolic effects of aripiprazole and lithium in bipolar I disorder. *Prim Care Companion CNS Disord*. 2011;13(6):11m01182. doi:10.4088/PCC.11m01182
67. Marazziti D, Rutigliano G, Baroni S, Landi P, Dell'Osso L. Metabolic syndrome and major depression. *CNS Spectr*. 2014;19(4):293–304. doi:10.1017/S1092852913000667
68. Silarova B, Giltay EJ, Van Reedt Dortland A, et al. Metabolic syndrome in patients with bipolar disorder: comparison with major depressive disorder and non-psychiatric controls. *J Psychosom Res*. 2015;78(4):391–398. doi:10.1016/j.jpsychores.2015.02.010
69. Delpech JC, Madore C, Nadjar A, Joffre C, Wohleb ES, Laye S. Microglia in neuronal plasticity: influence of stress. *Neuropharmacology*. 2015;96(Pt A):19–28. doi:10.1016/j.neuropharm.2014.12.034
70. Ullah R, Rauf N, Nabi G, Yi S, Yu-Dong Z, Fu J. Mechanistic insight into high-fat diet-induced metabolic inflammation in the arcuate nucleus of the hypothalamus. *Biomed Pharmacother*. 2021;142:112012. doi:10.1016/j.biopha.2021.112012
71. Yang C, Sui G, Li D, et al. Exogenous IGF-1 alleviates depression-like behavior and hippocampal mitochondrial dysfunction in high-fat diet mice. *Physiol Behav*. 2021;229:113236. doi:10.1016/j.physbeh.2020.113236
72. Sa-Nguanmoo P, Tanajak P, Kerdphoo S, et al. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. *Toxicol Appl Pharmacol*. 2017;333:43–50. doi:10.1016/j.taap.2017.08.005
73. Chan KL, Cathomas F, Russo SJ. Central and Peripheral Inflammation Link Metabolic Syndrome and Major Depressive Disorder. *Physiology*. 2019;34(2):123–133. doi:10.1152/physiol.00047.2018
74. Mikulska J, Juszczyk G, Gawronska-Grzywacz M, Herbet M. HPA Axis in the Pathomechanism of Depression and Schizophrenia: new Therapeutic Strategies Based on Its Participation. *Brain Sci*. 2021;11(10):1298. doi:10.3390/brainsci11101298
75. Johnston MV. Plasticity in the developing brain: implications for rehabilitation. *Dev Disabil Res Rev*. 2009;15(2):94–101. doi:10.1002/ddrr.64
76. Castren E, Monteggia LM. Brain-Derived Neurotrophic Factor Signaling in Depression and Antidepressant Action. *Biol Psychiatry*. 2021;90(2):128–136. doi:10.1016/j.biopsych.2021.05.008
77. Hwang LL, Wang CH, Li TL, et al. Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. *Obesity*. 2010;18(3):463–469. doi:10.1038/oby.2009.273
78. Li Y, Cheng Y, Zhou Y, et al. High fat diet-induced obesity leads to depressive and anxiety-like behaviors in mice via AMPK/mTOR-mediated autophagy. *Exp Neurol*. 2022;348:113949. doi:10.1016/j.expneurol.2021.113949
79. Goralczyk-Binkowska A, Szmajda-Krygier D, Kozlowska E. The Microbiota-Gut-Brain Axis in Psychiatric Disorders. *Int J Mol Sci*. 2022;23(19):11245. doi:10.3390/ijms231911245
80. Asadi A, Shadab Mehr N, Mohamadi MH, et al. Obesity and gut-microbiota-brain axis: a narrative review. *J Clin Lab Anal*. 2022;36(5):e24420. doi:10.1002/jcla.24420
81. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. *Annu Rev Physiol*. 2021;83(1):503–528. doi:10.1146/annurev-physiol-031620-095920
82. Ekanayake P, Hupfeld C, Mudaliar S. Sodium-Glucose Cotransporter Type 2 (SGLT-2) Inhibitors and Ketogenesis: the Good and the Bad. *Curr Diab Rep*. 2020;20(12):74. doi:10.1007/s11892-020-01359-z
83. Osataphan S, Macchi C, Singhal G, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -independent mechanisms. *JCI Insight*. 2019;4(5):e123130. doi:10.1172/jci.insight.123130
84. Cahill Jr GF, Veech RL. Ketoacids? Good medicine? *Trans Am Clin Climatol Assoc*. 2003;114:149–161.
85. Brietzke E, Mansur RB, Subramaniapillai M, et al. Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. *Neurosci Biobehav Rev*. 2018;94:11–16. doi:10.1016/j.neubiorev.2018.07.020
86. Achanta LB, Rae CD. beta-Hydroxybutyrate in the Brain: one Molecule, Multiple Mechanisms. *Neurochem Res*. 2017;42(1):35–49. doi:10.1007/s11064-016-2099-2
87. Kim SR, Lee SG, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nat Commun*. 2020;11(1):2127. doi:10.1038/s41467-020-15983-6
88. Liebers DT, Ebina W, Iosifescu DV. Sodium-Glucose Cotransporter-2 Inhibitors in Depression. *Harv Rev Psychiatry*. 2023;31(4):214–221. doi:10.1097/HRP.0000000000000374
89. Troise D, Mercuri S, Infante B, et al. mTOR and SGLT-2 inhibitors: their synergistic effect on age-related processes. *Int J Mol Sci*. 2024;25(16):8676. doi:10.3390/ijms25168676
90. Russell RC, Yuan HX, Guan KL. Autophagy regulation by nutrient signaling. *Cell Res*. 2014;24(1):42–57. doi:10.1038/cr.2013.166
91. Esterline RL, Vaag A, Oscarsson J. Endocrinology Mechanisms in SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? *Eur J Endocrinol*. 2018;178(4):R113–R125. doi:10.1530/EJE-17-0832
92. Bockaert J, Marin P. mTOR in Brain Physiology and Pathologies. *Physiol Rev*. 2015;95(4):1157–1187. doi:10.1152/physrev.00038.2014
93. Maciejczyk M, Zebrowska E, Chabowski A. Insulin Resistance and Oxidative Stress in the Brain: what's New? *Int J Mol Sci*. 2019;20(4):874. doi:10.3390/ijms20040874
94. Cuperfain AB, Kennedy JL, Goncalves VF. Overlapping mechanisms linking insulin resistance with cognition and neuroprogression in bipolar disorder. *Neurosci Biobehav Rev*. 2020;111:125–134. doi:10.1016/j.neubiorev.2020.01.022

95. Burillo J, Marques P, Jimenez B, Gonzalez-Blanco C, Benito M, Guillen C. Insulin Resistance and Diabetes Mellitus in Alzheimer's Disease. *Cells*. 2021;10(5):1236. doi:10.3390/cells10051236
96. Yao J, Zhu CQ, Sun Y, et al. Insulin resistance: the role in comorbid type 2 diabetes mellitus and depression. *Neurosci Biobehav Rev*. 2025;175:106218. doi:10.1016/j.neubiorev.2025.106218
97. Zlotek M, Kurowska A, Herbet M, Piatkowska-Chmiel I. GLP-1 Analogs, SGLT-2, and DPP-4 Inhibitors: a Triad of Hope for Alzheimer's Disease Therapy. *Biomedicines*. 2023;11(11):3035. doi:10.3390/biomedicines11113035
98. Xu L, Nagata N, Nagashimada M, et al. SGLT2 Inhibition by Empagliflozin Promotes Fat Utilization and Browning and Attenuates Inflammation and Insulin Resistance by Polarizing M2 Macrophages in Diet-induced Obese Mice. *EBioMedicine*. 2017;20:137–149. doi:10.1016/j.ebiom.2017.05.028
99. Sim AY, Choi DH, Kim JY, et al. SGLT2 and DPP4 inhibitors improve Alzheimer's disease–like pathology and cognitive function through distinct mechanisms in a T2D–AD mouse model. *Biomed Pharmacother*. 2023;168:115755. doi:10.1016/j.biopha.2023.115755
100. Chen X, Fan M, Xiao Z, Xiong X. Dapagliflozin Improves High-Fat Diet-Induced Cognitive Impairment in Female Mice. *Brain Behav*. 2025;15 (2):e70361. doi:10.1002/brb3.70361
101. Kullmann S, Hummel J, Wagner R, et al. Empagliflozin Improves Insulin Sensitivity of the Hypothalamus in Humans With Prediabetes: a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial. *Diabetes Care*. 2022;45(2):398–406. doi:10.2337/dc21-1136
102. Chen X, Xiao Z, Liu Q, Luo D, Cai Y, Fan M. Dapagliflozin Ameliorates Ovulation Disorders via Attenuating Activated Microglia-Mediated Hypothalamic Inflammation in HFD-Fed Mice. *Neuroendocrinology*. 2024;114(4):331–347. doi:10.1159/000535420
103. Menard C, Pfau ML, Hodes GE, et al. Social stress induces neurovascular pathology promoting depression. *Nat Neurosci*. 2017;20 (12):1752–1760. doi:10.1038/s41593-017-0010-3
104. Benedetti F, Aggio V, Pratesi ML, Greco G, Furlan R. Neuroinflammation in Bipolar Depression. *Front Psychiatry*. 2020;11:71. doi:10.3389/ fpsyt.2020.00071
105. Maes M, Almulla AF, You Z, Zhang Y. Neuroimmune, metabolic and oxidative stress pathways in major depressive disorder. *Nat Rev Neurol*. 2025;21(9):473–489. doi:10.1038/s41582-025-01116-4
106. Almeida PGC, Nani JV, Oses JP, Brietzke E, Hayashi MAF. Neuroinflammation and glial cell activation in mental disorders. *Brain Behav Immun Health*. 2020;2:100034. doi:10.1016/j.bbih.2019.100034
107. Rykova EY, Klimontov VV, Shmakova E, Korbut AI, Merkulova TI, Kzhyshkowska J. Anti-Inflammatory Effects of SGLT2 Inhibitors: focus on Macrophages. *Int J Mol Sci*. 2025;26(4):1670. doi:10.3390/ijms26041670
108. Abdollahi E, Keyhanfar F, Delbandi AA, Falak R, Hajimiresmaiel SJ, Shafiei M. Dapagliflozin exerts anti-inflammatory effects via inhibition of LPS-induced TLR-4 overexpression and NF-kappaB activation in human endothelial cells and differentiated macrophages. *Eur J Pharmacol*. 2022;918:174715. doi:10.1016/j.ejphar.2021.174715
109. Byrne NJ, Matsumura N, Maayah ZH, et al. Empagliflozin Blunts Worsening Cardiac Dysfunction Associated With Reduced NLRP3 (Nucleotide-Binding Domain-Like Receptor Protein 3) Inflammasome Activation in Heart Failure. *Circ Heart Fail*. 2020;13(1):e006277. doi:10.1161/CIRCHEARTFAILURE.119.006277
110. Yoo TT, Baek IH, Stoletniy L, Hilliard A, Sakr A, Doycheva D. Impact of sodium-glucose transport protein-2 (SGLT2) inhibitors on the inflammasome pathway in acute myocardial infarction in type 2 diabetes mellitus: a comprehensive review. *Cardiovasc Diabetol*. 2025;24 (1):227. doi:10.1186/s12933-025-02777-7
111. Wang D, Liu J, Zhong L, et al. The effect of sodium-glucose cotransporter 2 inhibitors on biomarkers of inflammation: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2022;13:1045235. doi:10.3389/fphar.2022.1045235
112. Gohari S, Ismail-Beigi F, Mahjani M, et al. The effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on blood interleukin-6 concentration: a systematic review and meta-analysis of randomized controlled trials. *BMC Endocr Disord*. 2023;23(1):257. doi:10.1186/ s12902-023-01512-1
113. Buttice L, Ghani M, Suthakar J, et al. The effect of sodium-glucose cotransporter-2 inhibitors on inflammatory biomarkers: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2024;26(7):2706–2721. doi:10.1111/dom.15586
114. Theofilis P, Sagris M, Oikonomou E, et al. The impact of SGLT2 inhibitors on inflammation: a systematic review and meta-analysis of studies in rodents. *Int Immunopharmacol*. 2022;111:109080. doi:10.1016/j.intimp.2022.109080
115. Heimke M, Lenz F, Rickert U, Lucius R, Cossais F. Anti-Inflammatory Properties of the SGLT2 Inhibitor Empagliflozin in Activated Primary Microglia. *Cells*. 2022;11(19):3107. doi:10.3390/cells11193107
116. Sim AY, Kim JY, Lee YH, Lee JE. Neuroprotective roles of SGLT2 and DPP4 inhibitors: modulating ketone metabolism and suppressing NLRP3 inflammasome in T2D induced Alzheimer's disease. *Exp Neurol*. 2025;390:115271. doi:10.1016/j.expneurol.2025.115271
117. Kounatidis D, Vallianou N, Evangelopoulos A, et al. SGLT-2 Inhibitors and the Inflammasome: what's Next in the 21st Century? *Nutrients*. 2023;15(10):2294. doi:10.3390/nu15102294
118. Elariny HA, Kabel AM, Selim H, et al. Repositioning Canagliflozin for Mitigation of Aluminium Chloride-Induced Alzheimer's Disease: involvement of TXNIP/NLRP3 Inflammasome Axis, Mitochondrial Dysfunction, and SIRT1/HMGB1 Signalling. *Medicina*. 2024;60(11):1805. doi:10.3390/medicina60111805
119. Abdelaziz AM, Rasheed NOA, Zaki HF, Salem HA, El-Sayed RM. Canagliflozin attenuates neurodegeneration and ameliorates dyskinesia through targeting the NLRP3/Nurr1/GSK-3β/SIRT3 pathway and autophagy modulation in rotenone-lesioned rats. *Int Immunopharmacol*. 2025;146:113839. doi:10.1016/j.intimp.2024.113839
120. Khedr LH, Rahmo RM, Eldemerdash OM, et al. Implication of M2 macrophage on NLRP3 inflammasome signaling in mediating the neuroprotective effect of Canagliflozin against methotrexate-induced cognitive impairment. *Int Immunopharmacol*. 2024;130:111709. doi:10.1016/j.intimp.2024.111709
121. Kuperberg M, Greenebaum SLA, Nierenberg AA. Targeting Mitochondrial Dysfunction for Bipolar Disorder. *Curr Top Behav Neurosci*. 2021;48:61–99. doi:10.1007/7854_2020_152
122. Jiang M, Wang L, Sheng H. Mitochondria in depression: the dysfunction of mitochondrial energy metabolism and quality control systems. *CNS Neurosci Ther*. 2024;30(2):e14576. doi:10.1111/cns.14576
123. Ji N, Lei M, Chen Y, Tian S, Li C, Zhang B. How oxidative stress induces depression? *ASN Neuro*. 2023;15(1):17590914231181037. doi:10.1177/17590914231181037

124. Carpita B, Betti L, Palego L, et al. Plasma redox and inflammatory patterns during major depressive episodes: a cross-sectional investigation in elderly patients with mood disorders. *CNS Spectr*. 2021;26(4):416–426. doi:10.1017/S1092852920001443
125. Akarsu S, Bolu A, Aydemir E, et al. The relationship between the number of manic episodes and oxidative stress indicators in bipolar disorder. *Psychiatry Invest*. 2018;15(5):514. doi:10.30773/pi.2016.12.31
126. Chiu CT, Wang Z, Hunsberger JG, Chuang DM. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. *Pharmacol Rev*. 2013;65(1):105–142. doi:10.1124/pr.111.005512
127. Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. *Redox Rep*. 2003;8(6):365–370. doi:10.1179/135100003225003393
128. Yaribeygi H, Atkin SL, Butler AE, Sahebkar A. Sodium-glucose cotransporter inhibitors and oxidative stress: an update. *J Cell Physiol*. 2019;234(4):3231–3237. doi:10.1002/jcp.26760
129. Amin EF, Rifaai RA, Abdel-Latif RG. Empagliflozin attenuates transient cerebral ischemia/reperfusion injury in hyperglycemic rats via repressing oxidative-inflammatory-apoptotic pathway. *Fundam Clin Pharmacol*. 2020;34(5):548–558. doi:10.1111/fcp.12548
130. Davri AS, Katsenos AP, Tulyaganova GK, et al. The SGLT2 inhibitor empagliflozin exerts neuroprotective effect against hydrogen peroxide-induced toxicity on primary neurons. *Metab Brain Dis*. 2024;40(1):15. doi:10.1007/s11011-024-01478-6
131. Ma J, Wang H, Jia J, et al. Empagliflozin Inhibits Neuronal Ferroptosis Induced by Oxygen-Glucose Deprivation/Reoxygenation by Activating the Nrf2/HO-1 Pathway. *Mol Neurobiol*. 2025;62(7):8768–8781. doi:10.1007/s12035-025-04800-0
132. Arab HH, Safar MM, Shahin NN. Targeting ROS-Dependent AKT/GSK-3beta/NF-kappaB and DJ-1/Nrf2 Pathways by Dapagliflozin Attenuates Neuronal Injury and Motor Dysfunction in Rotenone-Induced Parkinson's Disease Rat Model. *ACS Chem Neurosci*. 2021;12(4):689–703. doi:10.1021/acschemneuro.0c00722
133. Mohammed NN, Tadros MG, George MY. Empagliflozin repurposing in Parkinson's disease; modulation of oxidative stress, neuroinflammation, AMPK/SIRT-1/PGC-1α, and wnt/β-catenin pathways: NN Mohammed et al. *Inflammopharmacology*. 2024;32(1):777–794. doi:10.1007/s10787-023-01384-w
134. Gan H, Ma Q, Hao W, et al. Targeting autophagy to counteract neuroinflammation: a novel antidepressant strategy. *Pharmacol Res*. 2024;202:107112. doi:10.1016/j.phrs.2024.107112
135. Chen P, Liang L, Dai Y, Hui S. The role and mechanism of dapagliflozin in Alzheimer disease: a review. *Medicine*. 2024;103(39):e39687. doi:10.1097/MD.0000000000039687
136. Yang L, Guo C, Zheng Z, et al. Stress dynamically modulates neuronal autophagy to gate depression onset. *Nature*. 2025;2025:1–11.
137. Gassen NC, Rein T. Is there a role of autophagy in depression and antidepressant action? *Frontiers in Psychiatry*. 2019;10:337. doi:10.3389/fpsyt.2019.00337
138. Machado-Vieira R, Zanetti MV, Teixeira AL, et al. Decreased AKT1/mTOR pathway mRNA expression in short-term bipolar disorder. *Eur Neuropsychopharmacol*. 2015;25(4):468–473. doi:10.1016/j.euroneuro.2015.02.002
139. Jernigan CS, Goswami DB, Austin MC, et al. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. *Prog Neuro Psychopharmacol Biol Psychiatry*. 2011;35(7):1774–1779. doi:10.1016/j.pnpbp.2011.05.010
140. Abelaira HM, Réus GZ, Ignácio ZM, et al. Effects of ketamine administration on mTOR and reticulum stress signaling pathways in the brain after the infusion of rapamycin into prefrontal cortex. *J Psychiatr Res*. 2017;87:81–87. doi:10.1016/j.jpsychires.2016.12.002
141. Ibrahim WW, Kamel AS, Wahid A, Abdelkader NF. Dapagliflozin as an autophagic enhancer via LKB1/AMPK/SIRT1 pathway in ovariectomized/D-galactose Alzheimer's rat model. *Inflammopharmacology*. 2022;30(6):2505–2520. doi:10.1007/s10787-022-00973-5
142. Amer RM, Eltokhy AK, Elesawy RO, et al. The Ameliorative Effect of Empagliflozin in Vigabatrin-Induced Cerebellar/Neurobehavioral Deficits: targeting mTOR/AMPK/SIRT-1 Signaling Pathways. *Molecules*. 2022;27(12):3659. doi:10.3390/molecules27123659
143. Motawi TK, Al-Kady RH, Abdelraouf SM, Senousy MA. Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: targeting the GRP78/PERK/eIF2alpha/CHOP pathway and miR-211-5p. *Chem Biol Interact*. 2022;362:110002. doi:10.1016/j.cbi.2022.110002
144. Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci*. 2015;11(6):1164–1178. doi:10.5114/aoms.2015.56342
145. Chen S-D, Wu C-L, Hwang W-C, Yang D-I. More insight into BDNF against neurodegeneration: anti-apoptosis, anti-oxidation, and suppression of autophagy. *Int J Mol Sci*. 2017;18(3):545. doi:10.3390/ijms18030545
146. Yoshida T, Ishikawa M, Niitsu T, et al. Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. *PLoS One*. 2012;7(8):e42676. doi:10.1371/journal.pone.0042676
147. Zhao G, Zhang C, Chen J, et al. Ratio of mBDNF to proBDNF for Differential Diagnosis of Major Depressive Disorder and Bipolar Depression. *Mol Neurobiol*. 2017;54(7):5573–5582. doi:10.1007/s12035-016-0098-6
148. Kamel AS, Wahid A, Abdelkader NF, Ibrahim WW. Boosting amygdaloid GABAergic and neurotrophic machinery via dapagliflozin-enhanced LKB1/AMPK signaling in anxious demented rats. *Life Sci*. 2022;310:121002. doi:10.1016/j.lfs.2022.121002
149. Khamies SM, El-Yamany MF, Ibrahim SM. Canagliflozin Mitigated Cognitive Impairment in Streptozotocin-Induced Sporadic Alzheimer's Disease in Mice: role of AMPK/SIRT-1 Signaling Pathway in Modulating Neuroinflammation. *J Neuroimmune Pharmacol*. 2024;19(1):39. doi:10.1007/s11481-024-10140-y
150. Abdel-Lah ES, Sherkawy HS, Mohamed WH, et al. Empagliflozin and memantine combination ameliorates cognitive impairment in scopolamine + heavy metal mixture-induced Alzheimer's disease in rats: role of AMPK/mTOR, BDNF, BACE-1, neuroinflammation, and oxidative stress. *Inflammopharmacology*. 2025;33(6):3479–3498. doi:10.1007/s10787-025-01755-5
151. Mousa HH, Sharawy MH, Nader MA. Empagliflozin enhances neuroplasticity in rotenone-induced parkinsonism: role of BDNF, CREB and Npas4. *Life Sci*. 2023;312:121258. doi:10.1016/j.lfs.2022.121258
152. Abdelaziz HA, Hamed MF, Ghoniem HA, Nader MA, Suddek GM. Empagliflozin Mitigates PTZ-Induced Seizures in Rats: modulating Npas4 and CREB-BDNF Signaling Pathway. *J Neuroimmune Pharmacol*. 2025;20(1):5. doi:10.1007/s11481-024-10162-6
153. Shakil S. Molecular Interaction of Anti-Diabetic Drugs With Acetylcholinesterase and Sodium Glucose Co-Transporter 2. *J Cell Biochem*. 2017;118(11):3855–3865. doi:10.1002/jcb.26036
154. Arafa NMS, Ali EHA, Hassan MK. Canagliflozin prevents scopolamine-induced memory impairment in rats: comparison with galantamine hydrobromide action. *Chem Biol Interact*. 2017;277:195–203. doi:10.1016/j.cbi.2017.08.013

155. Yan C, Zhou Y, Chen Q, et al. Dysfunction of the neurovascular unit in diabetes-related neurodegeneration. *Biomed Pharmacother*. 2020;131:110656. doi:10.1016/j.biopha.2020.110656
156. Al Hamed FA, Elewa H. Potential Therapeutic Effects of Sodium Glucose-linked Cotransporter 2 Inhibitors in Stroke. *Clin Ther*. 2020;42(11): e242–e249. doi:10.1016/j.clinthera.2020.09.008
157. Hayden MR, Grant DG, Aroor AR, DeMarco VG. Empagliflozin Ameliorates Type 2 Diabetes-Induced Ultrastructural Remodeling of the Neurovascular Unit and Neuroglia in the Female db/db Mouse. *Brain Sci*. 2019;9(3):57. doi:10.3390/brainsci9030057
158. Tarnawska M, Walczak I, Paterek A, et al. Special focus on the mitochondria in endothelial cells: a novel therapeutic target for gliflozins? *Biomed Pharmacother*. 2025;188:118210. doi:10.1016/j.biopha.2025.118210
159. Ndefo UA, Anidiobi NO, Basheer E, Eaton AT. Empagliflozin (Jardiance): a Novel SGLT2 Inhibitor for the Treatment of Type-2 Diabetes. *P T*. 2015;40(6):364–368.
160. Pelletier R, Ng K, Alkabbani W, Labib Y, Mourad N, Gamble JM. Adverse events associated with sodium glucose co-transporter 2 inhibitors: an overview of quantitative systematic reviews. *Ther Adv Drug Saf*. 2021;12:2042098621989134. doi:10.1177/2042098621989134
161. Miyauchi T. Valproate intoxication in a patient with bipolar I disorder due to SGLT2 inhibitor-induced weight reduction. *DARU J Pharma Sci*. 2020;28(1):419–421. doi:10.1007/s40199-020-00333-0
162. Armstrong GP. Empagliflozin-Mediated Lithium Excretion: a Case Study and Clinical Applications. *Am J Case Rep*. 2020;21:e923311. doi:10.12659/AJCR.923311
163. Mei J, Li Y, Niu L, et al. SGLT2 inhibitors: a novel therapy for cognitive impairment via multifaceted effects on the nervous system. *Transl Neurodegener*. 2024;13(1):41. doi:10.1186/s40035-024-00431-y