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REVIEW ARTICLE

Bipolar disorder and type 2 diabetes mellitus: A bidirectional relationship

Dagmar Breznoscakova[a], **Maria Pallayova**[b,*]

[a] *Department of Social and Behavioral Medicine, Faculty of Medicine, Pavol Jozef Safarik University, Trieda SNP 1, Kosice 040 11, Slovak Republic*
[b] *Department of Human Physiology, Faculty of Medicine, Pavol Jozef Safarik University, Trieda SNP 1, Kosice 040 11, Slovak Republic*

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Abstract
Background and objectives: Over the past few decades, research has revealed complex interactions between type 2 diabetes mellitus (T2DM) and a wide range of comorbid conditions. The present paper sought to examine the relationship between bipolar disorder and T2DM and clarify the clinical impact of therapeutic interventions, highlighting the interpretation and implications of recent literature reports.
Methods: The PubMed electronic database was searched for keywords "bipolar disorder" AND "diabetes" OR "glucose". Based on this literature search, 15 meta-analyses/systematic reviews and numerous research studies were identified that examined interrelationships between bipolar disorders and T2DM.
Results: Patients with bipolar disorder have higher rates of T2DM compared to the general population. Further, type 2 diabetic patients with comorbid bipolar disorder often experience deteriorated long-term glucose control and increased cardiovascular morbidity and mortality. Recent literature suggests shared risk factors and underlying disease mechanisms. In addition, genetic factors, sedentary life-style, lack of exercise, increased simple carbohydrate intake, adverse effects of bipolar pharmacotherapy, and bipolar depressive symptoms phenomenology may affect glucose metabolism.
Conclusions: The observed bidirectional interaction merits screening for psychiatric disorders in T2DM and vice versa to allow for early detection and treatment of this at risk population. Selection of drugs with neutral metabolic effects and dose individualization hold significant promise for optimizing therapy with antipsychotic and antidiabetic agents.

Introduction

The prevalence of diabetes mellitus has more than doubled over the past two decades, approaching epidemic proportions globally. According to statistics, 464.1 million people (9.3 % of adults) are estimated to have diabetes worldwide.[1]

* Corresponding author.
E-mail addresses: dagmar.breznoscakova@upjs.sk (D. Breznoscakova), maria.pallayova@upjs.sk (M. Pallayova).

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The most common type of diabetes is type 2 diabetes mellitus (T2DM), accounting for around 90% of all diabetes cases. Because of the increase in its global prevalence, diabetes has been identified by the World Health Organization and the United Nations as a medical emergency.[2] Given the complex interactions between diabetes and a wide range of comorbid conditions, there is an increasing need for reporting of comprehensive information on these interactions and on disease management in such patients.

Bipolar disorder is a serious chronic illness characterized by lifelong periodic mood dysregulation with persistent mood changes involving elevated mood states with or without depressed mood states and energy levels. Bipolar disorder represents a major public health issue because of its relatively high frequency in the population. The lifetime prevalence rates of bipolar spectrum ranges up to 7.8%,[3] and although the annual incidence of bipolar illness is considered generally to be less than 1%, milder forms of bipolar disorder are often missed.[4] Bipolar disorder incorporates two classes of bipolar disorder, bipolar I and bipolar II, differentiated by the presence of major depression and the length and degree of mood elevation. The illness manifests as episodes of mania (one week of abnormally elevated or irritable mood) with or without major depression in bipolar disorder type I, and hypomania (at least 4 days of elevation different from a normal mood state) with major depression (depressed mood, loss of interest/pleasure, weight change, insomnia, psychomotor retardation, fatigue, feelings of worthlessness, suicidal ideology, diminished thought or concentration capacity) in bipolar disorder type II.[5]

In a meta-analysis of 18 studies, the overall prevalence of T2DM in people with bipolar disorder was 9.4% (95% confidence interval CI 6.5, 12.7%).[6] Compared with age- and sex-matched controls, people with bipolar disorder had double the risk of T2DM (relative risk = 1.98; 95% CI 1.6, 2.4; $p < 0.001$).[6] The two-way interaction between psychosocial factors and T2DM is complex. A high prevalence of bipolar disorder symptoms in concomitant T2DM can potentially compromise diabetes control. Changes in long-term glucose control and in fluid and electrolyte homeostasis have been observed between bipolar episodes,[7,8] suggesting mood state could serve as a blood glucose modulator in comorbid T2DM and bipolar disorder.[8]

The present paper examines the bidirectional relationship between bipolar disorder and T2DM and clarifies the clinical impact of therapeutic interventions, highlighting the interpretation and implications of recent literature reports.

Methods

Based on the Search, AppraisaL, Synthesis and Analysis (SALSA) Framework,[9] the present article represents a Literature Review. The PubMed electronic database was searched for keywords “bipolar disorder” AND “diabetes” OR “glucose”. Searches were not restricted by study design. References were identified for articles published from inception until August 2021 for relevant studies. Selection for inclusion was based on expertise of the authors who are specialized physicians and on their perception of the relevance and impact on the field of diabetes mellitus and mental disorders. Based on this literature search, 15 meta-analyses/systematic reviews (Table 1) and numerous clinical research studies were identified that evaluated glucose metabolism in bipolar disorders or examined interrelationships between bipolar disorders and T2DM.

Results

Bipolar disorder and diabetes mellitus − shared risk factors

It is well established that the person with bipolar disorder is at increased risk for developing T2DM.[6] An increasing body of evidence suggests shared risk factors and underlying disease mechanisms. Several possible pathophysiological mechanisms have been proposed to link bipolar disorder with T2DM. These include hypothalamic-pituitary-adrenal axis dysfunction,[10] thyroid hormone abnormalities,[11−15] mitochondrial dysfunction,[16−19] chronic inflammatory state related immune dysfunctions,[20] impaired fatty acid and phospholipid metabolism,[21−27] purinergic system dysfunction,[28] dysregulation of glycogen synthase kinase-3ß (GSK-3ß),[29,30] and dysregulation of noradrenaline signaling.[31]

It is well established that thyroid dysfunction impacts on various levels of the metabolic syndrome components.[12] Commonly proposed mechanisms for the modulatory effects of thyroid hormone on mood include interactions of thyroid hormone with serotonin and norepinephrine neurotransmitter systems.[13] Although most patients with bipolar disorder do not have overt thyroid disease, one exception is bipolar disorder with persistent rapid cycling (four or more episodes of mania and/or major depression per year).[14] This finding suggests that hypothyroidism during bipolar illness is a risk factor for the development of rapid cycling, leading to the hypothesis that a relative central thyroid hormone deficit occurring in bipolar patients predisposes to a rapid cycling course.[14] Importantly, add-on treatment with supraphysiologic doses of levothyroxine improves depressive symptoms in patients with refractory bipolar depression by modulating cerebral activity in the anterior limbic network.[15]

Cortisol is a potent diabetogenic hormone released in response to stress and is a major glucocorticoid produced by adrenal glands. Of importance, sustained hypercortisolemia and the dysregulation of cortisol in patients with bipolar disorder may significantly contribute to development and progression of hyperglycemia, metabolic syndrome, T2DM, abdominal obesity, dyslipidemia, and subsequently cardiovascular disease.[32]

Mitochondrial dysfunction in bipolar patients is characterized by the decreased aerobic- and increased anaerobic metabolism,[16,17] decreased mitochondrial membrane potential, increased mitochondrial DNA deletions in the brain, increased mitophagy, mitochondrial DNA mutations/polymorphisms, or nuclear encoded mitochondrial genes that may be involved in the calcium signaling abnormality found in bipolar disorder.[18,19] Similarly, in T2DM, muscle mitochondrial capacity to produce ATP is reduced [33] and abnormalities in mitochondrial size, number, structure, and function are present.[34] Chronic mood-stabilizing treatment with lithium and valproate has been shown to enhance mitochondrial

Table 1 Systematic reviews and meta-analyses concerning glucose metabolism in bipolar disorders and associations with T2DM.

Study	Number of studies	Number of participants	Outcome	Results
Correll, 2007 [91]	19	684	Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder	Weight loss was significant with topiramate and present with aripiprazole. Weight gain was greater with atypical antipsychotics plus mood stabilizers compared to mood-stabilizer monotherapy ($p < 0.05$) or mood-stabilizer co-treatment ($p < 0.05$), but not compared to antipsychotic monotherapy ($p > 0.05$). Nonfasting glucose/lipid changes were nonsignificant in two atypical antipsychotic trials (8.9%).
Bushe et al., 2009 [92]	11	495	The efficacy and safety of metformin in reducing weight gain and metabolic abnormalities in non-diabetic subjects taking antipsychotic medication	The addition of metformin to antipsychotic treatment was associated with significantly improved glucose parameters relative to controls.
De Hert et al., 2012 [58]	56	21691	Metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia (49 trials, n=19299) and bipolar disorder (7 trials, n=2392)	Changes in glucose levels were noticed during short-term treatment with asenapine (-3.95 mg/dL, 95% CI -7.37, -0.53, $p < 0.05$) and iloperidone (6.90 mg/dL, 95% CI 2.48, 11.32, $p < 0.01$), and during long-term treatment with paliperidone (3.39 mg/dL, 95% CI 0.42, 6.36, $p < 0.05$).
Moteshafi et al., 2012 [93]	33	4831	Olanzapine-induced cardiometabolic adverse effects in patients with schizophrenia (19 trials, n=2389) and affective disorders (14 trials, $n = 2442$)	Olanzapine increased glucose levels in both groups, the difference was not statistically significant between the schizophrenia and bipolar disorder groups (5.63 vs 2.02 mg/dL, respectively; $p = 0.116$).
Czepielewski et al., 2013 [94]	39	49999	Metabolic syndrome in bipolar disorder	The prevalence of metabolic syndrome was significantly higher in bipolar disorder individuals when compared to a control group. Rates of hyperglycemia were significantly greater in patients with bipolar disorder compared to the general population.
Vancampfort et al., 2013 [95]	37	6983	Metabolic syndrome and metabolic abnormalities in bipolar disorder	The overall metabolic syndrome rate was 37.3% (95% CI 36.1, 39.0). Compared with general population groups, bipolar patients had higher metabolic syndrome rates (odds ratio=1.98; 95% CI 1.74, 2.25). Of studies reporting hyperglycemia, the rate was 17.3% (95% CI 14.9, 20.1).
Kemp et al., 2014 [96]	17	5178	Weight change and metabolic effects of asenapine in patients with schizophrenia (13 trials) and bipolar disorder (4 trials)	Mean (standard error [SE]) weight change was greater with asenapine than with placebo (1.2 [0.2] vs 0.14 [0.2] kg; $p < 0.0001$). Mean changes differed for asenapine versus placebo in fasting glucose (1.9 [1.7] vs -1.6 [1.5] mg/dL; $p < 0.05$). Asenapine was not significantly different from olanzapine in change in glucose levels and lower than olanzapine with respect to triglycerides, weight gain, and increased cholesterol.
Galling et al., 2015 [97]	21	4919	Safety and tolerability of antipsychotic-mood stabilizer co-treatment in the management of acute bipolar disorder	Conventional mood stabilizers + antipsychotics co-treatment was associated with significant increases in fasting blood glucose than in conventional mood stabilizers monotherapy (SMD = 0.201, 95% CI 0.085, 0.317, $p = 0.001$), HbA1c (SMD = 0.252, 95% CI 0.082, 0.421, $p = 0.004$)
Vancampfort et al., 2015 [6]	19	18060	Prevalence and predictors of T2DM in people with bipolar disorder	The overall prevalence of T2DM was 9.4% (95% CI 6.5, 12.7%). Compared with age- and sex-matched controls (48.7% male),

Table 1 (*Continued*)

Study	Number of studies	Number of participants	Outcome	Results
				people with bipolar disorder (48.6% male) had double the risk of T2DM (relative risk = 1.98; 95% CI 1.6, 2.4, $p < 0.001$).
Charles et al., 2016 [98]	7	>35000000 of which 41980 had bipolar disorder	The risk of T2DM in patients with bipolar disorder in elderly	Age- and gender- adjusted risk for diabetes mellitus was increased in patients with bipolar disorder and vice versa (odds ratio range between 1.7 and 3.2).
Vancampfort et al., 2016 [99]	118	6060909 of which 438245 had severe mental illness	Pooled frequencies of T2DM in people with severe mental ilness, T2DM prevalence in studies directly comparing persons with bipolar disorder diagnosis to general population samples	The trim and fill adjusted pooled T2DM prevalence among 438245 people with severe mental ilness was 11.3% (95% CI 10.0, 12.6%). In antipsychotic-naïve participants, the prevalence of T2DM was 2.9% (95% CI 1.7, 4.8%). Multi-episode (versus first-episode) status was the only significant predictor for T2DM in a multivariable meta-regression analysis ($p < 0.001$). The T2DM prevalence was higher in patients prescribed antipsychotics, except for aripiprazole and amisulpride.
Amare et al., 2017 [48]	153	unknown[#]	The genetic overlap between mood disorders and cardiometabolic diseases - genome wide and candidate gene studies	Genome-wide association study of bipolar disorder in European Americans identified a new risk allele (rs12772424-A/T) within the TCF7L2 gene associated with regulation of glucose homeostasis and T2DM.
Kucukgoncu et al., 2019 [78]	31	2817 of which 1242 had first episode psychosis, 214 had mood disorders, and 1361 were healthy controls	Glucose intolerance in treatment-naïve, first episode patients with severe mental illnesses	Compared to healthy controls, first episode patients have higher insulin and insulin resistance levels, and both first episode patients group and mood disorders group have higher glucose tolerance test results.
Yu et al., 2019 [63]	40	3725	Insulin resistance induced by olanzapine and other atypical antipsychotics	Olanzapine is associated with a significantly greater insulin resistence index, fasting blood glucose, and fasting insulin, while aripiprazole, ziprasidone, and risperidone are associated with relatively lower risks.
Siskind et al., 2021 [85]	59 in the meta-analysis, 61 in the systematic review	8554	Weight and metabolic changes after antipsychotic switching (33 trials of patients with schizophrenia, 17 trials of patients with schizophrenia or schizoaffective disorder, 2 trials of bipolar patients, and 9 trials of patients with a mix of mental disorders)	Switching to aripiprazole significantly improved fasting glucose (-3.99 mg/dl, 95% CI -7.34, -0.64, $p = 0.02$). Aripiprazole (-1.96 kg, 95% CI -3.07, -0.85, $p < 0.001$) and ziprasidone (-2.22 kg, 95% CI -3.84, -0.60, $p = 0.007$) were associated with weight loss, whereas olanzapine (2.71 kg, 95% CI 1.87, 3.55, $p < 0.001$), and clozapine (2.80 kg, 95% CI 0.26, 5.34, $p = 0.03$) were associated with weight gain. No significant cardiometabolic changes were observed when switching to amisulpride, paliperidone/risperidone, quetiapine, or lurasidone.

[#] It was not possible to determine the number of participants based on the information published. The study systematically investigated genome-wide association studies and candidate genes for cardiometabolic diseases that are possibly associated with mood disorders. Rather than number of participants, the authors report number of significant single nucleotide polymorphisms and nearby genes in order to identify the Cardiometabolic Mood disorders hub genes.

function by increasing expression of the Bcl-associated athanogene-1 (BAG-1) gene, which inhibits glucocorticoid activation.[35] In T2DM, agents which inhibit the generation or scavenge mitochondrial superoxide and/or inhibit poly-ADP-ribose polymerase may prove to be beneficial in preventing the development of hyperglycemia-induced diabetic complications.[36]

Immune dysfunction appears to be an important mediator of the association observed between bipolar disorder and medical comorbidities. A systematic review by Rosenblat and colleagues [37] investigating the relationship between neuroinflammation and cognitive impairment in bipolar disorder included 8 studies that reported an increase in pro-inflammatory cytokines correlated with cognitive impairment, specifically, interleukin-1Ra, interleukin-6, and tumor necrosis factor-α. Increases in interleukin-6, C-reactive protein, and cortisol are seen in bipolar disorder and are possible mechanisms for the development of T2DM.[37—40]

A number of lipidomic alterations have been noted in bipolar patients,[21] including increases in plasma levels of lipid peroxidation in euthymic adults with bipolar disorder [23] and reduced essential polyunsaturated fatty acids in red blood cell membranes, including arachidonic and docosahexaenoic acid in individuals with bipolar mania.[25] Research has also demonstrated a link between greater intakes of long-chain omega-3 polyunsaturated fatty acids combined with lower intakes of long chain omega-6 fatty acids and a lower incidence of unipolar and bipolar depression.[24] Considering the two-way link between T2DM and bipolar disorder, there is a reasonable basis for the idea that the fatty acid abnormalities in diabetes may contribute significantly to different mood states in bipolar patients.[21–27]

Growing evidence points to the involvement of the purinergic signaling in the pathophysiology of bipolar disorder.[28,41,42] Decreased serum adenosine levels in euthymic bipolar disorder compared with controls indicates a systemic reduction of a neuroprotective agent.[41] In a study by Salvadore and colleagues,[28] acutely manic drug-naïve patients with bipolar disorder had significantly higher levels of plasma uric acid (4.85 $\pm$ 1.60 mg/dL) compared to healthy controls (2.96 $\pm$ 0.63 mg/dL, $p < 0.001$), suggesting that high levels of uric acid may represent a bipolar disorder state marker during mania.

GSK-3β is a serine/threonine protein kinase mediating phosphorylation on serine and threonine amino acid residues of several target molecules. The enzyme is involved in the regulation of multiple cellular processes including insulin pathways and dopamine D2 signaling.[43] Aberrant activity of GSK-3β plays a role in the pathophysiology of both T2DM and bipolar disorder.[29,30] GSK-3 inhibition has been shown to enhance insulin sensitivity and promote glycogen synthesis, suggesting GSK-3 inhibitors as new viable leads to treat T2DM.[44] One of the mechanisms of action of mood stabilizers such as lithium and valproate used for treatment of bipolar disorder is the inhibition of GSK-3β.[45] A previous study has demonstrated remarkable stabilizing properties of the novel GSK-3β inhibitor AF3581 on mood cycling in animal models of mood disorders, suggesting that AF3581 could be the prototype of a novel class of therapeutics for bipolar disorders.[46]

A growing body of evidence suggests that elevated noradrenaline signaling may be involved in the etiology of bipolar disorder and T2DM. The proposed mechanisms involve G protein-coupled receptor modulation of the Ras/MAP kinase, Stat3 and PI3K pathways, among others.[31] Noradrenaline transmission lowering drugs such as clonidine, guanfacine, propranolol or prazosin diminish noradrenaline signaling throughout the body and may protect against a wide range of diseases.[31]

In addition to shared pathophysiological mechanisms, sedentary life-style, lack of exercise, increased simple carbohydrate intake, adverse effects of bipolar pharmacotherapy, and bipolar depressive symptoms phenomenology may affect glucose metabolism.[47] Finally, genetic and epigenetic factors can mediate the link between the two disorders.[32] Both bipolar disorder and cardiometabolic diseases including T2DM are highly heritable and they are caused by a combination of genetic and environmental factors.[48]

Metabolic adverse effects of bipolar pharmacotherapy

The primary goal of the bipolar disorder treatment is to offer effective therapy that improves psychiatric and cognitive outcomes, psychological, social, and work functioning and minimizes recurrence of the episodes and medical risk factors. Use of various treatment options is guided by the phase of illness (mania/hypomania/depression/mixed/maintenance) in which patient presents to the clinician and past treatment history.[49] 1. Mania/ hypomania/ mixed: atypical (second-generation) antipsychotics (e.g., risperidone, paliperidone, ziprasidone, iloperidone, lurasidone, sertindole, olanzapine, clozapine, quetiapine, asenapine, amisulpride, aripiprazole, brexiprazole, cariprazine), mood stabilizers (lithium carbonate, valproic acid, lamotrigine, carbamazepine) eventually typical or conventional (first-generation) antipsychotics, 2. Depressive phase: mood stabilizers and atypical antipsychotics (preferentially multi-acting receptor-targeted antagonists, olanzapine, quetiapine, clozapine or other- aripiprazole, brexiprazole) 3. Maintenance phase: mood stabilizers and atypical antipsychotics.[50]

The introduction of the novel atypical antipsychotics with mood stabilizer properties was met with great expectations among clinicians regarding their potentially lower propensity to cause extrapyramidal syndrome.[51] In addition, atypical antipsychotics (in contrast to conventional antipsychotics) induce neuronal plasticity and synaptic remodeling in the striatum, prefrontal cortex and hippocampus, while normalizing glutamatergic dysfunction and structural abnormalities.[52] Based on their affinities for specific receptors, atypical antipsychotics are classified as: (1) serotonin-dopamine antagonists (SDA) = atypical antipsychotics with a high selectivity for serotonin 5-HT_{2A} receptors and dopamine D_2 receptors (and also α1-adrenoceptors), e.g. risperidone, its metabolite paliperidone, ziprasidone, iloperidone, lurasidone; (2) multi-acting receptor-targeted antagonists (MARTA) = drugs showing an affinity for 5-HT_{2A}, D_2 and receptors of other systems (cholinergic, histaminergic, 5-HT_{1A}, 5-HT_{1C} and others), e.g. clozapine, olanzapine, quetiapine, asenapine; 3) combined D_2/D_3 receptor antagonists = drugs that preferentially block D_2 and D_3 subtypes of the D_2-like receptors, e.g. amisulpride; and 4) the partial dopamine D_2 receptor agonists, e.g. aripiprazole and cariprazine.[52,53]

Nevertheless, the evidence demonstrates that adverse events associated with antipsychotic treatment can contribute to serious metabolic complications. The established relevant metabolic adverse antipsychotic treatment effects include weight gain, high waist circumference, insulin resistance, hyperglycemia, and dyslipidemia. Increased weight and central adiposity may be one factor that contributes to why people with bipolar disorders are more likely to develop metabolic syndrome, T2DM, and cardiovascular disease.[54] A recent meta-analysis [55] has reported that all atypical antipsychotics except lurasidone and aripiprazole were associated with significantly more weight gain than placebo. During the short-term trials (6-8 weeks), olanzapine had the largest mean weight gain relative to placebo (2.88 kg), followed by quetiapine (1.17 kg), cariprazine (0.65 kg), lurasidone (0.34 kg), and aripiprazole (0.20 kg).[55] The rates of clinically significant weight gain ($\geq$ 7%) were the lowest for

lurasidone (2.4%) followed by cariprazine (3.2%), aripiprazole (4.7%), quetiapine (6.9%), and olanzapine (20.3%).[55] Two other studies have reported that risperidone and quetiapine produced approximately 2 kg of mean weight gain and agents such as ziprasidone, haloperidol and aripiprazole, produced 1 kg or less weight gain over 10 weeks.[56,57] The current evidence regarding atypical antipsychotic-induced weight gain ranks clozapine and olanzapine as having the highest risk, followed by amisulpride, asenapine, iloperidone, paliperidone, quetiapine, risperidone and sertindole in the middle, and aripiprazole, brexiprazole, cariprazine, lurasidone and ziprasidone with the lowest risk.[54,55,57,58] The observed antipsychotic-induced weight gain is strongly associated with their anti-histaminergic profile; H1-histamine receptor affinity predicts weight gain with antidepressants and antipsychotics.[59]

Atypical antipsychotics are more likely than mood stabilizers to have treatment-emergent weight gain.[60] Specifically, out of mood stabilizers, carbamazepine and lamotrigine are associated with lower weight gain when compared to lithium or valproic acid.[61] Nevertheless, a recent systematic review and meta-analysis [62] has revealed that weight gain during lithium treatment was not significant, noting a weight increase of 0.462 kg (p = 0.158). Yet, the weight gain was significantly greater in those interventions with 12 weeks or shorter.[62] Eight studies in the same systematic review showed greater weight gain with the active comparator than with lithium; these used atypical antipsychotics (quetiapine, olanzapine, and risperidone) and valproate as active comparators.[62] These findings highlight the need of a constant monitoring of weight, BMI, and blood pressure particularly for patients taking valproate.

Existing data suggest that olanzapine is more likely to induce insulin resistance than are other atypical antipsychotics (aripiprazole, ziprasidone, risperidone).[63,64] A meta-analysis of 40 studies [63] demonstrated that patients treated with olanzapine had higher fasting blood glucose (FBG), fasting insulin (FINS) levels, and insulin resistance index (IRI) than did patients treated with aripiprazole, ziprasidone, or risperidone, with significant differences (aripiprazole vs. olanzapine: FBG: standardized mean difference [SMD] = -0.72, 95% CI -0.82, -0.61; FINS: SMD = -0.8, 95% CI -1.00, -0.61; IRI: SMD = -0.80, 95% CI -0.99, -0.61; ziprasidone vs. olanzapine: FBG: SMD = -1.19, 95% CI -1.30, -1.08; FINS: SMD = -0.66, 95% CI -0.85, -0.47; IRI: SMD = -0.71, 95% CI -0.88, -0.55; risperidone vs. olanzapine: FBG: SMD = -0.17, 95% CI -0.34, -0.00). Notably, the findings suggest that use of antipsychotics (olanzapine, aripiprazole) may alter adipokine levels, and that increased leptin/adiponectin ratio may play a role in the development of insulin resistance associated with use of antipsychotics independently of body mass index.[65] According to Calkin [66] and Cuperfain and colleagues,[67] insulin resistance may modify the course of bipolar disorder and promote neuroprogression in bipolar disorder. Notably, insulin resistance has a bidirectional association with oxidative stress and lipid peroxidation, and contributes to endothelial dysfunction (the pathomechanisms also found in bipolar patients), resulting in microvascular and macrovascular damage, which potentially leads to end-organ damage, including the cardiovascular disease, cerebrovascular disease, and neurodegeneration.[66]

Drug-induced hyperglycemia is one of the factors contributing to the increasing incidence of diabetes worldwide. Antipsychotics that induce hyperglycemia (and consequently diabetes) include especially clozapine and olanzapine.[68] In a meta-analysis of 56 trials evaluating metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone, statistically significant changes in glucose levels were noticed during short-term treatment with asenapine (-3.95 mg/dL, 95% CI -7.37, -0.53, $p < 0.05$) and iloperidone (6.90 mg/dL, 95% CI 2.48, 11.32, $p < 0.01$), and during long-term treatment with paliperidone (3.39 mg/dL, 95% CI 0.42, 6.36, $p < 0.05$).[58] Abnormalities of the gluco-regulatory pathways of hyperglycemia involve decreased insulin secretion and frequent insulin resistance. Both olanzapine and clozapine block insulin secretion as antagonists of acetylcholine muscarinic 3 receptors in the β-cells of the pancreas.[69] Pancreatic acetylcholine muscarinic 3 receptors regulate the glucose-stimulated cholinergic pathway of insulin secretion; their activation on β-cells stimulates insulin secretion, while muscarinic 3 receptors blockade decreases insulin secretion.[70] Data are sparse regarding glucose metabolism effects of mood stabilizers in adult bipolar disorder. The available evidence suggests that valproic acid derivatives inhibit glucose-stimulated insulin secretion in pancreatic beta cells.[71] In addition, increased insulin as well as the homeostatic model assessment of insulin resistance HOMA-IR levels and decreased adiponectin levels were found in valproate treated subjects when compared to the controls.[72,73]

Dyslipidemia belongs to the most relevant adverse cardiometabolic effects of psychotropic medications and appears strongly related to medication-induced weight changes. Out of the medications for bipolar disorder, dyslipidemia is most commonly associated with the use of the antipsychotics, clozapine and olanzapine, and mood stabilizers, valproic acid derivatives and carbamazepine.[73] In a retrospective cohort study of adolescents treated with antipsychotics, the adjusted hazard ratio of developing dyslipidemia in the schizophrenia or bipolar disorder cohort relative to the general population cohort was 1.66 (95% CI 1.22, 2.28).[74] Although statistically significant, no clinically meaningful differences were observed in a meta-analysis of 56 trials [58] between the asenapine, iloperidone, lurasidone and paliperidone and placebo regarding the mean change from baseline to endpoint in cholesterol levels [iloperidone: total cholesterol (11.6 mg/dL, 95% CI 4.98, 18.22, $p < 0.001$), high-density cholesterol (3.6 mg/dL, 95% CI 1.58, 5.62, $p < 0.001$) and low-density cholesterol (10.3 mg/dL, 95% CI 4.94, 15.66, $p < 0.001$); lurasidone: high-density cholesterol (1.5 mg/dL, 95% CI 0.56, 2.44, $p < 0.01$); asenapine: (6.53 mg/dL, 95% CI 1.17, 11.89, $p < 0.05$)].[58] Regarding triglycerides, only short-term and longer-term treatment with paliperidone had a statistically, but not clinically significant effect.[58] Naiberg and colleagues [75] found a significant relationship between executive dysfunction and elevated triglyceride levels among adolescents with bipolar disorder independent of age, IQ, and current use of atypical antipsychotics. While these findings could indicate a bidirectional relationship, continued research regarding the links between bipolar disorder and cardiovascular disease may offer insights regarding novel therapeutic approaches and cognitive dysfunction.

A bidirectional link between bipolar episodes and diabetes control

Several studies have reported impaired glucose metabolism in first episode, treatment-naïve patients with mood disorders when compared to the controls.[76–78] Kucukgoncu and colleagues [78] meta-analyzed 31 studies to find out that compared to healthy controls, treatment naïve first episode psychosis group had higher fasting insulin and insulin resistance levels and higher glucose tolerance test results. These results highlight impaired glucose metabolism at the onset of severe mental illnesses, suggesting both patients with psychosis and mood disorders are high-risk groups for diabetes development.[78] In a study by Guha and colleagues [76] newly diagnosed and psychotropically naïve bipolar disorder patients had significantly higher mean levels of fasting plasma insulin (13.2 $\pm$ 9.2 vs. 4.68 $\pm$ 3.1 μIU/ml, $p < 0.05$), postprandial plasma insulin (27.2 $\pm$ 14.5 vs. 18.1 $\pm$ 9.3 μIU/ml, $p < 0.05$) and a higher value of homeostasis model assessment of insulin resistance HOMA-IR (3.16 $\pm$ 2.2 vs. 1.19 $\pm$ 0.8, $p < 0.05$) when compared to the controls.

The influence of glucose control on course of bipolar disorder, rapid cycling, and response to lithium treatment has been explored by Calkin and colleagues.[79] Importantly, bipolar patients with T2DM had three times higher odds of a chronic course of bipolar disorder compared with euglycaemic patients (50% vs. 27.3%, odds ratio = 3.07, $p = 0.007$), three times higher odds of rapid cycling (38.5% vs. 18.2%, odds ratio = 3.13, $p = 0.012$) and were more likely to be refractory to lithium treatment (36.8% vs. 3.2%, odds ratio = 8.40, $p < 0.0001$).[79] These findings strongly indicate that T2DM is associated with an unfavourable clinical course of bipolar disorder and poor treatment outcomes.[79]

The dynamic longitudinal relationship between insulin resistance, glycemic status, and course of bipolar disorder has been assessed in a case series of six patients followed over the lifetime.[80] Importantly, all six patients with a previously episodic, relapsing-remitting course of bipolar disorder experienced a significant worsening of morbidity after the onset of laboratory-demonstrated insulin resistance or elevated fasting plasma glucose.[80]

To date, longitudinal data regarding the link between the course of bipolar disorder and glucose excursions are still lacking. Chu and Liang [8] have reported worsening of glucose control as indicated by increases in a three-month glycated hemoglobin (HbA1c) related to bipolar depressive episodes, whereas improvements in HbA1c accompanied periods of hyperthymia and manic episodes. The authors speculate that improvements in glucose control during manic phases might be related to a dopamine-triggered relative hemodilution with a subsequent decrease in hypothalamic-pituitary-adrenal axis activity, resulting in a decrease in hepatic gluconeogenesis.[7,8] Associations between symptoms of depression and higher HbA1c levels have been reported in other studies as well.[81,82] Clinical observations in specific cases suggest that modification of glucose metabolism may influence the course of bipolar illness; however, systematic evidence for this is lacking.[79]

Fasting hyperglycemia, impaired glucose tolerance (i.e. prediabetes) and overt T2DM are frequently present in bipolar patients treated with atypical antipsychotics. The most recent clinical practice guidelines of interventions for bipolar disorders associated with T2DM recommend switching from high metabolic liability atypical antipsychotics to safer atypical antipsychotics; switching from clozapine, olanzapine, or quetiapine to lower cardiometabolic-risk atypical antipsychotics, like aripiprazole, brexpiprazole, cariprazine, lurasidone, or ziprasidone, has been recommended.[83] Drug therapy using metformin as first-line therapy and glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors as add-on therapy, might be preferred in these patients as well, as they favorably influence glucose metabolism and body mass index, and provide cardio-renal benefits to the T2DM population; metformin is also useful for treatment of prediabetes.[83]

Discussion

Characterized by significant alterations in mood, cognition, and behavior, bipolar disorder can have a significant negative impact on the functioning and quality of life of the affected individuals. In a similar way, the complex demands of diabetes care (such as planning and scheduling, carbohydrate counting, regular exercising, monitoring blood glucose) along with unpredictable glucose excursions may affect the functioning and quality of life of persons with T2DM.

Of importance, bipolar patients with comorbid T2DM have a more severe course of bipolar illness and are more refractory to bipolar treatment.[32] Specifically, evidence shows that comorbid insulin resistance and T2DM are associated with a more chronic course, increased number of episodes (rapid cycling), poor response to lithium, possible neurocognitive deficits and adverse structural and chemical brain changes in bipolar patients.[66,84] With respect to insulin resistance we can conclude that: (1) significantly higher insulin resistance levels are typical for newly diagnosed and psychotropically naïve bipolar disorder patients,[76] (2) bipolar patients treated with olanzapine had significantly higher insulin resistance levels,[63–65] (3) sedentary life-style, lack of exercise, and increased simple carbohydrate intake may contribute to increased insulin resistance levels in bipolar disorder,[47] and (4) the increased insulin resistance may modify the course of bipolar disorder and promote neuroprogression in bipolar disorder.[66,67]

Type 2 diabetic patients with comorbid bipolar disorder often experience deteriorations of long-term glucose control, especially during the depressive phase of the disease.[82] Importantly, bipolar patients with comorbid T2DM have increased cardiovascular morbidity and mortality, the leading cause of death in bipolar disorder.[32] The available data indicates poorer quality of life and overall functioning and greater disability of bipolar patients with comorbid T2DM compared to those without T2DM.[84] Metabolic risks of individual antipsychotic medications and the weight-gain potential of hypoglycemic drugs should be considered when making treatment choices. Safety and tolerability of medications are key variables to inform treatment choice for T2DM patients with bipolar disorders. Early diagnosis and satisfactory treatment of T2DM using various types of techniques are essential to prevent devastating chronic diabetic complications, especially in high-risk subjects. Therefore,

monitoring of fasting plasma glucose levels and eventually HbA1c particularly in high-risk patients with bipolar disorder is important for timely diagnosis of prediabetes and its progression to overt T2DM.

Obesity and clinically significant adverse metabolic outcomes in bipolar patients are potentially preventable by switching to antipsychotics with a potential to reduce cardiometabolic burden. Siskind and colleagues [85] meta-analyzed 59 studies to demonstrate that switching to aripiprazole significantly improved fasting glucose (-3.99 mg/dl, 95% CI -7.34, -0.64, $p = 0.02$). Aripiprazole (-1.96 kg, 95% CI -3.07, -0.85, $p < 0.001$) and ziprasidone (-2.22 kg, 95% CI -3.84, -0.60, $p = 0.007$) were associated with weight loss, whereas olanzapine (2.71 kg, 95% CI 1.87, 3.55, $p < 0.001$), and clozapine (2.80 kg, 95% CI 0.26, 5.34, $p = 0.03$) were associated with weight gain.[85] No significant cardiometabolic changes were observed when switching to amisulpride, paliperidone/risperidone, quetiapine, or lurasidone.[85]

Physicians need to be aware of the increased risk for cardiovascular disease in bipolar patients with comorbid T2DM, and appropriate prevention, screening, case finding, treatment, and monitoring for illness progression are recommended.[32] Clinicians, including mental health professionals, primary health care providers, and diabetes specialists are often the first to recognize the metabolic impact of antipsychotic treatment. Early recognition of signs and symptoms of the metabolic syndrome is critical to initiation of timely preventive and treatment strategies. Therefore, understanding of the relationship between bipolar disorder and T2DM is important, highlighting the interpretation and implications of recent literature reports.

The main limitation of the present review is the specificity in regards to bidirectionality between T2DM and bipolar disorder (i.e. as opposed to major depressive disorder or schizophrenia). The available evidence suggests that bipolar disorder, major depressive disorder, and schizophrenia share some of the common risk factors for the development of prediabetes and its progression to overt T2DM. The average point prevalence of major depressive disorder among persons with T2DM is 14.5% (95% CI 7.9, 25.3),[86] and the overall prevalence of T2DM among patients with major depressive disorder is 8.7% (95% CI 7.3, 10.2%).[87] Meta-analyses have demonstrated that glucose homeostasis is altered in patients with first-episode schizophrenia.[88−90] suggesting that schizophrenia confers an inherent risk for glucose dysregulation, even in the absence of the effects of chronic illness and long-term treatment. The specificity of the bidirectionality between T2DM and bipolar disorder is supported by the results of a systematic review [48] introducing the 24 Cardiometabolic Mood Disorders hub genes and specific genetic variants across mood disorders and cardiometabolic diseases. Specifically, genome-wide association study of bipolar disorder in European Americans identified a new risk allele (rs12772424-A/T) within the TCF7L2 gene associated with regulation of glucose homeostasis and T2DM.[48] The published data support the concept that the Cardiometabolic Mood Disorders hub genes are centrally involved in the link between mood disorders and the cardiometabolic diseases.

With regard to other limitations, the present review is subject to substantial variability in quality and subject to potential bias. Like other studies, reviews are at risk for bias from a number of sources (e.g., reporting bias, evidence selection bias, publication bias, bias in review design, bias in locating studies, bias in selecting studies). Awareness of the potential biases in the review is important for readers as they incorporate the findings into clinical practice and policy making.

Conclusions

To conclude, patients with bipolar disorder have higher rates of T2DM compared to the general population. Further, type 2 diabetic patients with comorbid bipolar disorder often experience deteriorated long-term glucose control and increased cardiovascular morbidity and mortality, the leading cause of death in both T2DM and bipolar disorder. The observed bidirectional interaction merits screening for psychiatric disorders in patients with T2DM and vice versa to allow for early detection and treatment of this at risk population. Selection of drugs with neutral metabolic effects and dose individualization hold significant promise for optimizing therapy with antipsychotic and antidiabetic agents.

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Ethical considerations

In accordance with the Pavol Jozef Safarik University institution's policy, the institution does not require Institutional Review Board (IRB) review and exemption for review articles. Review articles do not require IRB approval if the data reviewed are public (including private and government databases) and if the articles reviewed have received IRB approval previously.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

CRediT authorship contribution statement

Dagmar Breznoscakova: Conceptualization, Resources, Data curation, Writing − review & editing. **Maria Pallayova:** Conceptualization, Resources, Data curation, Writing − review & editing.

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