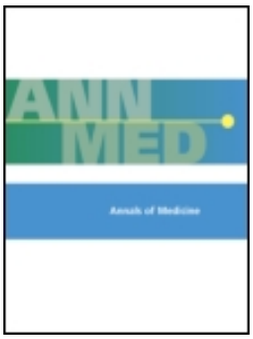

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REVIEW ARTICLE

The relationship between bipolar disorder and type 2 diabetes: More than just co-morbid disorders

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Type 2 diabetes mellitus (T2DM) rates are three times higher in patients with bipolar disorder (BD), compared to the general population. This is a major contributing factor to the elevated risk of cardiovascular mortality, the leading cause of death in bipolar patients. There may be shared pathophysiology linking the two disorders, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, common genetic links, and epigenetic interactions. Life-style, phenomenology of bipolar symptoms, and adverse effects of pharmacotherapy may be contributing factors. Patients with BD and T2DM have a more severe course of illness and are more refractory to treatment. Control of their diabetes is poorer when compared to diabetics without BD, and an existing disparity in medical care may be partly responsible.

Glucose abnormalities in bipolar patients need to be screened for and treated. Metformin appears to have the best benefit/risk ratio, and the dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists and analogues also appear promising, although these agents have not been specifically studied in populations with mood disorders. Physicians need to be aware of the increased risk for T2DM and cardiovascular disease in bipolar patients, and appropriate prevention, screening, case finding, and treatment is recommended.

Key words: Bipolar disorder, co-morbidity, diabetes, epigenetics, etiology, mortality, pharmacotherapy, pathophysiology, treatment

Key messages

- Patients with bipolar disorder have higher rates of type 2 diabetes mellitus (T2DM) compared to the general population. Several factors likely underlie this increased prevalence, including life-style factors, phenomenology of bipolar symptoms, adverse effects of pharmacotherapy for bipolar disorder, and possible common genetically and environmentally linked pathophysiologic processes.
- Bipolar patients with co-morbid T2DM have a more severe course of bipolar illness and are more refractory to bipolar treatment. They have increased cardiovascular morbidity and mortality, the leading cause of death in bipolar disorder.
- Monitoring fasting plasma glucose levels is important in patients with bipolar disorder. Diet and exercise is recommended for prevention and initial treatment of T2DM. When medication is required, metformin appears to offer some benefits to the management of T2DM in bipolar disorder, which other oral antihyperglycemics lack. While improving insulin resistance, it is associated with weight loss and does not risk hypoglycemia.

Introduction

Bipolar disorder is a recurrent major psychiatric illness with a lifetime prevalence of 1%–5%. The illness manifests as lifelong periodic mood dysregulation, with episodes of mania with or without depression in bipolar disorder type I, and depression and hypomania in bipolar disorder type II. Bipolar disorder exacts a heavy toll in terms of morbidity and mortality (1,2). The mortality rate is significantly higher in people with bipolar disorder, with cardiovascular (CV) disease as the leading contributor to excess deaths. Compared to the general population, risk of death due to CV disease is increased 2.3-fold (3).

Rates of CV risk factors (obesity, hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), and metabolic syndrome) are all higher in patients with bipolar disorder (4,5). For example, there is up to a three times increased risk of T2DM in patients with bipolar disorder compared to the general population (6–8). In a review of epidemiologic studies, Newcomer found the prevalence of T2DM in patients with bipolar disorder to be 8%–17% (for review please see Newcomer (9)).

Efforts to improve simple and routine diabetes prevention, detection, and treatment strategies could limit the associated elevated morbidity and mortality in this population (10). Despite the increased prevalence of medical co-morbidity in patients with bipolar disorder, diabetes in this population remains under-detected and under-treated (11,12).

This paper provides a focused review of the relevant literature on bipolar disorder and T2DM, with the aim of providing an overview of the relationship between the two disorders, with suggestions for an approach to the care of these patients.

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Etiology of increased diabetes risk in bipolar disorder

Why do patients with bipolar disorder have an increased risk of T2DM? Several factors likely underlie this increased prevalence. These include possible common pathophysiologic processes and genetic and epigenetic links, life-style factors, phenomenology of bipolar symptoms, and adverse effects of pharmacotherapy for bipolar disorder.

Possible shared pathophysiology

Hypothalamic-pituitary-adrenal dysfunction

Overlap in the underlying pathophysiology of bipolar disorder and T2DM likely exists. Abnormalities in hypothalamic-pituitary-adrenal (HPA) function are apparent in patients with bipolar disorder. Tests of the HPA axis show increased levels of basal cortisol, lack of suppression of cortisol levels by dexamethasone, and abnormal responses of the HPA system to various physical and psychological stressors (13). Further, the normal diurnal variation of cortisol is perturbed, the cortisol troughs normally present at night are not blunted (14), and the daytime peaks are higher (15). Hypercortisolemia is common in patients with bipolar disorder, even when euthymic (16). It is also noted in non-affected relatives of patients with bipolar disorder (17) and therefore is likely a trait in bipolar disorder. The stress that underlies elevated noradrenergic tone and activation of the HPA axis leading to hypercortisolemia in bipolar disorder can also lead to a decrease in insulin secretion and increase in gluconeogenesis, resulting in hyperglycemia with progression to diabetes (18). This in turn promotes the deposition of body fat as well as the formation of atherosclerotic plaques in the coronary arteries (19), contributing to abdominal obesity and cardiovascular disease, respectively. Increased visceral fat is also associated with a high density of glucocorticoid receptors, binding more cortisol and assimilating more triglycerides (20). Therefore, the dysregulation of cortisol in patients with bipolar disorder may contribute to common aspects of metabolic syndrome, including T2DM, abdominal obesity, and dyslipidemia.

Mitochondrial dysfunction

Mitochondrial dysfunction has been implicated in the pathogenesis of both bipolar disorder and diabetes (21). Patients with bipolar disorder have decreased pH, phosphocreatine, and adenosine triphosphate (ATP) in the brain, all hallmarks of decreased aerobic metabolism. Bipolar patients also have increased brain lactate levels, indicating an increase in anaerobic metabolism. Muscle mitochondrial capacity to produce ATP is reduced in patients with diabetes (22). There are increased mitochondrial DNA deletions in the brains of patients with bipolar disorder, and bipolar disorder is associated with mitochondrial DNA mutations/polymorphisms or nuclear encoded mitochondrial genes (23). Mitochondrial mutations are present in 2% of patients with diabetes, and the down-regulation of genes encoding for a subset of enzymes of oxidative phosphorylation and mitochondrial function has been demonstrated (24). Abnormalities in mitochondrial size and/or number, structure, and function are also present in insulin-resistant states (25).

A number of studies have shown that mood stabilizers used in the treatment of bipolar disorder are neuroprotective against oxidative stress. A study by Maurer et al. suggests that lithium stimulates mitochondrial respiratory chain enzyme activity (26). Chronic mood stabilizer use has been shown to enhance mitochondrial function by increasing expression of the Bcl-associated athanogene-1 (BAG-1) gene (27). BAG-1 is a co-chaperone involved in glucocorticoid (GC) receptor signaling, regulating both GC binding and gene transactivation of GC receptors. BAG-1 is one of the common brain targets of chronic mood-stabilizing treatment with lithium and valproate. It inhibits GC activation, suggesting that one mechanism by which some mood stabilizers might counteract the deleterious effects of hypercortisolemia seen in bipolar disorder is by up-regulating BAG-1. Whether mood stabilizers have an effect on insulin resistance or T2DM in bipolar patients by this mechanism has not been determined.

Other possible common pathophysiologic processes

Evidence implicates the dysregulation of glycogen synthase kinase-3 (GSK-3) in the pathogenesis of T2DM, bipolar disorder, and schizophrenia (28,29). GSK-3 regulates insulin pathways and is involved in the development of insulin resistance and neuronal cell death. GSK-3 also regulates the physiological effects of dopamine D2 signaling, and GSK-3 levels and activity are altered in the brains and lymphocytes of patients with schizophrenia (30), a process that may also occur in bipolar disorder. GSK-3 inhibition is being investigated for potential treatment of T2DM and may be one mechanism by which the mood stabilizer, lithium, stabilizes mood (see Rowe et al. for review (31)).

Impaired phospholipid metabolism and fatty acid-related signal transduction are also among those believed to be overlapping neurobiological networks leading to both bipolar disorder and diabetes (32).

Possible genetic and epigenetic links

Common genetic susceptibility

There may be common genetic abnormalities and shared susceptibility loci between bipolar disorder and diabetes. Torkamani et al. analyzed seven common diseases assessed by genome-wide association and found that bipolar disorder and T2DM shared 68 SNPs in common amongst the top 1000 most significant SNPs per disease (Pearson correlation coefficient 0.85, $P < 0.0001$) (33). The number of SNPs expected to be shared in common by maximum likelihood, according to the hypergeometric distribution, is two (see Torkamani (33) for calculation method). Among the top ten disease pathways enriched among the most significant SNPs identified in bipolar disorder, data implicate shared mood and metabolic disease pathways.

Research on the genetics of insomnia and metabolism showed that 16.5% of those reporting insomnia had distinct metabolic changes reflecting an increase in insulin secretion and a higher risk of diabetes (34). Insomnia-related genotypic differences were highly concentrated within genes known to be involved in bipolar disorder and schizophrenia, with the most significant SNPs residing in ROR1 and PLCB1, respectively. In neural cells, putative enhancers bound by PAX6, a neural transcription factor essential for central nervous system development and known to play a role in insulin secretion in the pancreas, were discovered within ROR1 and PLCB1 near the significant SNPs. This research suggests that dysregulation of ROR1 by PAX6 may be one mechanism that links neural and pancreatic function not only in insomnia, but also in bipolar disorder where circadian rhythm and metabolic dysfunction are common.

Nature versus nurture: epigenetics and the role of early adversity

Childhood adverse events, such as neglect and abuse, have been shown to be highly predictive of psychiatric disorders in adult life (35). Research suggests that the level of gene expression is modified in response to the environment. Early life stress may induce long-lasting HPA axis dysregulation by increasing methylation of

the promoter region of the glucocorticoid receptor gene, thereby inhibiting GC receptor gene expression in the hippocampus (36). This can result in up-regulation of corticotrophin-releasing hormone and hypersecretion of cortisol, resulting in increased stress responsiveness (37,38). Thus, early life stress may be associated with neurobiological changes that could permanently render neuroendocrine stress response systems ultra-sensitive, and may underlie the increased risk of psychopathology (39). The prevalence of childhood abuse in patients with bipolar disorder has been estimated at about 50% (40). More severe forms of abuse are more common in patients with bipolar disorder, with 24% reporting physical abuse and 21% reporting sexual abuse (41), compared to 15% and 12%, respectively, in the general population (42). Further, a history of early trauma has been associated with a more severe form of bipolar disorder, with an earlier age of onset, more suicide attempts, and higher rates of rapid cycling and psychosis (41,43). Higher rates of abuse may account in part for the elevated cortisol levels seen in patients with bipolar disorder.

Early life stress may also be a predictor of T2DM (44). In the short term, the stress response and associated elevated cortisol result in energy mobilization. However, chronically elevated cortisol levels lead to decreased insulin production and increased gluconeogenesis, potentially resulting in T2DM. Glucocorticoid hypersecretion over the long term can also lead to immune response activation. Danese et al. found that children exposed to adversity are not only at elevated risk of psychopathology, but have high inflammation levels and an increase in metabolic syndrome risk factors (for example, diabetes) in adulthood (45). Elevated C-reactive protein (CRP; an inflammatory marker for cardiovascular risk) has been found in adults who experienced childhood maltreatment and have current depression, and in children who have experienced maltreatment (46, 47). This suggests that early adverse life events may predict enduring abnormalities in stress-sensitive biological systems, namely, the nervous, immune, and endocrine/metabolic systems. Stress-related elevation in clinically relevant inflammatory proteins such as CRP and interleukin-6 (IL-6), could contribute to the biological embedding of childhood stress (48), leading to both an increase in psychopathology and medical co-morbidity. Elevated levels of CRP and IL-6 predicted the development of diabetes in a 4-year follow-up period in healthy women after adjustments for body mass index (BMI), family history of diabetes, smoking, exercise, alcohol, and hormone replacement therapy (49) and therefore appear to confer independent risk for diabetes. IL-6 is a potent stimulator of corticotropin-releasing hormone production, a mechanism leading to heightened HPA activity and increase in cortisol. Some studies have found that bipolar disorder is associated with increased production of CRP and IL-6 (50,51). So it appears that early life stress may stimulate production of IL-6 which further increases cortisol and in turn promotes the production of CRP (52). Increases in IL-6, CRP, and cortisol are seen in bipolar disorder and are possible mechanisms for the development of diabetes.

Bipolar disorder itself may be a risk factor for T2DM

Life-style factors

Patients with bipolar disorder have higher rates of obesity (elevated BMI) compared to the general population, and, not surprisingly, those patients with elevated BMI have higher rates of co-morbid T2DM (53). Life-style factors in patients with bipolar disorder such as lack of exercise and increased simple carbohydrate intake may play an etiologic role in the higher prevalence of obesity and T2DM. Total daily sucrose and percentage of energy from simple carbohydrates are higher in patients with bipolar disorder compared to those without bipolar disorder. Patients with bipolar disorder consume greater amounts of sweetened drinks and are less physically active when compared to the general population (54). In addition, socio-economic status and income may restrict dietary choices to less expensive simple carbohydrates. Family of origin dietary habits may also influence a patient's diet.

Phenomenology of psychiatric symptoms

Phenomenology of depressive symptoms may contribute to the development of obesity, potentially leading to insulin resistance and T2DM. Patients with bipolar disorder spend half of their lives in a depressed state, and for those with atypical features (hypersomnia, hyperphagia, and psychomotor retardation) increased caloric intake and decreased energy expenditure can lead to weight gain and potentially insulin resistance and T2DM.

Patients with bipolar disorder have disordered sleep, not only during depressive and manic episodes, but also when euthymic (55). This may be at least in part mediated by the abnormalities in cortisol seen in patients with bipolar disorder (even when euthymic). Sleep restriction has been associated with a reduction in insulin sensitivity, with a lack of adequate compensatory insulin release, increasing diabetic risk. A recent meta-analysis showed that difficulty initiating sleep had a combined relative risk of incident diabetes of 1.57 (1.25–1.97), while for difficulty maintaining sleep the relative risk was even larger 1.84 (1.39–2.43) (56). Therefore, sleep abnormalities associated with all phases of bipolar illness may be contributing to the higher rates of T2DM seen in bipolar patients.

Adverse effects of bipolar pharmacotherapy on glucose metabolism

Adverse metabolic effects of commonly used mood-stabilizing medications are of great concern in clinical practice. These can result from significant weight gain associated with medication-induced cravings for simple carbohydrates and high-fat foods and/or sedation leading to reduced activity level (57). For decades, these were problems sometimes associated with lithium, valproic acid, and the use of tricyclic antidepressants, but focus on these issues intensified with the growing use of second-generation antipsychotic (SGA) agents, several of which are associated with marked weight gain, glucose dysregulation, and dyslipidemia. SGAs are now being used routinely in the management of patients with bipolar disorder, depression, and schizophrenia.

Antipsychotic agents

It has been proposed that antipsychotics may contribute to the development of T2DM by several possible mechanisms. Antipsychotic drugs act on dopaminergic, serotonergic, and histaminergic receptors to varying degrees (58,59). Serotonin and histamine have both been associated with weight gain, and serotonin and dopamine are involved in central regulation of blood glucose. Antagonism of serotonin $5HT_{2A/C}$ receptors is associated with regulation of feeding and weight control, potentially resulting in weight gain and insulin resistance, particularly in those with a genetic predisposition to developing diabetes. However, not all of the antipsychotic drugs that induce hyperglycemia are potent 5HT receptor antagonists, and weight gain is not a prerequisite to the development of T2DM.

It may be that genetic predisposition plays a role in the risk of developing T2DM when taking antipsychotics. The serotonin $5HT_{2C}$ and $5HT_{2A}$ receptor coding gene polymorphisms, HTR_{2C} and HTR_{2A}, appear to be associated with the occurrence of metabolic abnormalities in patients taking olanzapine or clozapine (60,61). The HTR_{2C} polymorphism has been associated with antipsychotic-induced weight gain. Depending on the haplotype,

patients with HTR_{2A} polymorphisms can be more or less likely to develop metabolic abnormalities like C-peptide and insulin elevations during clozapine and olanzapine treatment. In addition, polymorphisms of the peroxisome proliferator-activated receptor (PPAR) have been implicated in olanzapine-induced weight gain (62). Significant differences between olanzapine pre-treatment and post-treatment BMI and weight change in the Pro12Ala polymorphism of PPAR-gamma2 have been found, suggesting that the genetic variance of patients might be considered in antipsychotic medication selection in the future.

Selected antipsychotics appear to inhibit glucose transport by blocking the glucose transporter protein in cell membranes (63,64) and may possibly represent another mechanism involved in the increased risk of hyperglycemia with antipsychotics. Drug-induced insulin resistance via a direct stimulating effect of antipsychotics on pancreatic beta cells resulting in increased insulin secretion is yet another possibility (58,65).

The other important concern with antipsychotics is their effect on glucose control in those with established diabetes. Ideally, the care of patients with diabetes includes avoiding, when possible, the use of medications that can promote hyperglycemia. While there have been fewer studies assessing the effect of antipsychotics on glucose control in patients with diabetes, the data available indicate a deleterious effect. Lipscombe et al. conducted a nested case-control study of people with diabetes older than 65 years who started an antipsychotic agent (66). They found that the rate of emergency visits and hospitalizations due to hyperglycemia was significantly increased overall (odds ratio 1.50; 95% CI 1.29–1.74) and was especially high during the initial course of treatment. Whether diabetes was treated with an insulin regimen or oral antihyperglycemics, the risk for hyperglycemia-related hospitalizations increased 15-fold upon starting an antipsychotic. The estimated annual number needed to harm for patients with diabetes taking insulin, oral antihyperglycemics, and no diabetes medications were 21, 42, and 37, respectively. It is unlikely that the initiation of an antipsychotic is the only factor contributing to this risk; for example, dementia-related behavioral problems leading to non-adherence with antihyperglycemics could account for both the antipsychotic therapy and the hyperglycemic event (67). Regardless of the cause, clinicians caring for elderly patients with diabetes should be wary of the high risk of hyperglycemia when antipsychotics are initiated. Until data are available for younger patients with diabetes, a similar increase in monitoring for hyperglycemia is recommended when starting an antipsychotic.

While SGAs have been associated with hyperglycemia, the attributable risk of new-onset T2DM (including cases of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic non-ketotic syndrome (HHNS)) has been difficult to quantify due to differences among study populations, methodological limitations, and inconsistent findings (58,65). The propensity for metabolic complications appears to vary among antipsychotics, with clozapine and olanzapine having a greater association than aripiprazole, quetiapine, risperidone, or ziprasidone (68,69). First-generation antipsychotic drugs are less of a concern regarding metabolic adverse effects, with the notable exception of the low-potency agents, in particular chlorpromazine (68).

Cases of DKA and HHNS in patients not previously known to be diabetic, including several fatalities, have been associated with initiation of treatment with SGAs (70,71). All SGAs have been implicated in these cases, and their relative infrequency makes it difficult to determine whether one agent increases risk for diabetic emergencies more than another. Most convincing are those cases with early onset of glucose complications that reverse upon antipsychotic discontinuation. However, in many cases patient-specific risk factors likely have played a role in promoting severe glucose dysregulation. These include obesity and possibly illness-related cortisol elevation. It is reassuring that very few, if any, cases of DKA and HHNS have been reported in clinical trials with the SGAs, implying that improved screening for hyperglycemia may limit this risk (70).

Some studies have failed to report increases in glycosylated hemoglobin (HbA_{1c}) levels with SGA treatment (72), and the majority of patients who develop T2DM on SGAs already have risk factors for diabetes (71). Estimated risk of T2DM among patients treated with antipsychotics also appears to be influenced by study design. Gianfrancesco et al. found that when a more rigorous design was used in large database studies, only clozapine and olanzapine (and not quetiapine, risperidone, ziprasidone, or first-generation antipsychotics) were associated with diabetes risk that was significantly greater than that in untreated patients (73).

Lithium

The effect of classic mood stabilizers (including lithium and valproic acid) on glucose regulation has not been as extensively studied compared to antipsychotics, despite the well-established increased risk of T2DM in bipolar disorder (4,6,7). Lithium's potential stimulating effect on appetite leading to weight gain is well established, but its effect on glucose and insulin appears variable and complex. Some findings suggest impaired glucose tolerance via insulin resistance, and others indicate that lithium promotes an antihyperglycemic effect by increasing glycogenesis, either through insulin sensitization or enzyme activation of hepatic glycogenesis (74,75). Two cases, one of developing diabetes transiently when lithium was stopped and the other of hyperglycemia correlated with lithium levels, exemplify the complexity of lithium's effect on diabetes risk (76,77). However, in a 6-year follow-up study that observed a total of almost 500 patient-years of lithium exposure, no change in mean fasting plasma glucose (FPG) was observed despite increases in age and weight, suggesting that new-onset diabetes is unlikely to be caused by lithium therapy (78), and, in fact, lithium's insulin-like effects may even stave off the development of T2DM. It should be kept in mind that while diabetes may not be a primary concern with lithium, lithium can cause hypothyroidism that, if under-treated, can lead to weight gain and potentially insulin resistance and T2DM.

Anticonvulsant mood stabilizers

Bilo and Meo concluded that bipolar patients taking valproic acid may have a higher risk of polycystic ovarian syndrome (PCOS) compared to those treated with other mood stabilizers; however, the prevalence of PCOS in valproic acid-treated bipolar patients is not much higher than that reported in the general population and is significantly lower than what is reported for those treated for epilepsy (see Bilo and Meo for review (79)). PCOS is associated with hyperinsulinemia and increased risk of insulin resistance and T2DM, particularly in those who gain weight. However, the literature linking valproic acid use *directly* to diabetes is scant with only a few studies documenting increased fasting serum insulin levels (indicating insulin resistance), and there is very little evidence that carbamazepine causes or worsens diabetes after several decades of extensive clinical use (80,81). As with lithium, weight gain with valproic acid and, to a lesser extent, with carbamazepine is common (82) and could lead to insulin resistance and therefore to T2DM. Lamotrigine, another commonly used mood-stabilizing anticonvulsant, is not associated with weight gain and has not been linked to diabetes (83).

Has the role of psychotropic medications been exaggerated?

Some argue that T2DM in bipolar patients is largely caused by the medications used to treat their psychiatric disorder; however, rates of T2DM in patients with bipolar disorder exceeded that of the general population well before the widespread use of these drugs. Evidence of abnormal glucose metabolism in psychiatric patients has been accumulating since the early twentieth century, with numerous reports of increased rates of impaired glucose tolerance, insulin resistance, and frank diabetes in bipolar disorder and schizophrenia, prior to the existence of antipsychotic treatment (84,85). Drug-induced metabolic changes cannot explain the abnormal response to glucose (sustained hyperglycemia after glucose challenge, prolonged hyper-insulinemia, and elevated lactic acid levels in the blood) in treatment-naive patients (84). Additionally, the co-occurrence of obesity that can increase insulin resistance and risk of T2DM in bipolar disorder was noted long before the advent of current mood-stabilizing medications (86). In a more recent study by Regenold et al., patients 50–74 years of age with bipolar disorder type I had a higher prevalence of T2DM compared to the general United States population (50% versus 10%, respectively) after controlling for age, race, and gender. In this study, the bipolar patients with diabetes did not have significantly greater use of psychotropic medications associated with new onset of T2DM, and psychiatric diagnosis and BMI were the only significant independent predictors of a diagnosis of T2DM (4). Bipolar disorder itself appears to confer an increased risk of T2DM, as has been established in schizophrenia.

Adverse effect of diabetes on bipolar disorder outcomes

Cardiovascular risk factors, such as diabetes, appear to herald greater psychiatric symptom severity. Previous investigations have shown increased psychiatric morbidity in patients with bipolar disorder and co-morbid T2DM (a more chronic course, with increased rapid cycling, increased number of psychiatric admissions to hospital) and increased mortality (30% shortened life expectancy) (87,88). Patients with bipolar disorder and co-morbid T2DM also have a poorer quality of life and overall functioning compared to those without diabetes. They have lower scores on the Global Assessment of Functioning Scale and are more frequently on disability for their bipolar disorder. Hypertension occurs more frequently, and BMI is increased on average (87). We have also found an inverse correlation between BMI and response to lithium, the gold standard treatment for bipolar disorder. Subjects achieving complete remission of symptoms on lithium showed significantly lower BMI (in the healthy range), compared to those in the obese range who had no clinical response to lithium (53). Kemp et al. found that for every 1-unit increase in BMI, the likelihood of response to any bipolar treatment decreased by 7.5%, and the likelihood of remission decreased by 7.3% (89). Therefore, co-morbid obesity, insulin resistance, and T2DM may contribute to bipolar treatment refractoriness. This raises the intriguing possibility that identifying and treating underlying abnormalities in glucose metabolism may improve bipolar treatment response and may be one approach to improving refractory bipolar illness. In a pilot study by Rasgon et al., rosiglitazone was added to treatment as usual for depression in 12 insulin-resistant patients (90). The eight patients who completed the 12-week trial exhibited significant improvement in depression, as measured by the Hamilton Depression Rating Scale and the Clinical Global Impression scale, with moderate effect sizes. Kemp et al., found that over an 8-week period of adjunctive treatment with pioglitazone for acute bipolar depression, bipolar patients with insulin resistance ($n = 15$) had clinically significant reductions in both clinician- and patient-rated assessments of depression severity (91). This suggests that insulin-sensitizing agents may be useful in the treatment of depressive disorders in patients with depression and insulin resistance. More research in this area is needed.

Adverse effect of mood disorders on diabetes outcomes

While there are no studies examining the effects of bipolar disorder specifically on diabetes outcomes, there are a number of studies looking at the effects of depression. Bipolar patients spend half of their lives in a depressed state, so one might infer that the effects of bipolar depression on diabetes outcomes would approximate those of unipolar depression. Cortisol abnormalities associated with depressive states contribute to hyperglycemia, making glycemic control in diabetic patients difficult (92). Lustman et al. have shown that remission of depression was associated with a reduction in HbA_{1c} levels in diabetic patients (93). Co-morbid depression in diabetes was also associated with increased medical symptom burden (94), more frequent ICU admissions (95), and increased mortality compared to those with diabetes alone (96). Depression makes it more difficult to initiate and maintain healthy behavior changes and is an important risk factor for poor patient adherence to medications (97). Lin et al. found that co-morbid depression was associated with poorer self-care (adherence to diet, exercise, antihyperglycemic medications, and smoking cessation recommendations), while preventive care of diabetes was similar among depressed and non-depressed patients in this study (98). Diabetic patients with co-morbid depression had a significantly higher risk of developing diabetic complications such as retinopathy, nephropathy, foot ulcers, dementia (92,99–102), and clinically significant microvascular and macrovascular complications, even after adjusting for diabetes severity and self-care activities (103).

Coexisting baseline major depression in diabetic patients was significantly associated with all-cause mortality (hazard ratio 2.26; 95% CI 1.79–2.85) compared to those without depression (104). Major depression at baseline was associated with a 2.95-fold greater risk of mortality among diabetic patients with stage five chronic renal disease (105), and a persistent 2-fold increased risk of mortality at 5 years in patients with their first diabetic foot ulcer (106). There appears to be a complex interrelationship between mood and glycemic control, with each disorder affecting the morbidity and mortality of the other.

Disparity in diabetes care between patients with and without bipolar disorder

The rate of diabetes and other modifiable risk factors (including obesity, smoking, hypertension, and dyslipidemia) and cardiovascular mortality in patients with bipolar disorder is estimated to be more than doubled (2). These patients should be closely followed by their primary care physicians; however, data suggest that this is not the case. Several studies indicate that the standard of diabetes care is lower for people with diabetes and bipolar disorder (12,107,108). A large observational study ($n > 300{,}000$) of the US Veterans Affairs diabetes population found that glycemic and lipemic control was poorer in people with psychiatric disorders, especially those with psychosis, bipolar disorder, substance use disorders, and personality disorders (107). Those with a psychiatric diagnosis were less likely to have HbA_{1c} and LDL cholesterol

tests, eye examinations, or any standard diabetes monitoring in the past year compared to those with no psychiatric diagnosis.

A recent Danish study reiterated the findings of earlier investigations showing increased mortality due to somatic, chronic diseases among people with bipolar disorder. The co-occurrence of bipolar disorder conferred a higher risk for developing diabetes and related end-organ damage, moderate to severe renal disease, cerebrovascular disease, and congestive heart failure. The overall risk for 'natural' deaths (due to 19 somatic diseases) was 2.5–4 times higher in women and men with bipolar disorder, implying under-treatment of chronic medical disorders, including diabetes (109).

Why does this gap exist between increased need and decreased provision of medical care? Patient, physician, and systems factors are likely involved; nonetheless, improved quality of care appears to make a difference. One randomized trial of medical care management in psychiatrically ill patients in the community showed an association between improvement in the quality of care and reduction in estimated cardiovascular risk (110). Patients were randomized to either medical intervention or care as usual. At 1 year, the rates of indicated preventive medical services (e.g. physical exam, screening, education, and vaccinations) were 59% in the intervention group and 22% in the usual care group. The estimated 10-year risk for developing cardiovascular disease was reduced (baseline 7.8%, final 6.9%) compared to the usual care group (baseline 8.2%, final 9.8%), indicating that improvement in diabetes care could decrease morbidity and mortality in psychiatric patients.

T2DM risk reduction and management in patients with bipolar disorder

Prevention

Evidence-based measures that reduce T2DM risk include a healthy diet that is low in simple carbohydrates in conjunction with regular aerobic exercise, and should ideally be a component of every bipolar patient's care. Addressing sleep disturbance in bipolar disorder is also important, not only for decreasing risk of episodes of bipolar illness, but also for potentially decreasing the risk of insulin resistance and T2DM (See Table I).

Screening

The first step is to identify impaired glucose tolerance and occult T2DM in patients with bipolar disorder. It is important periodically to screen for diabetes by evaluating fasting plasma glucose (FPG) levels. For patients treated with antipsychotics long-term, a baseline FPG level, BMI, and fasting lipid panel should be established and rechecked periodically thereafter. We recommend repeating FPG tests at 3 and 6 months, then every 6 months for chlorpromazine, clozapine, and olanzapine therapy, and at 6 and 12 months, then every 12 months for other antipsychotics when used long-term (68). Due to the increased risk for T2DM in bipolar disorder, we recommend that FPG be assessed at least every 2–3 years regardless of pharmacotherapy. The frequency of surveillance should take into account such risk factors as family history of diabetes, significant weight gain, or the presence of other cardiovascular (CV) risk factors (dyslipidemia, hypertension, or evidence of CV or cerebrovascular disease). In addition, physicians and psychiatrists need to determine which patients may be at greater risk for insulin resistance or T2DM and other CV risk factors, as this is likely to inform decisions regarding choice of mood-stabilizing treatment.

Patients should also be informed about the symptoms of diabetes and prompted to see their physician immediately if symptoms occur. If a patient develops hyperglycemia or dyslipidemia believed to be the result of current bipolar disorder treatment, alternative treatment should be sought. If switching mood-stabilizing medication is not an option, then these metabolic abnormalities need to be treated.

Management of medication-induced weight gain/T2DM in bipolar patients

Prevention of antipsychotic-induced weight gain and T2DM can also be achieved through diet and exercise. In a prospective, comparative, open, naturalistic study, 110 patients with schizophrenia, schizoaffective disorder, and bipolar disorder were divided into active and non-active (control) groups with the aim of preventing antipsychotic-induced weight gain and associated co-morbidity over 18 months (111). In addition to the diet and exercise education received by both groups, the active group received a structured, supervised exercise program (exercising for 60 minutes twice weekly). Eighty-five percent of patients adhered to the program over the 18-month follow-up. After 18 months, the active group had statistically significant decreases in fasting plasma glucose, HbA_{1c}, BMI, waist circumference, triglycerides, LDL cholesterol, and a beneficial increase in HDL cholesterol. The control group who did not participate in the exercise program had statistically significant increases in BMI, waist circumference, triglycerides, and LDL cholesterol.

Beyond diet and exercise, metformin is being used increasingly as a weight maintenance strategy in patients taking antipsychotics long-term. A collection of relatively small, randomized trials has demonstrated that metformin is associated with weight loss in patients who have experienced weight gain due to treatment with antipsychotics (112). Praharaj et al. conducted a systematic review and meta-analysis of randomized controlled trials of metformin for the treatment of olanzapine-induced weight gain and found the weighted mean difference for body weight was 5.02 kg lower with metformin compared to placebo after 12 weeks (95% CI 3.93–6.10) (113). Preliminary data also showed that metformin can *prevent* weight gain linked to antipsychotics such as olanzapine, especially in treatment-naive patients (114). Other gains of treatment with metformin included reduced waist circumference and insulin resistance, as estimated by the Homeostasis Model of Assessment–Insulin Resistance (115).

Whether or not the early, long-term use of metformin can also delay or prevent the onset of T2DM in bipolar patients or patients taking antipsychotics has not been sufficiently investigated. A meta-analysis of three randomized trials (203 participants taking antipsychotics for 12–16 weeks' duration) using metformin for weight control failed to show any significant effect (RR = 0.3 (a 70% relative risk reduction), $P = 0.13$) (115). The Diabetes Prevention Program trial randomized patients to metformin, intensive life-style modification, or standard life-style, to determine which strategy best prevented the onset of T2DM. It demonstrated that metformin could reduce the rate of new-onset T2DM over 3 years from 28.9% in the standard life-style placebo group to 21.7% ($P < 0.001$) in the metformin group (116). While this trial did not specifically assess people taking antipsychotic agents or those with bipolar disorder, we recommend that treatment with metformin be considered for those at imminent risk of developing diabetes (e.g. those with impaired FPG) or for those wishing to use it as a weight control intervention, or otherwise at high risk of CV morbidity and mortality.

While metformin can increase insulin sensitivity and possibly prevent or delay the onset of T2DM, topiramate is limited to potential weight loss, and data supporting topiramate in the prevention and treatment of SGA-induced weight gain are limited. As

Table I. Type 2 diabetes risk reduction and management in patients with bipolar disorder.

Prevention:
Diet low in simple carbohydrates
Regular aerobic exercise
Address sleep disturbance if present
Screening/surveillance:
Fasting plasma glucose (FPG) every 2–3 years, regardless of bipolar treatment
FPG at 3 and 6 months, then every 6 months if on chlorpromazine, clozapine, or olanzapine
FPG at 6 and 12 months, then every 12 months if on other antipsychotic
Management of medication-induced weight gain or type 2 diabetes:
Diet and exercise (see Prevention)
Consider switching antipsychotic to another mood stabilizer, if possible
If unable to switch, consider adding metformin
Treatment of type 2 diabetes in patients with bipolar disorder:
Non-pharmacologic
Diet and exercise (see Prevention)
Weight and glycemic control
Decrease cardiovascular risk factors
Ensure vaccinations are up to date
Pharmacologic
Consider metformin as first-line treatment if non-pharmacologic measures ineffective
Consider glucagon-like peptidase-1 receptor agonists/analogues or dipeptidyl peptidase-4 inhibitors
Consider other oral antihyperglycemics
Consider insulin, if oral antihyperglycemics not effective

with metformin, topiramate may be effective in helping patients lose weight, but to a lesser degree. Topiramate is also associated with cognitive impairment and could be disadvantageous in patients who may already have cognitive deficits related to their bipolar disorder. Treatment of antipsychotic-induced weight gain with metformin is probably a better option (117), but more randomized placebo-controlled trials are needed.

Treatment of T2DM in patients with bipolar disorder

Non-pharmacologic treatment

Once T2DM has been identified in patients with bipolar disorder, the second step is to recognize the benefits of providing aggressive management and monitoring. Education and management strategies should begin with focusing on nutrition, exercise, weight and glycemic control, minimizing cardiometabolic risk factors, psychological aspects of diabetes, and other preventative strategies including vaccinations. In this regard, management of diabetes in patients with bipolar disorder does not differ from those who do not have bipolar disorder.

In addition to the benefits of better glycemic control, staving off insulin resistance, and helping patients maintain a healthy BMI, there may be further benefits from exercise for bipolar patients. Exercise may also improve mood and prevent exacerbation of depressive symptoms over time (118). Patients with bipolar disorder who regularly walked for exercise reported lower scores on depression and anxiety symptom scales compared to those who did not walk (119). Further, studies of patients with bipolar disorder have found that regular exercise (walking 30 minutes 4 times per week) may have an important impact on an individual's perception of, and response to, stressful life events and decreased physiologic reaction to stress (118). Studies have found that exercise increases gene expression of brain-derived neurotrophic factor (BDNF). Although the exact mechanism is unknown, BDNF promotes proliferation and differentiation of neural stem cells in the hippocampus and enhances survival of these new neurons. Exercise-induced neurogenesis may enhance cognitive functioning, allowing greater capacity and flexibility to deal with stress, or may directly decrease the physiologic burden associated with repeated adaptations to stress (i.e. may decrease allostatic load), which could protect against further mood episodes (120).

Although not studied specifically in bipolar disorder, the neurocognitive-enhancing effects of aerobic exercise have been demonstrated in patients with schizophrenia as well as controls (121). There is a documented array of persisting neurocognitive deficits in patients with bipolar disorder, and physical exercise may be a viable neurocognitive-enhancing adjunctive treatment for these patients, warranting further study. Further, there is a consistent and growing literature reporting memory impairment and other cognitive dysfunction not only among diabetics in the general population, but among those who are insulin-resistant as well (122,123). Reduction in hippocampal volumes have been reported in diabetic and insulin-resistant patients, as well as in bipolar patients. Whether the neurocognitive dysfunction associated with bipolar disorder and insulin resistance/T2DM is additive is unknown; nonetheless, patients with bipolar disorder and abnormalities in glucose metabolism have ample reason to benefit from exercise.

Pharmacologic treatment

There are very few studies evaluating the use of antihyperglycemic medications specifically in the bipolar population. Current classes of medications used for the treatment of T2DM include biguanides (i.e. metformin), sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists and analogues. For most of these agents, the effect on glucose regulation has been well delineated (124). However, in a recent update on the effectiveness and safety of medications for the treatment of T2DM, Bennett and colleagues critically reviewed 166 publications and concluded that there is very little known about the effects of the majority of antihyperglycemics on the long-term complications of diabetes (125).

Sulphonylureas are known effectively to reduce HbA_{1c}, but they are associated with early treatment failure (i.e. loss of glycemic control) and a high rate of hypoglycemic events. They are also associated with weight gain and therefore not the best choice for the large proportion of bipolar patients who are overweight or obese. In addition, long-term studies have demonstrated little or no value in preventing diabetes complications when comparing diet to sulphonylurea use over time (126,127). Thiazolidinediones

would appear, on the surface, to be the perfect choice for bipolar patients with diabetes: they act intracellularly, at a level that might address the proposed shared pathophysiology underlying the two disorders. Unfortunately, the benefits of thiazolidinediones have been offset by important CV risks. Rosiglitazone is associated with an increased risk of heart failure and myocardial infarction, and pioglitazone with heart failure (128). This is an important consideration for any patient, in particular bipolar patients already at increased risk of CV morbidity and mortality. Metformin appears to have the best benefit-to-risk ratio. It is associated with weight loss, improves insulin resistance, and does not risk hypoglycemia. It has been shown to reduce diabetes complications more so than sulphonylureas and diet therapy, particularly in overweight patients, and its noted risk of lactic acidosis in at-risk patients appears to have been overstated (129,130).

Assessment of the risks and benefits of newer therapies is based on short-term studies and surrogate end-points and is therefore limited. DPP-4 inhibitors and GLP-1 receptor agonists and analogues have garnered interest based on their HbA_{1c} benefits, low risk for hypoglycemia, and effect on weight (especially GLP-1 agents). For these reasons, the newer agents may be of particular benefit in bipolar patients, although these agents have not been specifically studied in populations with mood disorders.

Conclusion

In general, patients with bipolar disorder are more likely to have T2DM, and the relationship appears to be one of more than unrelated co-morbidity. The two disorders may have common pathophysiologic origins and may share common genetic links and epigenetic processes. Medications used to treat bipolar disorder may further contribute to the high rates of T2DM in this population. Bipolar patients with co-morbid T2DM have a more severe course of bipolar illness and are more refractory to treatment for their bipolar disorder. Their T2DM often remains undiagnosed or under-treated. Control of their diabetes is poorer, and the rate of diabetes complications is greater compared to diabetics without bipolar disorder. As a result, bipolar patients with T2DM have significantly higher CV morbidity and mortality.

While it appears that treating mood disorders improves glycemic control, there remain intriguing questions, like whether identifying and treating co-morbid insulin resistance/T2DM might actually improve bipolar symptoms or treatment response while simultaneously improving CV risk. More research is needed to address such questions.

Finally, psychiatrists need to take a leading role in monitoring for metabolic abnormalities and working collaboratively with physicians when treatment of diabetes is necessary. Physicians need to be aware of the increased risk of diabetes and CV disease in patients with bipolar disorder. Treating co-morbid metabolic disorders and minimizing CV risk factors, including diabetes, is critical in reducing overall mortality and improving the quality of life of patients with bipolar disorder.

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