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Cardiometabolic Health in Bipolar Disorder

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Although bipolar disorder is characterized by adverse effects on mood and social functioning, it is also associated with poor physical health. Some of the most prevalent comorbidities affecting individuals with bipolar disorder include those of a cardiometabolic nature, such as obesity, insulin resistance, and cardiovascular disease.^{1,2} In addition to detracting from physical wellbeing, there is growing awareness that comorbid medical conditions in people with bipolar disorder contribute to poorer psychiatric treatment outcomes and are associated with more severe mood symptoms.^{3–5} These comorbid conditions may arise from overlapping biological pathways that promote the development of both mood dysregulation and altered metabolism. In this article, the scope of cardiometabolic health concerns in bipolar disorder will be reviewed, including the prevalence of modifiable risk factors, pathophysiological correlates linking metabolic dysregulation and mood, and potential genetic vulnerabilities that contribute to the development of cardiometabolic illness and mood disorders. Novel treatment approaches that target improvement of metabolic health as a means of improving mood, cognition, and other psychiatric symptoms will also be discussed.

CARDIOMETABOLIC HEALTH IN BIPOLAR DISORDER

Although bipolar disorder is characterized by adverse effects on mood and social functioning, it is also associated with poor physical health. Some of the most prevalent comorbidities affecting individuals with bipolar disorder include those of a cardiometabolic nature, such as obesity, insulin resistance, and cardiovascular disease.^{1,2} In addition to detracting from physical wellbeing, there is growing awareness that comorbid medical conditions in people with bipolar disorder contribute to poorer psychiatric treatment outcomes and are associated with more severe mood symptoms.³⁻⁵ These comorbid conditions may arise from overlapping biological pathways that promote the development of both mood dysregulation and altered metabolism. In this article, the scope of cardiometabolic health concerns in bipolar disorder will be reviewed, including the prevalence of modifiable risk factors, pathophysiological correlates linking metabolic dysregulation and mood, and potential genetic vulnerabilities that contribute to the development of cardiometabolic illness and mood disorders. Novel treatment approaches that target improvement of metabolic health as a means of improving mood, cognition, and other psychiatric symptoms will also be discussed.

Metabolic Syndrome and Premature Mortality

The majority of US and international surveys have documented a higher than expected prevalence of metabolic syndrome in individuals with bipolar disorder, often occurring at a rate double that found in the general population.⁶ The metabolic syndrome predisposes affected individuals to an earlier mortality and increases the risk for heart disease and type 2 diabetes (DM-2). According to one of the most highly referenced definitions of metabolic syndrome, the components include abdominal adiposity, hypertension, impaired fasting glucose, low HDL cholesterol, and hypertriglyceridemia.⁷ Insulin resistance is believed to be the underlying pathophysiologic process that unifies these various metabolic risk factors. Although originally thought to predominantly affect individuals with psychotic disorders, the metabolic syndrome has been shown to occur at an equivalent rate in bipolar disorder as in schizophrenia.⁸ In the majority of bipolar disorder studies, each component of the metabolic syndrome is generally abnormal, with increased waist circumference as the most consistently reported abnormality.⁶

Given the well-documented association between metabolic syndrome and increased cardiac mortality, it is not surprising that people with bipolar disorder die earlier in comparison with the general population. After adjusting for demographic factors, one naturalistic study found a significant risk of excess mortality in association with psychiatric illness, with over 95% of deaths attributed to medical rather than unnatural causes, such as suicide.⁹ Although the widespread use of weight-promoting mood stabilizers and atypical antipsychotics may contribute to the obesity epidemic, they cannot be wholly blamed for the increase in premature mortality, as early studies have shown an increase in premature deaths even among those not receiving pharmacological treatment.¹⁰ Rather, a combination of factors appears to collectively perpetuate cardiometabolic risk. These include poor lifestyle choices (ie, cigarette smoking), lack of health insurance coverage or access to preventive medicine services, and the core mood disorder symptoms of decreased energy and anhedonia which

may lead to a sedentary activity level and decreased focus on self-care. The cumulative burden of manic symptoms has also been identified as a contributor to increased cardiovascular mortality in bipolar I versus bipolar II disorder.¹¹ After controlling for age, gender, baseline cardiovascular risk, and treatment exposure, the higher burden of lifetime manic symptoms (as opposed to depressive symptoms) explained the greater increase in cardiovascular mortality in those with the bipolar I subtype.¹¹

Associations between Mood and Metabolic Health

Obesity, in particular, has been correlated with adverse clinical outcomes. Obese individuals with bipolar disorder suffer from more subthreshold anxiety disorders than non-obese individuals; they also experience an increased lifetime number of depressive and manic episodes.^{3,5} During maintenance therapy, obese individuals relapse more quickly into new mood episodes and have a poorer response to lithium treatment.^{3,12} Increased abdominal obesity has also been associated with a lower rate of improvement in manic symptoms.¹³

From the standpoint of general medical comorbidity, the number of organ systems affected by medical illness has been positively correlated with depression severity.⁵ However, in rapid-cycling patients receiving the combination of lithium and valproate, only illnesses of the endocrine/metabolic system were inversely correlated with remission from depression.⁴ A lower rate of response and remission to the combination of lithium and valproate has been incrementally associated with elevations in body mass index (BMI).⁴

Brain morphology also appears differentially affected in obese individuals with bipolar disorder. In first-onset mania, increased BMI was significantly associated with decreased white matter volume and temporal lobe volume.¹⁴ Such regions are areas of known vulnerability in early-onset cases and may explain some of the clinical associations linking obesity with a more complex bipolar illness trajectory.¹⁴ Another explanation that potentially accounts for greater bipolar illness severity includes increased secretion of proinflammatory cytokines from visceral fat stores.¹⁵ Inflammatory markers have been correlated with greater depression severity and may mediate the development of mood symptoms.¹⁶

Overlapping Pathophysiology

Drug treatment outcomes in the treatment of bipolar disorders, including inter-individual differences in antipsychotic-induced weight gain, can be influenced by a variety of environmental (ie, nutrition, co-administered drugs) and genetic factors. Many previous pharmacogenetic studies have focused on variants in candidate genes or gene pathways believed to influence the absorption, distribution, metabolism and elimination of drugs and their targets (ie, pharmacokinetics) or mediate their mechanisms of actions by interactions with receptors or transporters and downstream second messengers (ie, pharmacodynamics).¹⁷ These studies have identified several promising genes that may contribute to antipsychotic-induced weight gain.¹⁸ As an example, Reynolds and colleagues identified that patients with the 759T variant allele of the 5-HT_{2C} receptor gene polymorphism (-759 T/C, rs3813929) gained significantly less weight than patients without this allele.¹⁹

Despite the large number of published pharmacogenetic studies in psychiatry, the promise of personalized medicine has remained unfulfilled. It is notable that genetic variants have yet to be confirmed as a predictive factor for antipsychotic-induced weight gain, since the initial significant findings have not been consistently confirmed in replication studies. Ambiguous pharmacogenetic study findings are not unusual for genetic analyses of complex genetic diseases.²⁰ Many factors can contribute to variability in association studies. Among them, small sample sizes lead to low statistical power, with a concomitant increased rate of both false-positive and false-negative results and subsequent difficulty in replicating or refuting previous findings. Still, further large-scale studies are warranted.

Although the exact pathophysiology responsible for mood dysregulation in bipolar disorder is uncertain and likely involves complex heterogeneous mechanisms, several biological substrates contribute to cardiometabolic risk and appear involved in mood regulation. For example, individuals with bipolar disorder commonly show disruption of the hypothalamic-pituitary-adrenal axis (HPA-axis), resulting in elevated levels of cortisol or glucocorticoid resistance.²¹ Hypercortisolemia is associated with obesity and disruption of gluco-regulatory mechanisms that lead to hyper-insulinemia and insulin resistance.¹⁵

Mood symptoms may also be the consequence of inflammatory overactivation or an imbalance between pro- and anti-inflammatory cytokines. Elevated concentrations of IL-6, tumor necrosis factor-alpha, and C-reactive protein have been frequently reported in both manic and depressed phases of bipolar disorder.¹⁶ Illness behaviors induced by pro-inflammatory cytokines often resemble depression, including anhedonia, anorexia, sleep disruptions, and decreased self-care. Inflammatory cytokines are also elevated in obesity and DM-2, mediating the relationship between cardiovascular disease and insulin resistance.²²

Alterations in hormones directly produced by adipose tissue have likewise been tied to bipolar disorder, suggesting a novel role for adipokines in the regulation of mood.²³ Leptin, an adipokine well known for its function in the control of energy homeostasis, acts as a satiety signal to decrease food intake.²³ Low levels of leptin have been associated with depressive behaviors in animal models and humans, thus insufficiency or resistance to leptin may contribute to both obesity and depression.²⁴

In contrast to leptin, adiponectin is an adipokine that promotes insulin sensitivity. Adiponectin levels are lower in mood disorder patients, a finding that may be specific to depression and not accounted for by somatic factors such as coronary heart disease and metabolic disorders.²⁵ Reduction of adiponectin has been reported in prospective studies to increase the risk for DM-2 and cardiovascular disease.²⁶

Oxidative stress also represents an overlapping factor relevant to the pathogenesis of mood disorders and insulin resistance. Vulnerable to the effects of oxidative stress, when exposed to reactive oxygen species the brain may endure DNA damage, ultimately resulting in cell death and the manifestation of depression.²⁷ Pancreatic beta-cells that produce insulin also have very low intrinsic levels of antioxidant proteins, making them susceptible to oxidative damage. In turn, these oxidative effects result in progression of pancreatic beta-cell dysfunction that leads to DM-2.²⁸

Taken together, inflammation, adipose-derived hormones, glucocorticoid signaling, and excitotoxicity all appear to contribute to cardiometabolic risk, resulting in downstream effects on central nervous system function including the development of depressive symptoms. Some researchers have described the physiologic toll produced by these adaptations as “allostatic load”.²⁹ The cumulative effect of allostatic load may leave individuals with bipolar disorder more vulnerable to cardiometabolic illnesses and vice versa.³⁰

Finally, candidate gene and genome-wide association studies have identified many genetic risk factors for bipolar disorder or cardiometabolic conditions. A small number of overlapping genes have emerged that appear to increase susceptibility to both bipolar disorder and metabolic syndrome. For example, the TSPAN8 gene, which encodes a tetraspanin protein involved in organizing cellular receptors and signaling, represents a susceptibility locus for both DM-2 and bipolar disorder in genome-wide association studies.^{31,32} The nonsynonymous genetic variant (rs6265: Val66Met) located within the brain-derived neurotrophic factor gene was found to have strong association with BMI;³³ a meta-analysis also found significant evidence for an association between the same Val-66Met polymorphism and bipolar disorder susceptibility.³⁴ Although these points of commonality are intriguing and suggest genetic and pathophysiologic overlap between cardiometabolic illnesses and bipolar disorder, further large-scale studies are warranted to elucidate the relevant genetic variants that act as mutual risk factors.

Antipsychotics and Metabolic Risk

While atypical antipsychotic drugs can be helpful in treating bipolar disorder, they are known to be associated with elevated risk of hyperglycemia and DM-2.³⁵ A consensus statement encouraged clinicians to monitor all patients who were taking atypical antipsychotics, including the documentation of physical measurements such as body mass index (BMI), blood pressure and waist circumference, along with collection of fasting glucose and lipids.³⁶

When measuring the parameters of metabolic syndrome, clinicians may consider calculating the ratio of triglycerides to HDL cholesterol (Trig/HDL) obtained from a fasting lipid profile. The Trig/HDL ratio is a simple, readily available measure that can be used as a surrogate to identify patients who are more likely to be insulin resistant and have a higher proportion of atherogenic small LDL particles.³⁷ In addition to the recommended monitoring, comprehensive care of individuals with bipolar disorder should also assess medical and behavioral factors that may influence cardio-metabolic risk. This includes screening for the presence of comorbid eating disorders, nicotine use, and alcohol consumption; discussing exercise habits and strategies to improve physical activity; and assessing for medical factors affecting mood and metabolism, such as abnormal thyroid levels or vitamin D deficiency.³⁸

Targeting Metabolic Health to Improve Mental Health

Recent publications have highlighted treatment approaches that may reduce metabolic risk in people with bipolar disorder.³⁸ Emerging lines of research have focused on addressing

physical health as a novel means of improving mental health outcomes. For instance, programs that integrate medical care into community mental health settings have been found to not only reduce risk of cardiovascular disease but also improve mood and general well-being. These programs are typically managed by a clinician who provides medical care or helps to coordinate care between psychiatrists, primary care physicians, and other medical specialists. Preliminary evidence also suggests that integrated psychosocial programs that combine exercise and dietary interventions along with cognitive behavioral therapy to improve self-efficacy may decrease medical burden and depressive symptoms.³⁹

Building upon overlapping pathophysiology, other investigations have targeted insulin or insulin resistance as a pathway to improve mood and cognition. Insulin is a regulatory peptide that plays critical roles in physiologic processes such as neuroplasticity, neuroprotection, and facilitation of memory.⁴⁰ In animal models, intranasal insulin treatment has been shown to reduce diabetes-related cerebral atrophy and preserve memory.⁴¹ In humans, administration of intranasal insulin to patients with amnesic mild cognitive impairment or Alzheimer disease resulted in improved delayed memory and functional ability.⁴²

Insulin-sensitizing treatments, including the thiazolidinedione class of anti-diabetic medications, have been shown to induce antidepressant-like effects in animal models.⁴³ Preliminary evidence has demonstrated a reduction in depression severity when open-label rosiglitazone or pioglitazone were administered to depressed individuals with features of insulin resistance.^{44,45} Pioglitazone treatment also resulted in significantly reduced triglyceride and cholesterol levels, potentially representing an antidepressant treatment that can simultaneously reduce cardiometabolic risk.

Also promising are agents intended to reduce oxidative stress, such as N-acetylcysteine. Superoxide generation is a cause of glucose-induced pancreatic beta-cell dysfunction and is a key contributor to allostatic load. Acting to replenish brain glutathione, open-label N-acetylcysteine administration has been preliminarily associated with a reduction in depression severity during the maintenance treatment of bipolar disorder.⁴⁶

CONCLUSION

Cardiometabolic health concerns in patients with bipolar disorder are anticipated to remain an expanding clinical priority. Not only do these conditions lead to premature mortality, but they appear associated with more severe mood episodes and poorer response to mood-stabilizing therapies. The bi-directional link between bipolar disorder and cardiometabolic disease is likely due to shared pathophysiology, including inflammatory activation, abnormal glucocorticoid signaling, and excitotoxicity. Monitoring for cardiometabolic risk factors should be a routine part of treatment, especially in those with underlying obesity or those being treated with atypical antipsychotics. In the future, genetic variants may help to identify those at greatest risk for developing DM-2 or antipsychotic-induced weight gain. Emerging therapies for bipolar disorder are intended to improve psychiatric health by targeting and better integrating physical health treatments.

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Biography

Dr. Kemp, within the past 12 months, has acted as a consultant to Bristol-Myers Squibb and Janssen and has served on the speaker's bureau for AstraZeneca and Pfizer. His spouse has been a minor shareholder of Abbott and Sanofi within the past 12 months. Dr. Fan has no disclosures to report.

EDUCATIONAL OBJECTIVES

1. Describe the shared pathophysiology that contributes to the development of both bipolar disorder and cardiometabolic disease.
2. Recognize genetic variants that increase risk for antipsychotic-induced weight gain and type-2 diabetes.
3. Describe treatment strategies that target physical or cardiometabolic health as a means of improving psychiatric outcomes.