Cardiovascular Disease and Bipolar Disorder: Risk and Clinical Implications

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Bipolar disorder is a multisystemic disorder[1] affecting not only thymic regulation but also immunologic function[2] and cardiovascular status.[3] Although many psychotropic medications clearly exacerbate medical risk,[4] bipolar disorder itself appears to confer risk for cardiovascular disease independent of treatments used to manage the disorder.[5] In this article, we review the current understanding of the reciprocal relationships between medical burden and bipolar disorder and discuss the implications for the care of individuals who are likely to require treatment for more than just their psychiatric symptoms.

Cardiovascular Risk and Bipolar Disorder

The association between cardiovascular risk and bipolar disorder is well established and comparable to the association between cardiovascular risk and schizophrenia.[6] Individuals with bipolar disorder have levels of cardiovascular risk at least as high as—and some studies suggest higher than—those of individuals who suffer from unipolar depression.[7] When affected by cardiovascular diseases, those with bipolar disorder experience them at a much younger age than do nonpsychiatric controls.[7,8] Below, we briefly define cardiovascular risk factors and highlight several important studies examining cardiovascular risk in bipolar disorder.

Identified cardiovascular risk factors for both psychiatric and nonpsychiatric populations include metabolic factors[9] such as obesity, hypertension, dyslipidemia, and insulin resistance, as well as behavioral risk factors[10] such as tobacco use, physical inactivity, and saturated fat intake. These risk factors are interrelated and reciprocal and often co-occur in a single individual. Biological processes such as proinflammatory pathways[11] may predispose individuals to multiple metabolic risk factors (elevated triglycerides, low high-density lipoproteins, hypertension, etc). Behaviors such as physical inactivity confer risk directly by contributing to high-risk metabolic parameters and indirectly by contributing to intermediate processes such as increased adiposity.[12] For individuals with bipolar disorder, cardiovascular risk is complicated by the disorder itself, which causes intermittent periods of decreased physical activity due to depression and often requires treatments that may themselves cause weight gain. Further, there is evidence to suggest shared common etiopathologic processes such as inflammation associated with both bipolar disorder and cardiovascular disease.[1] It is not surprising, therefore, that elevated cardiovascular risk is associated with bipolar disorder.

In a study of 441 individuals enrolled in the Bipolar Disorder Center for Pennsylvanians (BDCP), 40% met criteria for the metabolic syndrome,[13] a clustering of cardiovascular risk factors including insulin resistance, abdominal obesity, mild dyslipidemia, and hypertension, which appears to identify substantial risk for cardiovascular disease beyond any single risk factor.[14] In a group of patients treated with second-generation antipsychotics, over 43% of individuals with bipolar disorder met criteria for the metabolic syndrome, which was comparable to the percentage in a group of individuals with schizophrenia (43.2% vs 45.9%, $P = .71$).[15] Among individuals with schizophrenia, prevalence rates of the metabolic syndrome are estimated to be 1.8 to 2.5 times greater than the rates among those without psychiatric disorders,[16] a finding that has been duplicated in those with bipolar disorder.[6]

Elevated cardiovascular risk translates to elevated rates of cardiovascular disease. A group of predominantly (90%) male individuals with bipolar disorder receiving care through the Veterans Administration (VA) experienced high rates of hypertension (35%), diabetes (17%), ischemic heart disease (11%), congestive heart failure (3%), peripheral vascular disease (3%), and stroke (2%). Those with cardiovascular comorbidities in the bipolar disorder sample were roughly 4–7 years younger than a national VA comparison group.[8] Similarly, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study showed that individuals with bipolar I disorder were 4.95 times more likely to experience cardiovascular disease (including angina, arteriosclerosis, and myocardial infarction) and 2.38 times more likely to experience hypertension compared to controls.[7] Like the VA study, the NESARC study also showed that the mean age of individuals with bipolar disorder who had hypertension and cardiovascular disease was much younger than that of controls with cardiovascular diseases, with onset of illnesses being approximately 13 years earlier than in control populations.[7]

Increased and Premature Mortality

Individuals with bipolar disorder are at risk for increased and premature mortality compared to the general population, with mortality rates approximately twice as high as the expected rates. Studies show that premature mortality in bipolar disorder is best explained by deaths related to general medical illnesses, in particular, cardiovascular disease. A review[17] of 17 studies comparing mortality rates in individuals with bipolar disorder to those in age- and sex-matched controls without psychiatric illness found that cardiovascular diseases were the most consistent cause of excess mortality in the bipolar disorder population. In a large Swedish study,[18] standardized mortality rates (SMRs; number of observed deaths divided by the number of expected deaths) for cardiovascular-related causes among individuals with bipolar disorder were 1.9 and 2.6 for males and females, respectively. In a prospective Swiss study[19] in which individuals were followed for over 30 years, SMRs for patients with bipolar disorder were 1.4 for all nonsuicide causes (including neoplasm, accidents, and other causes) and 1.8 for cardiovascular-related causes. These studies clearly demonstrate that individuals with bipolar disorder are dying earlier than those without psychiatric disorders and that cardiovascular diseases are the primary culprits driving premature mortality.

Relationship Among Cardiovascular Risk, Obesity, and Psychiatric Outcomes

Elevated cardiovascular risk is associated with an increase in morbidity and mortality related to cardiovascular diseases themselves. However, it appears that for individuals with bipolar

disorder, having comorbid medical risk factors is associated with worse psychiatric outcomes as well. In the BDCP study, individuals meeting criteria for obesity and the metabolic syndrome were more likely to report a lifetime history of suicide attempts.[20] In a maintenance treatment study[21] of individuals with bipolar I disorder, obesity was associated with a shorter time to recurrence of bipolar illness. Obesity was also associated with decreased likelihood of remission among individuals treated with lithium or valproate for rapid-cycling bipolar disorder.[22] Canadian investigators showed an inverse relationship between clinical outcomes and body mass index (BMI) in bipolar disorder such that those with a higher BMI had a more chronic course of illness and were more likely to be on disability. Conversely, those who achieved complete remission of symptoms on lithium showed significantly lower BMI.[23]

In one study,[21] although there were no statistically significant differences reported in lithium levels between the obese and nonobese groups, among the relatively small subset of patients treated with flexibly dosed valproate, there was a statistically significant difference in valproate levels between the groups, with the nonobese group having higher levels (although all mean levels were within the therapeutic range). This finding raises the possibility that obesity, a common side effect of mood stabilizers, may be an important cause of medication nonadherence, which may, in turn, contribute to poor outcomes.

Therefore, cardiovascular risk—in particular obesity—appears to be associated with poorer response to psychiatric treatment. Obesity is of special concern to psychiatrists, as it constitutes a specific cardiovascular risk factor,[24] predicts worse psychiatric outcomes,[20–22] is a consequence of treatment with atypical antipsychotic medications,[25] and leads to other cardiometabolic sequelae including insulin resistance,[26] dyslipidemia,[27] and hypertension.[28]

Etiology of Cardiovascular Risk

Although medications used to treat bipolar disorder, such as second-generation antipsychotics, exacerbate cardiovascular risk by contributing to weight gain and abnormalities in lipid and glucose metabolism,[4] they do not entirely explain liability to cardiovascular disease. Cardiovascular risk in individuals with psychiatric illness is probably multifactorial. It may be related, in part, to an increased prevalence of traditional cardiovascular risk factors such as smoking, obesity, and diabetes *as well as* exposure to psychotropic medication. Alternatively, it may be related to an unrecognized increased prevalence of other risk factors such as inflammation,[11] high-risk lipoproteins, and abnormal metabolism (ie, insulin resistance/metabolic syndrome).[29] The pathophysiology of cardiovascular disease associated with bipolar disorder may differ from that in the general population through pathways that expose patients to mechanisms that may play roles in the genesis and/or maintenance of both disease states.

Elevated levels of circulating inflammatory markers such as proinflammatory cytokines have been linked to a variety of cardiovascular and general health outcomes including cardiovascular events, diabetes onset, and all-cause mortality.[30–33] These markers have been shown to be elevated in individuals with unipolar depression[34] as well as bipolar disorder.[35,36] Youth with bipolar disorder have been found to have elevations in peripheral inflammatory markers,[37] suggesting that this process is intrinsic to the disease itself rather than simply a consequence of years of treatment, although there is no question that exposure to psychotropic medications confers significant and additive risk as well.[25]

Conclusions and Treatment Implications

Few would dispute that vigorous efforts to manage cardiovascular risk factors are warranted—regardless of psychiatric diagnosis—in accordance with recommendations from the American Heart Association and the American Diabetes Association.[38,39] Thus, treating psychiatrists are urged to collaborate with primary care physicians to facilitate appropriate cardiovascular risk management and treatment for their patients with bipolar disorder. However, in individuals with bipolar disorder, management of cardiovascular risk and disease are most likely complicated by severity of illness (ie, earlier onset and higher rates of death related to cardiovascular factors) and by psychiatric factors that interfere with optimal cardiovascular disease management (ie, poor insight, low motivation, low energy). Therefore, specialized models of care that seamlessly integrate medical treatment with psychiatric care are being developed to address the comprehensive needs of this patient population.

We compared 20 patients with bipolar I disorder and medical comorbidities treated with an integrated risk reduction intervention (IRRI) to 20 patients who received psychiatric care only.[40] Over the 1-year study period, there were 2 psychiatric hospitalizations in the IRRI sample versus 4 in the psychiatric care–alone sample. Equally important is that there were no medical hospitalizations in the IRRI group, compared with 2 hospitalizations in the psychiatric care–alone group. Larger studies are needed to demonstrate that good management of medical illness is associated with improved psychiatric outcomes and vice versa, but this preliminary study suggests that an integrated approach to management of medical and psychiatric care may be preferable to traditional "stand alone" medical and psychiatric services for this population. Improved recognition of the pan-systemic nature of bipolar disorder with concomitant decreases in the fragmentation of mental and physical health care services delivery may constitute important pathways to reducing both psychiatric and cardiovascular burden. Better research in this area will ultimately clarify optimal strategies to improve both cardiovascular and psychiatric outcomes for individuals with bipolar disorder.

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