The search for mediators of vascular mortality with mania

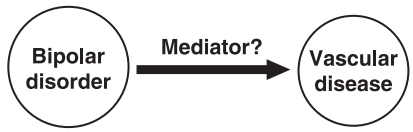
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In a recent issue of Revista Brasileira de Psiquiatria, Chiarani et al. reported a unique investigation to identify hypothesized state or trait biomarkers for cardiovascular risk in bipolar disorder.[1] Large, epidemiological studies have consistently found an increased risk of cardiovascular mortality in bipolar disorder, approximately twice that expected on the basis of age and gender.[2] This risk is higher in bipolar I disorder, which conveys a greater burden of manic and hypomanic symptomatology, than in bipolar II disorder.[3] The time course by which vasculopathy develops in bipolar disorder is unclear, although cross-sectional data suggest the excess risk is acquired over the long-term course of illness in those with a more persistent symptomatology.[4] Cardiovascular mortality and endothelial dysfunction are related to manic symptom burden in a dose-dependent fashion, as demonstrated in a well-characterized prospective cohort,[3,5] though specific mediators that may explain this apparent state-related risk remain elusive.

To identify state-related differences in potential mediators, Chiarani et al. followed individuals with mania to a period of euthymia, and utilized a separate control group to identify trait differences.[1] No biomarkers associated with cardiovascular risk were associated with mania, apart from reductions in ferritin, an acute phase reactant. It is not clear how to interpret this finding. If not a false positive finding or the result of historical/instrument bias, it could reflect differences in diet, though low ferritin seems unlikely to explain any state-dependent effects on vascular disease risk.

Assuming the relationship between mania and vascular disease is temporal and cannot be entirely explained by confounding or adverse effects of treatments, there are a few explanations for the generally negative findings in the Chiarani et al.[1] study: type II error, a non-causal relationship between mania and vascular disease, or the causal pathway for mania-related risk involves other mediators (Figure 1). One potential non-causal explanation involves shared genetic risk: that is, some genes which predispose an individual to mania may also convey risk for vascular disease. The brain, heart, blood vessels, and pancreatic islets of Langerhans all contain excitable cells, and any genetic abnormalities that impair function of excitable cells could increase the risk of neuropsychiatric conditions, vascular disease, and diabetes mellitus. Additionally, there are several biologically plausible mechanisms by which disturbances of mood could induce physiological or behavioral changes that impact vascular disease risk. Putative physiological changes include, but are not limited to, autonomic nervous system dysfunction, dysregulation of the hypothalamic-pituitary-adrenal axis, oxidative stress, and pro-inflammatory cytokines. Behavioral influences may involve adherence to treatment, diet, physical activity, and tobacco or other drug use.

1. Bipolar disorder leads to vascular disease



2. Relationship between bipolar disorder and vascular disease due to shared risk factor

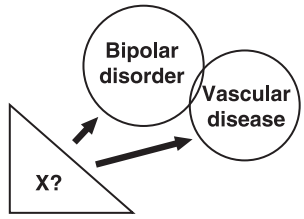


Figure 1 Causal pathways to explain the relationship between bipolar disorder and vascular disease

Although cases of late onset or post-stroke mania may challenge this rule, bipolar disorder can generally be considered to precede vascular disease. Barring confounding, this temporal relationship could be explained by a causal pathway leading from bipolar disorder to vascular disease, mediated by unknown variables presumably influenced by mood state. As shown in Figure 1, a non-causal relationship between bipolar disorder and vascular disease could also demonstrate temporality through a shared risk factor with causal pathways of varying durations for lag times from exposure to outcome.

Future research to investigate the most relevant mechanisms by which bipolar disorder and mood states may impact cardiovascular risk is required. The study design used by Chiarani et al.[1] may serve as a template to survey state- and trait-dependent variables which may mediate risk of vascular disease. It is further important to mind the authors' concluding message: integrated medical and psychiatric care is needed to clinically address the medical comorbidities frequently present in those with bipolar disorder.

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Disclosure

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Cardiovascular risk in bipolar disorder: beyond medication effects and lifestyle factors

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Bipolar disorder (BD) is associated with substantial functional impairment, high health care costs, and premature mortality. The World Health Organization (WHO) ranks BD in the top 10 causes of global disability and premature mortality.[1] The morbidity, mortality, and personal suffering associated with BD are not simply the result of psychiatric symptoms, but are also the consequence of a wide range of comorbid medical disorders. The study from Gomes et al. complements a wide array of worldwide studies pointing to the high burden of cardiovascular disease (CVD) risk factors in BD in developed countries. Globally, over 80% of patients with BD have some degree of medical comorbidity,[2,3] with the vast majority suffering or dying from CVD. The toll of the high rate of medical burden for patients with BD is not only premature mortality, but also worse prognosis with less favorable response to treatment, lower psychosocial functioning, higher rates of unemployment and, thus, a higher overall higher societal cost.[4,5] Nevertheless, one aspect that has not yet entirely permeated the culture of health policy makers is the notion that patients with BD have even higher rates of medical comorbidities than those reported for other severe psychiatric disorders such as schizophrenia. In fact, in most health care settings, integrating psychiatric care with medical care and prevention is still a challenge.

Most implicated in the rampant increase in CVD risk in BD are the widespread use of atypical antipsychotics and the sedentary lifestyle and high-fat diet that prevail in most developed countries. Yet some lines of evidence suggest that cultural and environmental factors account for only part of the problem. This new report by Gomes et al. provides a snapshot of BD-associated CVD risk in developing countries and contributes to the evidence that medical burden – and, more specifically, cardiovascular burden – tends to be higher among patients with BD than in the surrounding general population in a wide variety of geographical contexts, across urban and rural settings, widely different cultural and lifestyle characteristics, and different prescribing practices.

We now have enough evidence to lay the groundwork for two main future developments: on one hand, clinicians and administrators need to develop ways to better integrate prevention and treatment of cardiovascular risk factors and diseases in mental health care settings. On the other, research into the root causes of cardiovascular risk in persons with serious mental illness needs to undertake a more critical approach and uncover those pathways to CVD in BD that go beyond lifestyle factors and medications.

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N-acetylcysteine in the treatment of skin-picking disorder

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N-acetylcysteine (NAC) is a precursor to the amino acid cysteine, a modulator of the glutamatergic system. Thus,