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Elevated Cardiovascular Risk in Patients With Bipolar Disorder: When Does It Start and Where Does It Lead?

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A growing number of studies have demonstrated that rates of obesity, diabetes, dyslipidemia, hypertension, smoking, and metabolic syndrome, all serious cardiovascular disease risk factors, as well as standardized mortality rates, are between 1.5 and 3 times greater in adults with bipolar disorder compared to the general population.[1–19] Differences and similarities in prevalence rates between studies and compared to those observed in patients with schizophrenia are influenced, in part, by patient demographics, but also by the proportion of patients who receive conventional mood stabilizers, (medium to high metabolic risk) antipsychotics, or both.[13] At the same time, studies have also shown that obesity and metabolic syndrome are associated with greater psychopathology, comorbidities, suicidality, and relapse and rehospitalization rates in adults with bipolar disorder.[16–21] However, the reasons for both the greater prevalence rates and the associations between cardiovascular risk and symptomatic as well as functional outcomes in bipolar disorder are complex and not well understood. Open questions relate to the underlying mechanisms, the strength and directionality of cause-and-effect relationships, and the degree to which a better understanding of these questions could inform interventions that would be able to minimize and/or prevent the medical and psychiatric burden in bipolar disorder.

As has been discussed for schizophrenia, it is possible that bipolar disorder and cardiovascular disease/risk states share genetic links.[22] In addition, both conditions are also affected by shared environmental and behavioral factors, such as stress and early adversity, socioeconomic drift, subthreshold symptomatology, and unhealthy lifestyle behaviors. On the other hand, the onset and/or cumulative effects of bipolar illness could also affect diet and exercise behavior as well as biological pathways involved in appetite regulation, energy homeostasis, and metabolism, increasing long-term cardiovascular risk.[19,23] Moreover, most treatments used for bipolar disorder have been associated with varying degrees of weight gain and abnormalities in glucose and lipid metabolism.[22,24] Finally, recent studies suggest that patients with severe mental disorders, such as bipolar illness, are likely to receive substandard medical care because of reduced rates of health monitoring, illness recognition, follow-up, and/or adherence to medical advice,[23,25–28] limiting the beneficial effect of secondary prevention efforts that have been successful in the general population.

In view of this complexity of very likely additive and interactional factors that link bipolar disorder with cardiovascular disease risk, the study of children and adolescents with bipolar disorders provides a unique opportunity to attempt dissecting some of the driving forces involved in the accumulation of cardiometabolic risk, premature cardiovascular morbidity, poor psychiatric outcomes, and increased mortality from medical and psychiatric conditions. This opportunity stems from the fact that children and adolescents are closer to the onset of the illness, opening a window for the research of illness-related effects relatively independent of multiple mood episodes and illness chronicity; the fact that informants are usually available, which makes the study of past experiences (trauma, treatment history, illness course) and of lifestyle factors more reliable; and the fact that the effects of the illness or of initiated treatments are less obscured by years of the effects of prior treatments that are most often unrecorded and unknown. Given these opportunities to disentangle some of the threads that tie bipolar disorder to the web of cardiometabolic disorders, it is surprising that very little information exists about the weight status and metabolic health of first-episode and drug-naive patients with bipolar disorders.

The study by Goldstein and colleagues[29] published in this month's issue of the *Journal* is the first attempt to

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search for the origins of increased cardiovascular risk associated with bipolar disorder in childhood and to look for associated illness variables that could provide leads for the identification of etiopathologically relevant environmental and biological mechanisms. As part of the Course and Outcome of Bipolar Illness in Youth (COBY) study, the authors investigated 348 children and adolescents aged 7 to 17 years who met DSM-IV criteria for bipolar I or bipolar II disorder or study-operationalized criteria for bipolar disorder not otherwise specified. In this article, the authors focus on the baseline weight status of their sample based on self- and parent-reported height and weight, using age- and sex-adjusted body mass index thresholds that appropriately account for developmental differences. The authors report a prevalence rate of obese or overweight status of 42%, i.e., 16.5% obese and 25.5% overweight, which is modestly greater compared to rates in the general pediatric population during a similar time period in the United States.[30] In addition, Goldstein et al.[29] found in logistic regression analyses the following significant predictors of overweight/obese status: younger age, nonwhite race, lifetime physical abuse, substance use disorders, psychiatric hospitalizations, and exposure to ≥ 2 medication classes associated with weight gain.

The authors openly discuss the limitations of this study, which include the lack of objective height and weight measures in youth undergoing dynamic body composition changes as part of their regular development; lack of detailed information about prebaseline mood state and pharmacologic treatment history; lack of knowledge about premorbid/pretreatment weight status, which was most likely heterogeneous; absence of information about cardiovascular family history, metabolic indices, diet, and exercise; and lack of data about the timing of obesity in relationship to the associated variables that emerged in the logistic regression analyses. On the other hand, clear strengths of this study include the focus on this timely and underresearched topic; use of developmentally appropriate thresholds to define overweight and obese weight status; and the careful diagnostic characterization of this sample with bipolar spectrum disorder, a set of diagnoses that have received much recent attention and scrutiny regarding the validity of the construct, the way research groups arrive at the diagnosis, and the increase in prescribed treatments that follow the making of such a diagnosis.[31–34]

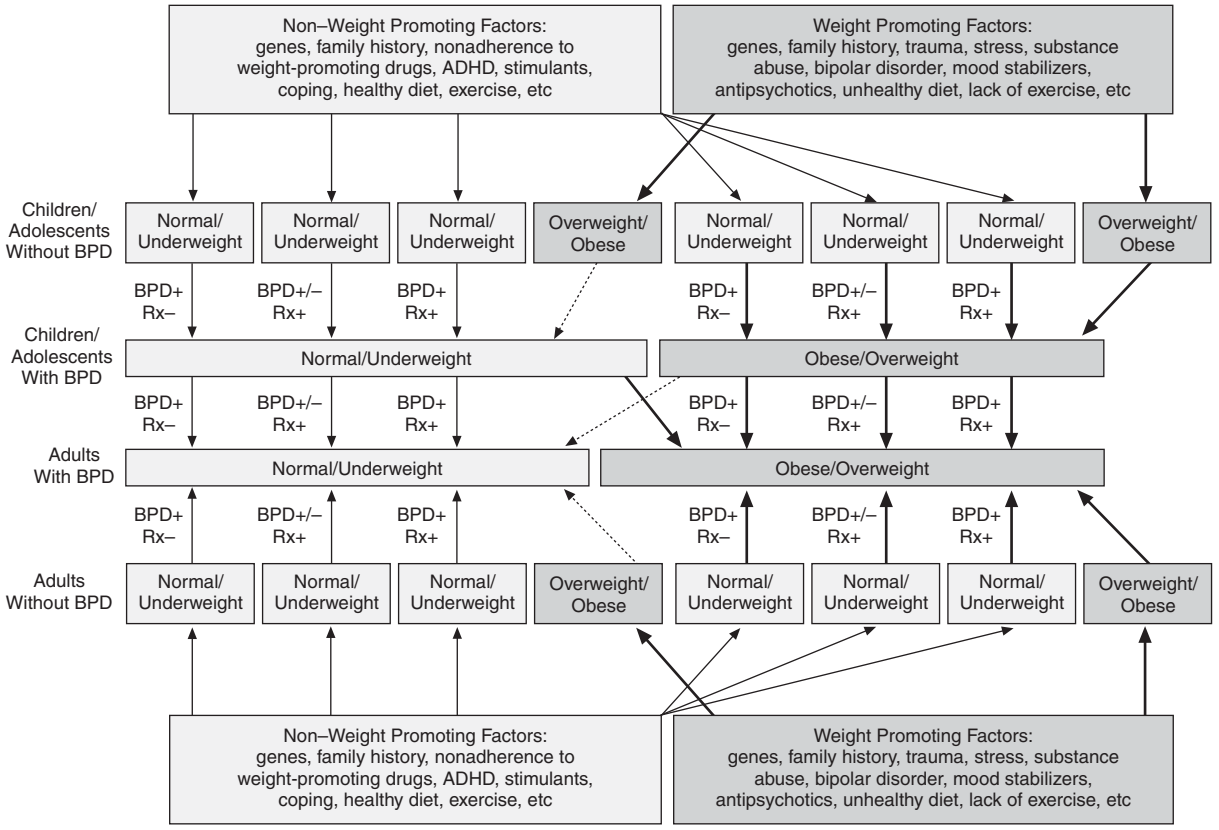
Within the limitations outlined above, the collected data by Goldstein and colleagues[29] are informative and hypothesis-generating. Importantly, they can help the design of much-needed further studies.

In addition to direct and objective measures of height and weight, future studies should include additional metabolic and risk markers for cardiovascular illness, both cross-sectionally and longitudinally. Moreover, studies should also attempt to examine the effects of the duration and type of treatments, duration and type of mood states, and the relationship to family history of cardiometabolic risk factors, changes in parental body mass index, and existing mental or physical illness, as well as of healthy lifestyle behaviors at baseline and over time. Finally, the mere documentation of risk and protective factors will not suffice. Rather, mechanisms for adverse cardiometabolic outcomes need to be better understood to allow for the development of targeted interventions that either cause less cardiometabolic abnormalities or can ameliorate or, even, reverse and correct cardiometabolic risk factors in this very vulnerable population that is at the beginning of developing a sense of physical, psychological, and social self.

However, to understand the mechanisms and directionality of mediators and moderators of interacting cardiovascular and psychiatric illness factors, it is important to take into consideration the different pathways into overweight/obesity that have already occurred when assessing a patient with bipolar disorder, either in childhood or in adulthood. As depicted in Figure 1, the patients assessed by Goldstein et al.[29] are very likely quite heterogeneous in that some of them were premorbidly overweight/obese, while others developed the abnormal weight status only after the onset of bipolar illness (i.e., during periods of depression, mania, and/or euthymia) and yet others transitioned into overweight/obesity only after receiving weight-inducing treatments. The weight-inducing effects of treatments used in bipolar disorder may be observed more readily in youth,[35] either due to a greater biological sensitivity or due to the fact that earlier treatment effects are larger as they are unconfounded by prior weight gain.[36,37] The problem of differences in baseline weight status and in the duration and type of weight-altering treatments is exemplified by the lack of an association between illness severity and overweight/obese status in the study by Goldstein et al.,[29] which is in contrast to findings in adults.[20–22] One could argue that patients who are more overweight/obese required more and longer treatment, which should have put them at greater risk for overweight/obesity.

Moreover, the association of overweight/obesity with younger age at onset found by Goldstein et al.[29] could be related to both younger age at onset and longer duration of illness, which could lead to both an earlier onset and longer duration of psychotropic treatment and be associated with greater illness severity, all leading to a greater likelihood of being/becoming overweight/obese. On the other hand, though, patients who have an earlier onset of illness are also more likely to have attention-deficit/hyperactivity disorder and to have received stimulant treatment, which may have reduced their body weight prior to bipolar illness and mood stabilizer treatment,[38] mitigating against a signal of greater prevalence of overweight/obese status in patients with greater illness

Figure 1. Overweight and Obesity in Patients With Bipolar Disorder: Pathways to the Heterogeneity of the Phenotype[a]



[a]Dashed lines indicate that categorical transitions to healthier weight (and metabolic) status (i.e., obese to overweight, obese or overweight to normal weight, underweight to normal weight) need to be promoted. Solid black lines indicate that factors involved in the development and sustainment of abnormal weight (and metabolic) status need to be minimized.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BPD = bipolar disorder, BPD+ = effect of bipolar illness, BPD+/– = minimal duration/effect of bipolar illness, Rx+ = relevant/lengthy psychotropic treatment, Rx– = psychotropic treatment–naive.

severity and/or earlier illness onset. Thus, some patients may have gained significant amounts of weight that significantly increase their cardiovascular risk, but they may still be at normal weight because they had been underweight or at low normal weight due to premorbid attention-deficit/hyperactivity disorder (prevalence rate of 59% in the study by Goldstein et al.[29]) and/or prior or ongoing stimulant treatment.

Therefore, in addition to attempting to identify and follow treatment-naive patients with bipolar disorder, pediatric growth curves should be obtained to investigate the trajectories of body composition in relationship to illness and treatment onset. However, the mere assessment of temporality of potential risk factors in relationship to the onset of overweight/obesity will also not suffice, as the strength and directionality of effects may differ, or even reverse, depending on the developmental phase or the environment a child or adolescent is in when exposed to certain mediating factors. The time- and setting-dependent interaction between biological and environmental variables is a likely explanation for the disconnect between the positive association between substance use disorders and overweight/obese status found in youth[29] compared to the negative correlation observed in adults.[16] The positive association between increased caloric and substance use in youth points to shared biological mechanisms of dysregulated/increased consumptive behaviors, possibly related to common preexisting or negatively affected neurotransmitter pathways through early adverse life events, attempts at self-regulating ego-dystonic mood states during depression, or results of ego-syntonic risk-taking behaviors. On the other hand, the negative association between substance use disorders and obesity found in adults may be mediated by the strong correlation between substance abuse and medication nonadherence,[39,40] which may be a mediating factor that is even more relevant for weight/metabolic status, at least in subgroups of patients. This example highlights the possibility that changes in environmental control and increase in independence during late adolescence and adulthood interact with biological relationships, weakening their effects. This example also highlights the need for further

investigations of interactions between risk factors and mechanisms, as well as of phase or developmentally specific susceptibilities for the development and worsening of psychopathology and physical health.

In conclusion, the study by Goldstein et al.[29] is an important first step toward framing critical questions that can be tested by future studies and that are likely to inform and, thus, improve the treatment and preventive efforts regarding both the physical and psychiatric well-being of patients with bipolar disorders. Future studies should attempt to take into account the various influences and confounders discussed above by measuring as many of these variables as possible. The ultimate question raised by the results by Goldstein et al.,[29] however, is whether a better understanding of the overlapping and interacting trajectories to dysregulated mood and body composition/metabolic status in patients with bipolar disorder could help dissect the heterogeneous illness expressions and treatment responses, leading to the discovery of more targeted and individualized treatments for subgroups of these patients. Clearly, carefully conducted, prospective studies in children and adolescents with severe psychiatric disorders are likely to contribute to any advance that this line of research can offer. Until such data are available, however, clinicians ought to proactively monitor and promote not only psychiatric but also physical health in youth and adults with bipolar disorder. In children and adolescents, developmentally adjusted measures of body composition and metabolic parameters need to be used,[35,37] as the tracking of the simple body mass index and of metabolic measures and thresholds used in adults underestimates the degree of overweight, obesity, and adverse metabolic status in youth. This underestimation likely diminishes appropriate actions by clinicians, such as the more aggressive education about and promotion of healthy lifestyle behaviors and the timely alteration of treatments that lead to a negative effect on body weight and metabolic health in a given patient. In this sense, it is hoped that the article by Goldstein and colleagues[29] will raise the awareness of an important issue in the management of pediatric mood disorders, benefiting both research and clinical practice.

REFERENCES

1. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156(9):1417–1420
2. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord 2004;6(5):368–373
3. Ucok A, Polat A, Bozkurt O, et al. Cigarette smoking among patients with schizophrenia and bipolar disorders. Psychiatry Clin Neurosci 2004;58(4):434–437
4. Garcia-Portilla MP, Saiz PA, Benabarre A, et al. The prevalence of metabolic syndrome in patients with bipolar disorder. J Affect Disord 2008 Feb;106(1–2):197–201
5. Cardenas J, Frye MA, Marusak SL, et al. Modal subcomponents of metabolic syndrome in patients with bipolar disorder. J Affect Disord 2008 Feb;106(1–2):91–97
6. Birkenaes AB, Opjordsmoen S, Brunborg C, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry 2007 Jun;68(6):917–923
7. Yumru M, Savas HA, Kurt E, et al. Atypical antipsychotics related metabolic syndrome in bipolar patients. J Affect Disord 2007 Mar;98(3):247–252
8. van Winkel R, De Hert M, Van Eyck D, et al. Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. Bipolar Disord 2008 Mar;10(2):342–348
9. Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, et al. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Ann Clin Psychiatry 2008 Jul–Sep;20(3):131–137
10. Sicras A, Rejas J, Navarro R, et al. Metabolic syndrome in bipolar disorder: a cross-sectional assessment of a Health Management Organization database. Bipolar Disord 2008 Jul;10(5):607–616
11. van Winkel R, van Os J, Celic I, et al. Psychiatric diagnosis as an independent risk factor for metabolic disturbances: results from a comprehensive, naturalistic screening program. J Clin Psychiatry 2008;69(8):1319–1327
12. Salvi V, Albert U, Chiarle A, et al. Metabolic syndrome in Italian patients with bipolar disorder. Gen Hosp Psychiatry 2008 Jul–Aug;30(4):318–323
13. Correll CU, Frederickson AM, Kane JM, et al. Equally increased risk of metabolic syndrome in patients with bipolar disorder and schizophrenia receiving atypical antipsychotics. Bipolar Disord 2008;10:788–797
14. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58(9):844–850
15. McIntyre RS, McElroy SL, Konarski JZ, et al. Substance use disorders and overweight/obesity in bipolar I disorder: preliminary evidence for competing addictions. J Clin Psychiatry 2007;68(9):1352–1357
16. Wang PW, Sachs GS, Zarate CA, et al. Overweight and obesity in bipolar disorders. J Psychiatr Res 2006;40(8):762–764
17. Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry 2006;63(7):824–830
18. Fagiolini A, Frank E, Scott JA, et al. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005;7(5):424–430
19. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002;63(3):207–213
20. Fagiolini A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 2002;63(6):528–533
21. Fagiolini A, Kupfer DJ, Houck PR, et al. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 2003;160(1):112–117
22. Fagiolini A, Chengappa KN, Soreca I, et al. Bipolar disorder and the metabolic syndrome: causal factors, psychiatric outcomes and economic burden. CNS Drugs 2008;22(8):655–669
23. Kilbourne AM, Rofey DL, McCarthy JF, et al. Nutrition and exercise behavior among patients with bipolar disorder. Bipolar Disord 2007 Aug;9(5):443–452
24. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. J Clin Psychiatry 2006;67(suppl 9):25–30
25. Kilbourne AM, Post EP, Bauer MS, et al. Therapeutic drug and cardiovascular disease risk monitoring in patients with bipolar disorder. J Affect Disord 2007;102(1–3):145–151
26. Suppes T, McElroy SL, Hirschfeld R. Awareness of metabolic concerns and perceived impact of pharmacotherapy in patients with bipolar disorder: a survey of 500 US psychiatrists. Psychopharmacol Bull 2007;40(2):22–37; quiz 38–40
27. Druss BG, Bradford WD, Rosenheck RA, et al. Quality of medical care and excess mortality in older patients with mental disorders. Arch Gen Psychiatry 2001;58(6):565–572
28. Frayne SM, Halanych JH, Miller DR, et al. Disparities in diabetes care: impact of mental illness. Arch Intern Med 2005 Dec;165(22):2631–2638
29. Goldstein BI, Birmaher B, Axelson DA, et al. Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. J Clin Psychiatry 2008;69:1953–1959

30. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006 Apr;295(13): 1549–1555
31. Leibenluft E, Charney DS, Towbin KE, et al. Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003 Mar;160(3):430–437
32. Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry 2007;64(9):1032–1039
33. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004. Biol Psychiatry 2007 Jul;62(2):107–114
34. Holden C. Bipolar disorder: poles apart. Science 2008 Jul;321(5886): 193–195
35. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry 2006;45(7):771–791
36. Alvarez-Jiménez M, González-Blanch C, Crespo-Facorro B, et al. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs 2008;22(7): 547–562
37. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. J Am Acad Child Adolesc Psychiatry 2008;47(1):9–20
38. Faraone SV, Biederman J, Morley CP, et al. Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry 2008;47(9):994–1009
39. Sajatovic M, Valenstein M, Blow F, et al. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatr Serv 2007;58(6):855–863
40. Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord 2006 Jun;8(3):232–241

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