The Relevance of Body Mass Index in Bipolar Disorder

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Body mass index (BMI) is the most common metric used for the assessment of weight variation. Despite some criticisms of its validity as measure of increased risk of morbidity and mortality (1), there is vast consensus that BMI is an objective and relatively easy-to-collect phenotype that offers insights on a person's global health status. A U-shaped relationship has been described between BMI and mortality, not only for specific disorders, but also for the whole spectrum of causes (2). Not surprisingly, this epidemiologic figure also applies to severe psychiatric illnesses, such as bipolar disorder. Indeed, the prevalence of obesity is significantly higher (about 30%) among patients with bipolar disorder compared with healthy control subjects (3), and its presence substantially worsens the clinical course of the disorder (4). However, little is known about the long-term longitudinal relationship between pathological changes in BMI and bipolar disorder.

This gap in the literature has been filled by an epidemiological study by Najar et al., reported in this issue of the *Journal* (5). Using data from the Swedish National Quality Register for Bipolar Disorder (BipoläR) (for case subjects) and the Swedish Living Conditions Surveys (ULF) national survey (for control subjects), the authors analyzed the secular trends and distribution of BMI among patients with bipolar disorder and the general population over a 12-year period. Several important findings are reported. First, BMI was significantly higher among patients with bipolar disorder compared with control subjects, and this gap was more evident with increasing percentiles of BMI. This result acquires significance especially in the context of the clinical phenomenology of bipolar disorder, which is characterized by substantial heterogeneity (6). It is conceivable that stratification of patients with bipolar disorder by BMI could be of relevance in reducing this heterogeneity and facilitating personalized approaches to treatment as well as clinical and neurobiological research. This approach has proved effective in subgroups of patients with bipolar disorder who share specific clinical characteristics and distinct genetic signatures, such as early onset, mood-incongruent psychosis, and lithium response (7). The latter subgroup is of particular relevance. Lithium-responsive patients manifest distinct clinical characteristics that appear to represent the *core phenotype* of bipolar disorder (8). These include, among others, episodicity of the clinical course, a familial load for bipolar disorder, absence of rapid cycling, a later age at onset (8), and, according to a recent meta-analysis (9), lower BMI. Indeed, patients with bipolar disorder who achieve complete remission of symptoms on lithium show significantly lower BMI compared with nonresponders (10). This is also mediated by the effects of BMI on serum lithium levels (11). Thus, a lower BMI predicts a good response to lithium and could be used to guide the choice of treatment in patients with bipolar disorder.

The Najar et al. study did not report on the relationship between pharmacological treatment and BMI. One could only hypothesize that lithium-treated (and lithium-responsive) patients might have been in the lower percentiles of mean BMI and of its incremental secular trend, possibly confirming the relevance of this measure in the personalized management of bipolar disorder. At the same time, nonresponsive or non-lithium-treated patients could have manifested more severe presentations and been treated with other mood stabilizers, atypical antipsychotics, or a combination of both, all treatment strategies less neutral with respect to weight gain. In support of this view is evidence that bipolar disorder patients with higher BMI are at high risk of suicidal behavior and tend to present a more chronic course, a pattern of treatment resistance, and a worsening trajectory of core depressive symptoms (12).

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Another relevant finding concerns the identification of a secular trend showing that both cases and controls had a statistically significant increase in mean BMI per decade, but that this was substantially higher among patients with bipolar disorder. In addition, stratification by sex revealed that women had both a higher mean BMI and a greater time-dependent increment of BMI compared with men, with a more evident effect in the bipolar disorder group. This implies that BMI trends vary substantially over time according to illness status and sex and points to this measure as a possible moderator of the developmental trajectory of bipolar disorder. The Najar et al. study did not assess the same cohort longitudinally for the duration of the observation and therefore was unable to correlate prospectively changes in BMI with variation in affective morbidity. However, the higher BMI observed among women with bipolar disorder is consistent with novel data on high-risk populations (13). Indeed, Adepalli et al. (13) found that women at familial risk for major

mood disorders showed a rapid peripubertal increase in body weight, leading to significantly increased standardized BMI at age 12 and older compared with control subjects, independent of socioeconomic status, prematurity, or birth weight. This finding complements the Najar et al. finding in the adult population, providing a developmental perspective indicating that changes in BMI could predate the onset of mood disorders. In addition, it points to BMI as an important target for primary and secondary prevention of bipolar disorder. Modifications of diet, introduction of physical exercise, and promotion of a healthier lifestyle would decrease BMI, possibly reducing the risk of developing comorbid somatic conditions that could predispose to proinflammatory states and, in turn, increase the risk of bipolar disorder in susceptible populations. In addition, BMI is a proxy of metabolic alterations (insulin resistance or type 2 diabetes) that in bipolar disorder are associated with poorer outcomes, including nonresponse to lithium (14), and if targeted with specific treatments could lead to substantial psychopathological improvements (15). Indeed, Calkin et al. (15) showed that patients with treatment-resistant bipolar disorder and insulin resistance had substantial improvement in depressive symptoms once metformin had led to resolution of glucose dysmetabolism.

The lack of influence of diagnostic subtype (bipolar I vs. bipolar II disorder) on the secular trend of BMI should be interpreted taking into account the longitudinal course of the disorder. In fact, approximately three-quarters of the affective morbidity in bipolar disorder is depressive (16), and it is generally higher in patients with bipolar II disorder compared with those with bipolar I disorder. Further, bipolar depression is typically characterized by atypical presentations that include, among diverse symptoms, increased appetite and consequent weight gain. Thus, it could have been assumed that patients with bipolar II disorder would present a higher BMI compared with those with bipolar I disorder. Conversely, the opposite was demonstrated at the 50th BMI percentile, although with a non–statistically significant difference. Since the Najar et al. study captured the variation of BMI over time among diverse subjects whose data were collected periodically but was not strictly a longitudinal prospective study, patients with bipolar II disorder had point-prevalent but not cumulative depressive morbidity over the duration of the secular trend. This could have confounded the identification of an association between bipolar disorder subtype and higher BMI.

A final comment concerns the research implications of the Najar et al. findings. The higher BMI observed in this epidemiological study is in line with genetics (17) and neuroimaging (18). Indeed, shared genetic predisposition for bipolar disorder and BMI may underlie pathophysiological mechanisms involving the glucocorticoid-dependent modulation of expression of a novel noncoding transcript of the transcription factor 7-like 2 (TCF7L2) gene, a key modulator of bipolar disorder risk genes (17). In addition, higher BMI was associated with lower cortical thickness across the cerebral mantle, in regions also associated with bipolar disorder (18). Importantly, the higher the BMI in patients with bipolar disorder, the more pronounced were the brain alterations.

In sum, the secular trend of BMI in patients with bipolar disorder observed by Najar et al. highlights the relevance of BMI as measure of clinical outcome, making it an essential factor for personalized management of the disorder. Further research in large-scale registry data should explore the relationship of BMI with clusters of symptoms, depressive morbidity, and patterns of treatment response to increase clinical utility.

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