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Commentary

Recognizing the Extent of Overlap Between Bipolar Disorder and Anxiety Disorders

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The meta-analysis of prevalence of anxiety disorders among patients with bipolar disorder in this issue of *E-Biomedicine* (Nabavi et al., 2015) provides a timely summary of knowledge to date regarding this important co-occurrence of psychiatric conditions. The authors report that 43% of people with bipolar disorder have had at least one lifetime anxiety disorder. This figure is very similar to the 45% rate of people with bipolar disorder having had at least one lifetime anxiety disorder recently reported in a recent different meta-analysis, based on an only partially (less than half) overlapping set of studies (Pavlova et al., 2015).

Individuals with bipolar disorder commonly have had more than one lifetime anxiety disorder. Indeed, the sum of the lifetime prevalences reported by Nabavi and associates for the individual anxiety disorders (panic disorder, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder, specific phobia, obsessive compulsive disorder, and agoraphobia) was approximately twice as high (nearly 85%) as that for any anxiety disorder. Nabavi and associates' 43% meta-analytic lifetime prevalence rate of any anxiety disorder is slightly below the 48% mid-point between the lowest (17%) (Angst et al., 2013) and highest (79%) (Pini et al., 1997) lifetime prevalence rates reported in the individual studies reviewed, highlighting the substantial heterogeneity of anxiety disorder lifetime prevalence across samples. This important heterogeneity was evident despite only including studies that used the rigorous approach of using interview-based diagnosis for comorbid anxiety disorders. As such heterogeneity likely has meaningful relationships with not only neurobiology but also clinical outcomes, researchers and clinicians alike need to account for anxiety disorder comorbidity in their efforts to understand, diagnose, and treat patients with complicated bipolar disorders.

The very substantial percentage of bipolar disorder patients with a lifetime anxiety disorder has particularly profound clinical implications. Anxiety disorders and alcohol/substance use disorders commonly co-occur with one another and with mood disorders. Indeed, anxiety disorders and alcohol/substance use disorders constitute the two most commonly encountered comorbid conditions in people with bipolar disorder (Merikangas et al., 2007). As the authors point out, management of comorbid anxiety disorders in bipolar disorder patients with antidepressants and benzodiazepines may be limited by the risks of mood destabilization and exacerbation of substance use problems, respectively. Moreover, the utility of other medications, such as second-generation antipsychotics may be limited by inefficacy and/or adverse effects, whereas the utility of adjunctive psychotherapy may be limited by inefficacy, particularly in individuals challenged by more than one anxiety disorder in addition to bipolar disorder (Deckersbach et al., 2014).

Like many good studies, Nabavi and associates' article raises more questions than it answers. Prior studies have consistently reported associations in bipolar disorder patients between comorbid anxiety disorders and multiple unfavorable illness characteristics, including earlier bipolar disorder onset age, and increased suicidality, rate of substance use disorders, and mood episode severity and frequency, as well as treatment resistance. Teasing out how this multivariate "web of causality" of factors (that include comorbid anxiety disorders) mediates poorer outcomes could help inform prioritization of efforts to enhance prognosis in patients with bipolar disorder and comorbid anxiety disorders. In addition, Nabavi and associates' study (which focused on individuals with bipolar I disorder) did not address the important question of putative differential lifetime anxiety disorder comorbidity rates in people with bipolar I disorder compared to those with bipolar II disorder. Finally, Nabavi and associates' study did not address important questions regarding the degree to which co-occurring anxiety and bipolar disorders may be independent or inter-related problems.

Although meta-analysis of the clinical correlates of anxiety disorder comorbidity in bipolar disorder patients was beyond the scope of this paper, and as pointed out by the authors, may have substantial feasibility limitations; such information could importantly inform clinical efforts to mitigate the adverse effects of concurrent anxiety disorders in patients with bipolar disorder. Information regarding the impact of interventions focusing on relieving comorbid anxiety upon overall mood and anxiety disorder illness burden in individuals remains an important research priority.

Nevertheless, Nabavi and associates' study leaves both researchers and clinicians with a very clear take-home message – that the very common occurrence of anxiety disorders in people with bipolar disorder contributes in an important fashion to challenges faced by those striving to accurately assess neurobiology and diagnosis and to provide effective treatment for individuals struggling with both conditions.

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