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Bipolar II Disorder: Not So Sure It Is Time for Something New

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There are a lot of reasons to maintain the diagnosis of bipolar II disorder (BP II), even though I agree that some of the cutoff or boundary issues Dr. Gin Mahli and associates[1] raise are real and need improvement. There is a rich literature on BP II, and if BP II disappears, we will not know how future studies relate to the older ones. Also, if you cannot name it, you cannot study it. In contrast to Mahli et al.'s assertions, I would submit that a number of aspects of BP II illness differ from bipolar I disorder (BP I), as noted below. Patients with BP II have a lower rate of switching on antidepressants than those with BP I,[2,3] so in this and other respects, it has some clinical utility. Until recently, BP II patients were excluded from essentially all pharmacological studies, so a relative paucity of differences between BP II and BP I in drug response needs to be distinguished from a lack of sufficient data and study.

My recommendation is to be cautious about giving up the terminology for both scientific and clinical reasons. What I would suggest is keeping the clinically relevant severity distinction, hypomania is less severe than mania, but fixing the duration issues. I would be agnostic and data driven about duration and frequency cutoffs. Hypomania can break through for a matter of hours, days, weeks, or months, and as Mahli and colleagues suggest, these could be quantitated. The same is true for frequency of cycling, which can occur from 1 to many times per day (ultradian cycling), per week, per month, or per year.[4-6] If these duration and frequency modifiers are included, clinical and neurobiological correlates can be studied and found if they are there. If they do not appear upon further study, one can always collapse the categories, but the opposite is not true. Once diagnoses disappear and data are not collected on them, they cannot be reincarnated.

If one changes the diagnostic categories, it should be for a good reason. It is not clear what would be gained by dropping BP II, and much could be lost. I suggest, instead, that we should have it both ways. Add some further specifics, clarifications, and quantitation, but keep the general distinctions of bipolar disorder not otherwise specified (BP NOS), BP II, and BP I. A largely functional patient with BP II during the up phases has little resemblance to a full-blown and psychotic BP I mania. These categories are clinically useful and, as we will see below, are also scientifically relevant.

Comments on Specific Points in Mahli et al.'s Article

Malhi et al.[1] cite the statement from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) that after 4 to 6 days of hypomania, if a 7th day occurs, this makes you BP I. This is clearly ludicrous; it confounds duration with severity. It needs to be fixed, not eliminated. Some people do have a prolonged hypomanic runup to a full-blown psychotic BP I mania, but this can be stated with some precision, as Malhi et al.[1] suggest.

Malhi et al.[1] state BP II is hard to distinguish from "normality itself." He forgets that the depressive phase of BP II is often severe, immobilizing, cognitively impairing, and associated with marked increased premature mortality from both cardiovascular disease and suicide. They also talk about patients enjoying the hypomanic state, which is often true of the euphoric version of the state. However, some two-thirds of women and about 40% of men experience it as dysphoric, filled with anxiety and feeling pressured, agitated, and irritable, and do not like it all.[7]

Blaming the apparent recent increase in the diagnosis of BP II on the pharmaceutical industry seems a little lame,

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especially since a cohort effect for both unipolar and bipolar disorder, as well as attention-deficit hyperactivity disorder and substance abuse, has been demonstrated over many generations,[8,9] although Parker and Fletcher[10] did see a bigger effect for BP II than BP I patients.

The issue of comorbidities commonly accompanying both BP I and BP II such as personality disorder or substance abuse should not be used to invalidate the diagnosis. Mahli et al.[1] state, "Bipolar II overlaps considerably with borderline personality disorder (BPD), and indeed the two are frequently mistaken." Yet the two can readily be separable with carful history taking. We know that BPD can occur by itself, and bipolar disorder can also occur by itself without BPD, even though the two are very commonly comorbid. When the two are comorbid, bipolar disorder is more complicated and treatment refractory.[11,12] When the two occur together, pharmacological treatments for bipolar disorder are appropriate. Moreover, in some reviews of BPD (in the absence of bipolar disorder), they state the disorder is better treated with medications appropriate to bipolar disorder rather than antidepressants or benzodiazepines, which are often assumed to be the conventional treatments.[13,14] Finally, it is hard to see how the recommendations for a new diagnostic system would do anything to clarify the distinctions of bipolar disorder from its common comorbidities.

Genetic Evidence for the BP I Versus BP II Distinction

The findings of the large Swedish study (involving a cohort of 15.6 million people) indicating that BP I and BP II do in fact tend to breed true and run in separate families are somehow dismissed by Mahli and colleagues[1] because there was some genetic overlap.[15] There is considerable genetic overlap between multiple psychiatric illnesses, so using this as a reason to drop BP II is highly suspect. Moreover, even in the Song et al.[15] study, there was genetic overlap between schizophrenia and BP I rather than BP II. The largest genome-wide association study (GWAS) to date found that the genetic profile of those with BP I tended to overlap with patients with schizophrenia, while those with BP II were more similar to those with depression.[16] Similarly, Charney et al.[17] in a study of more than 19,000 subjects found a greater load of polygenic risk alleles for schizophrenia and bipolar disorder in those with BP I compared to those with BP II disorder. Also, the best replicated GWAS finding for the risk allele of CACNA1C in various major psychiatric illnesses was related to altered intracellular calcium metabolism in BP I but not BP II.[18] These and other data suggest that the statement by Mahli[1] that there are no biological differences between BP I and BP II is a bit short-sighted, and if the BP I versus BP II categories disappeared, these types of studies of genetic and other pathophysiological differences would not be possible.

Pharmacological Differences

There are also pharmacological response differences such as those noted above in which antidepressants are significantly more likely to switch patients with BP I depression compared to those with BP II. Moreover, it appears that those with BP II are more likely to have a positive clinical response to antidepressant monotherapy than those with BP I.[19,20] Conversely, despite a larger sample size, those with BP II depression showed no antidepressant effect of valproate but a highly significant effect of valproate in those with BP I depression,[21] mirroring the very robust effects of valproate in acute bipolar I depression.[22] Another pharmacological distinction between response in BP I versus BP II is in the work of Greil et al.[23] They found that long-term treatment with lithium was superior to carbamazepine in patients with classical BP I with euphoric mania, discrete episodes and well-intervals, no anxiety or substance abuse comorbidity, no mood-incongruent delusions, and a positive family history of bipolar disorder. In contrast, carbamazepine was more effective in those with BP II and nonclassical presentations, which were essentially the opposite of all the other lithium predictors, as well as a negative family history of bipolar disorder.[5]

The story Mahli et al.[1] present with lamotrigine (LTG) seems to be on shaky ground in making a case for dropping BP II. LTG is approved by the US Food and Drug Administration (FDA) only for BP I in the United States. However, clinicians have used its profile of much better efficacy in preventing depression than mania to appropriately see that it fills a needed therapeutic niche that matches up well with those with BP II who need good antidepressant prophylaxis and in whom LTGs' poorer antimanic effectiveness is less important. One study has validated this clinical observation with a finding that LTG was better in those with BP II than BP I over a 1-year period in preventing depression as well as hypomania/mania.[24] So along with the difference in switch rate on antidepressants,[2,3] the LTG data actually support the utility of the BP II/BP I distinction. If BP II were dropped, we would miss out on these clinical, mechanistic, and genetic differences.

Summary and Conclusions

Mahli et al.[1] conclude that the categories of BP I, BP II, and unspecified (what used to be and we would still call BP NOS) are of "little use." However, the arguments supporting this contention appear a "little loose." In addition, Birmaher et al.[25,26] found those with BP NOS had an earlier age of onset, were essentially as ill and impaired as those with BP I and BP II, and took much longer (more than a year longer) to stabilize. A key argument for replacing BP II would be that something else would clearly be better. I believe the argument for the replacement being better is not well supported. In fact, while I love a graphic display of data, I find that Mahli et al.'s Figure 1B more likely would help someone sail

downwind "wing on wing" off into the sunset than a more precise and practical way of characterizing and classifying the illness.

Therefore, I would take many of Malhi et al.'s useful suggestions to fix and not nix BP II. A last important but not telling argument is that patients like the concept, and it has some destigmatizing potential. Those with BP II and their relatives like the distinction that they have a less severe upside of the manic-depressive pole than those with BP I (i.e., they do not get psychotic or "crazy").

Mahli et al.[1] state, "Ultimately, arbitrarily separating bipolar disorders into bipolar I, II, and 'unspecified' in order to capture the heterogeneity of the illness has proven to be of little use." As noted in the many examples cited above, I do not believe they have made a strong case for this position. Another very compelling argument for the utility of the current classification has been the ability to submit studies for FDA and other regulatory agency approval. While bipolar disorder has been grossly understudied compared to schizophrenia for more than 4 decades, the advent of the new classification scheme of the research domain criteria would seem to further doom treatment studies in bipolar disorder to an even further new low. It is hard to see how Mahli et al.'s system could enhance treatment research if the BP I, BP II, and BP NOS types of distinctions were dropped altogether.

Mahli and colleagues[1] say, "It's time for something new." This is true, but fixing the old to make it new and better would be preferable to having something totally new and unhinged from the history of pathophysiological and treatment research and drug approvals, with the potential result of soon needing another new replacement as we learn more about the illness.

Declaration of Conflicting Interests

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