Curr Psychiatry Rep (2016) 18: 27
DOI 10.1007/s11920-016-0669-2

PSYCHIATRIC DIAGNOSIS (MB FIRST, SECTION EDITOR)

The Prevalence and Diagnostic Validity of Short-Duration Hypomanic Episodes and Major Depressive Episodes

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Published online: 1 February 2016

Abstract Current diagnostic criteria for a hypomanic episode, as outlined in both the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and DSM-5), require a minimum duration of four consecutive days of symptoms of mood elevation. The 4-day criterion for duration of hypomania has been challenged as arbitrary and lacking empirical support, with many arguing that shorter-duration hypomanic episodes are highly prevalent and that those experiencing these episodes are clinically more similar to patients with bipolar disorder than to those with unipolar major depressive disorder. We review the current evidence regarding the prevalence, diagnostic validity, and longitudinal illness correlates of shorter-duration hypomanic episodes and summarize the arguments for and against broadening the diagnostic criteria for hypomania to include shorter-duration variants. Accumulating findings suggest that patients with major depressive episodes and shorter-duration hypomanic episodes represent a complex clinical phenotype, perhaps best conceptualized as being on the continuum between those with unipolar depressive episodes alone and those with DSM-5-defined bipolar II disorder. Further investigation is warranted, ideally involving large prospective, controlled studies, to elucidate the diagnostic and treatment implications of depression with shorter-duration hypomanic episodes.

Keywords Short · Hypomania · Major depressive episodes · Bipolar disorder

This article is part of the Topical Collection on *Psychiatric Diagnosis*

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Introduction

The nosological boundaries of bipolar disorder have long been the subject of debate. The Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) [1], outlined clear diagnostic criteria differentiating the characteristics of the mood episodes comprising bipolar I disorder, bipolar II disorder, and unipolar major depressive disorder (MDD). These diagnostic boundaries were largely maintained in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [2], with a few notable exceptions, such as the addition of the "mixed features" specifier which could be applied to unipolar as well as bipolar mood episodes, the potential for certain antidepressant-induced mood elevation episodes to qualify for a primary diagnosis of bipolar I or II disorder, and the requirement of persistently increased goal-directed activity or energy (in addition to euphoric or irritable mood) to diagnose manic and hypomanic episodes. Still, many have argued that the DSM-based distinctions between bipolar II disorder and MDD rely upon arbitrary criteria for the symptom count and duration of hypomanic episodes that are exceedingly stringent and diverge from empirical evidence, which supports a broader spectrum of bipolarity often characterized by recurrent depression with subthreshold hypomanic episodes [3–9]. On the other hand, several experts have warned against the broadening of bipolar disorder diagnostic criteria, arguing that such an approach may compromise the integrity of the bipolar disorder construct from a both research

and clinical perspective, resulting in false-positive diagnoses and inappropriate treatment exposures [10–12].

Many proposals have been made to expand the boundaries of the bipolar spectrum, such as inclusion of individuals with recurrent unipolar depression in the context of a first-degree family history of bipolar disorder [3, 9], major depressive episodes in combination with hyperthymic or cyclothymic temperament [3], or major depressive episodes with subthreshold hypomania (i.e., hypomanic symptoms that fail to meet symptom count and/or duration criteria for hypomanic episodes) [6, 8, 13]. This article will focus exclusively on the duration criterion for hypomanic episodes, reviewing the evidence for and against the proposal that individuals with a history of major depressive episodes and shorter-duration (<4 days) hypomanic episodes should be included under the diagnosis of bipolar II disorder. Of note, for the purposes of this article, we will consider only distinct short-duration hypomanic episodes, as opposed to hypomanic symptoms occurring within major depressive episodes (e.g., major depressive episodes with mixed features).

Prevalence of Shorter-Duration Hypomania

Several cross-sectional and longitudinal studies have assessed the prevalence of patients presenting with shorter- compared to longer-duration hypomanic episodes (Table 1). However, these studies demonstrated considerable variability with respect to study design, patient population, and diagnostic criteria for hypomanic episodes, making comparison of findings across studies challenging.

Cross-sectional Studies In a single-site, cross-sectional study involving 501 patients meeting DSM-IV criteria for past major depressive episodes and DSM-IV symptom (but not necessarily duration) criteria for past hypomanic episodes (occurring independently of depressive episodes), Parker and colleagues found the majority (62.9 %) of these patients had only brief (<4 days) hypomanic episodes, while 37.1 % had hypomanic episodes ≥4 days in duration [14•]. In contrast, the BRIDGE study, an international multi-center cross-sectional study involving 5635 patients in a current DSM-IV major depressive episode, found a relatively lower prevalence of shorter- (1 or 2–3 days) compared to longer- (4–6 days, ≥7 days, or ≥1 month) duration hypomanic episodes, which occurred in 25.1 versus 74.9 % of the 3635 patients with a history of hypomanic symptoms, respectively [15•]. One limitation of this study was its divergence from strict DSM-based symptom criteria for hypomanic episodes: overactivity was added as a gateway criterion (such that hypomania could be diagnosed in the absence of euphoric or irritable mood, in contrast to DSM-5 which requires that overactivity be present concurrently with euphoric or irritable mood), and only three additional DSM-IV hypomanic symptoms were required, regardless of whether predominant mood was euphoric or irritable. In another cross-sectional analysis of currently depressed outpatients presenting for treatment to a single private practice clinic, Benazzi showed that among 284 patients with DSM-IV-based symptoms of bipolar II disorder (though requiring only a 2-day minimum duration for hypomania), the majority (71.5 %) had prior hypomanic episodes lasting at least 4 days, whereas 28.5 % had 2–3-day episodes [16]. Similarly, in a Korean sample of 111 currently depressed outpatients, 29.7 % of patients met DSM-IV criteria for bipolar II disorder, while only 15.3 % had shorter-duration (1–3 days) hypomanic episodes [17].

Longitudinal/Prospective Studies The Zurich cohort study involved a community-based sample of 4547 individuals who were interviewed by trained psychologists with standardized assessment tools every 1–6 years from 19–20 through 40–41 years of age. Two hundred forty-four of these participants met criteria for a mood disorder, among whom only 19.7 % presented with shorter-duration (1–3 days) hypomanic episodes, compared to 38.9 % with longer-duration (≥4 days) hypomanic episodes and 41.4 % with pure depression (no history of hypomanic symptoms) [18]. Thus, considering only those patients reporting prior hypomanic symptoms ($N = 143$), shorter- versus longer-duration hypomanic episodes occurred in 33.6 versus 66.4 % of patients, respectively. This study utilized the same modified diagnostic criteria for hypomanic episodes described above for the BRIDGE study [15]. In the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS), a longitudinal cohort study involving 86 patients with bipolar II disorder (based on Research Domain Criteria, but modified to align with DSM-IV criteria), 19.8 % had 2–6-day episodes of hypomania, while 80.2 % had ≥7-day episodes of hypomania, but no comparisons were reported between those with <4 and ≥4-day hypomanic episodes [19].

In a naturalistic study of 393 patients already diagnosed with DSM-IV bipolar I disorder or bipolar II disorder, Bauer and colleagues prospectively assessed the occurrence of shorter- versus longer-duration hypomanic episodes based on daily mood ratings provided by patients using ChronoRecord software, in which a 100-unit visual analogue scale was used to rate mood between extremely depressed and extremely manic [20]. Hypomanic episodes were determined from an algorithmic calculation based on these daily self-ratings. The authors found that over a 6-month period, 43.0 % of patients only experienced short (≤3 days) hypomanic episodes, while 26.0 % of patients experienced hypomanic episodes ≥4 days in duration. While the prospective approach of this study was advantageous, the reliance on single daily mood ratings rather than DSM-based criteria to diagnose mood episodes may diminish the generalizability of the findings. Perhaps more importantly, all participants had been previously diagnosed with bipolar I disorder or

Table 1 Summary of studies evaluating patients with shorter-duration hypomania

Author	Sample size	Hypomania definition	Episode duration		Prevalence			Features of bipolarity			
			SH	LH	MDD	SH	LH	Family history bipolar	Early-onset age	Recurrent MDEs	Hypo/manic switch
Cross-sectional studies											
Angst et al. 2012 [15•]	$N = 5635$ in current MDE ($N = 5623$ with hypomania duration information)	(a) Presence of irritability, elevated mood, or overactivity; (b) ≥3 manic symptoms; (c) meet DSM-IV criteria C, D, E for hypomania	1 or 2–3 days	4–6 days, ≥7 days, or ≥1 month	35.4 % $N = 1988$	16.2 % $N = 911$	48.5 % $N = 2724$	M < S < L	M < S = L	M < S < L	M < S < L
Benazzi and Akiskal 2006 [8]	$N = 206$ BDII $N = 178$ MDD	DSM-IV symptom criteria for hypomania, 2-day minimum duration	2–3 days	≥4 days	46.4 % $N = 178$	16.1 % $N = 62$	37.5 % $N = 144$	M < S = L	M < S = L	M < S = L	NR
Benazzi 2007 [16]	$N = 284$ BDII $N = 196$ MDD	DSM-IV symptom criteria for hypomania, 2-day minimum duration	2–3 days	≥4 days	40.8 % $N = 196$	16.9 % $N = 81$	42.3 % $N = 203$	M < [S + L]	M < [S + L]	M < [S + L]	NR
Kim et al. 2008 [17]	$N = 111$ in current MDE[a]	DSM-IV symptom criteria for hypomania, 1-day minimum duration	1–3 days	≥4 days	46.8 % $N = 52$	15.3 % $N = 17$	29.7 % $N = 33$	M < [S + L]	M < [S + L]	M = [S + L]	NR
Parker et al. 2014 [14•]	N = 501 with prior MDE and DSM-IV symptom criteria for hypomania	DSM-IV symptom criteria for hypomania, any duration	<4 days	≥4 days	None	62.9 % $N = 315$	37.1 % $N = 186$	S = L	S = L	NR	NR
Longitudinal studies											
Angst et al. 2003 [18]	$N = 4547$ initially screened ($N = 244$ with mood disorder)	(a) Presence of irritability, elevated mood, or overactivity; (b) ≥3 manic symptoms; (c) meet DSM-IV criteria C or D for hypomania	1–3 days	≥4 days	41.4 % $N = 101$	19.7 % $N = 48$	38.9 % $N = 95$	M = S, M < L	M = S = L	NR	NR
Bauer et al. 2011 [20]	$N = 393$ (247 BDI, 146 BDII)	Assessed by algorithmic calculation based on daily self-rated mood	1–3 days	≥4 days	None	1 day: 43.0 % ($N = 169$) 2 days: 22.4 % ($N = 88$) 3 days: 10.9 % ($N = 43$)[b]	26.0 % $N = 102$[b]	NR	SH = LH (for all 3 SH groups)	NR	NR
Judd et al. 2003 [19]	$N = 86$ BDII in current MDE or hypomanic episode	Research Domain Criteria	2–6 days	≥7 days	None	19.8 % $N = 17$	80.2 % $N = 69$	S = L	S = L	S = L	NR

MDE major depressive episode, *BDI* bipolar I disorder, *BDII* bipolar II disorder, *S* or *SH* shorter-duration hypomania, *L* or *LH* longer-duration hypomania, *M* or *MDD* unipolar major depressive disorder, *NR* not reported

[a] $N = 7$ with history of antidepressant-induced hypomania were excluded from shorter- versus longer-duration hypomania analyses

[b] *N* represents the number of individuals with prospectively observed hypomanic episodes of the specified duration; SH groups not mutually exclusive

bipolar II disorder, such that all had presumably experienced a prior lifetime mood elevation episode of at least 4-day duration. Thus, although this study does not inform our understanding of the prevalence of individuals who experience only shorter-duration hypomanic episodes, the findings do suggest that shorter hypomanic episodes may be common among patients with diagnosed bipolar I or II disorder.

Overall, findings are mixed regarding the relative prevalence of shorter- versus longer-duration hypomanic episodes among mood disorder patients. In addition, variability across studies with respect to methodology, patient population, and diagnostic criteria can render the results difficult to interpret. Nevertheless, the majority of studies suggest that among those patients reporting a history of hypomanic symptoms (distinct from depressive episodes), overall, 2–3 times more patients experience episodes of longer duration (greater than 4 days), versus shorter-duration episodes (>4 days).

Validity of Shorter-Duration Hypomania as a Bipolar Disorder Phenotype

Of considerable interest to both clinicians and researchers is whether individuals who experience only shorter-duration hypomanic episodes and major depressive episodes are more nosologically aligned with bipolar II disorder or unipolar MDD patients. Addressing this controversial issue has substantial implications for the diagnosis and treatment of such patients. Several of the aforementioned studies have approached this question by comparing the prevalence rates of bipolar validators (clinical features commonly associated with bipolarity) such as early-onset age or family history of bipolar disorder across groups with differing durations of hypomanic episodes (Table 1). Perhaps the most comprehensive and informative of these was the BRIDGE study, in which 11 bipolar validators were compared across individuals from six different groups: 1988 patients with unipolar MDD (i.e., no reported lifetime history of hypomanic symptoms), 285 who reported a lifetime history of 1-day hypomanic episodes (i.e., no prior episodes longer than 1 day in duration), 626 with 2–3-day hypomanic episodes, 409 with 4–6-day hypomanic episodes, 1096 with ≥7-day hypomanic episodes, and 1219 with ≥1-month hypomanic episodes [15•]. Pooling these individuals into three groups—1988 MDD patients, 911 shorter-duration (1 and 2–3 days) hypomania patients, and 2724 longer-duration (4–6 days, ≥7 days, and ≥1 month) hypomania patients—the shorter- and longer-duration hypomania groups were significantly more likely than the MDD patients to exhibit numerous bipolar validators including family history of hypomania, early onset of symptoms (<30 years), mood episode recurrence (≥2 episodes), and manic/hypomanic switches. However, the longer-duration hypomania group was also significantly more likely than the shorter-duration hypomania group to exhibit most of these traits, such that the shorter-duration hypomania group may represent an intermediate-severity phenotype between unipolar and bipolar disorders. Thus, the findings of this study suggest there may be sufficient heterogeneity between patients with shorter- and longer-duration hypomanic episodes to warrant maintaining diagnostic separation between the two groups.

As shown in Table 1, other studies comparing bipolar validators across groups showed that patients with shorter- and longer-duration hypomanic episodes were broadly similar to one another [8, 14•, 18, 20], but only two of these analyses [8, 18] included a unipolar MDD group for comparison. In the Zurich cohort study, 101 MDD patients were less likely than 95 patients with longer-duration (≥4 days) hypomania, but similarly likely as 48 patients with shorter-duration (1–3 days) hypomania, to have a family history of mania, and all three groups had comparable onset age [18]. In contrast, in an analysis of depressed outpatients in a single private practice, Benazzi and Akiskal demonstrated that both patients with shorter-duration (2–3 days; $N = 62$) and longer-duration (≥4 days; $N = 144$) hypomanic episodes were significantly more likely than 178 patients with unipolar MDD to have younger onset age, family history of bipolar disorder, recurrent illness (>4 major depressive episodes), atypical features of depression, and a depressive mixed state [8]. The shorter- and longer-duration hypomania groups did not significantly differ from one another on any of these parameters, with the exception of shorter-duration patients being more likely to experience atypical features [8].

In summary, data from a large, multi-center, international study support the possibility that patients with shorter-duration hypomanic episodes represent an intermediate-severity phenotype, having indicators of somewhat greater clinical severity compared to patients with unipolar MDD without hypomania and somewhat lesser clinical severity compared to patients with longer-duration hypomanic episodes (i.e., DSM-IV- or DSM-5-based bipolar II disorder). Findings from several smaller, mostly single-site studies suggested that patients with shorter- and longer-duration hypomanic episodes shared considerable overlap with respect to features of bipolarity, and this finding was supported by another study where both long- and short-duration cohorts separated from a unipolar MDD comparison. Other studies have yielded more mixed results. Perhaps importantly, in considering data from work in this area, potential anomalies of geography, regional differences in diagnosis, sample selection, and physician bias need to be considered as limitations.

Impact of Hypomania Duration on Illness Course

In contrast to the relatively more substantial body of cross-sectional data regarding the prevalence and associated bipolar

validators of shorter-duration hypomania, prospective assessments of illness course in patients with shorter-duration hypomanic episodes are sparse, and there are virtually no controlled studies assessing treatment outcomes in such patients.

A few of the prospective studies described above provided information regarding the longitudinal course of illness among those with shorter- compared to longer-duration hypomanic episodes. Thus, in the Zurich cohort study, patients with shorter-duration (1–3 days) hypomanic episodes reported fewer days hypomanic in the past year, but a similar number of days depressed, compared to those with longer-duration (≥4 days) hypomanic episodes [18]. In the NIMH CDS, patients with longer-duration (≥7 days) hypomanic episodes spent more weeks with minor depressive symptoms compared to those with shorter-duration (2–6 days) hypomanic episodes, but these groups were otherwise similar with respect to weeks spent with specific affective symptom severity levels, or number of changes in symptom status or polarity, over the course of longitudinal follow-up [19]. However, as previously noted, this study did not provide direct comparisons between those with hypomanic episodes of <4- versus ≥4-day duration. In their naturalistic prospective study of 393 bipolar I and II disorder patients using ChronoRecord software to enter daily mood ratings, Bauer and colleagues found that decreasing the minimum duration for a hypomanic episode from 4 to 1 day more than doubled the number of patients experiencing a hypomanic episode and the percent of days spent in a hypomanic episode, over 6 months of follow-up [20]. However, as discussed previously, patients were required to have met DSM-IV criteria for bipolar I or II disorder in order to participate in the study and therefore had previously experienced syndromal mood elevation episodes. Thus, while these data demonstrate the frequent nature of short-duration hypomanic episodes across longitudinal follow-up in an already diagnosed bipolar I or II disorder cohort, they do not permit us to compare prospective illness course in patients who experience shorter- versus longer-duration hypomanic episodes.

Overall, findings from at least two prospective studies suggest that patients with shorter-duration hypomanic episodes may experience a longitudinal course of illness that is similar in some ways and less severe in other ways, compared to those with longer-duration episodes. However, the inconsistency of diagnostic criteria and findings across these studies indicate the need for additional prospective studies, to clarify the effect of hypomania duration on longitudinal illness severity.

Advantages and Disadvantages of Shortening the Hypomania Duration Criterion

Reducing the minimum duration threshold for hypomania from ≥4 to <4 days has the potential advantage of increasing sensitivity and capturing more patients who may benefit from bipolar disorder-specific treatment approaches. Although evidence-based strategies for managing bipolar II disorder are limited [21, 22], with more research being needed in this area, there is general agreement among experts that antidepressants should be used cautiously (if at all) for individuals with bipolar II disorder, and mood stabilizing treatments may prove more beneficial than antidepressants for such patients [23, 24]. Thus, different treatment approaches are warranted for bipolar II disorder compared to unipolar MDD patients, and broadening the diagnostic criteria for bipolar II disorder may alert clinicians to the need to consider mood stabilizers, and perhaps avoid antidepressants, for susceptible individuals. Indeed, in a recent longitudinal study involving youth at high risk for bipolar disorder, the presence of subthreshold hypomanic symptoms (i.e., inadequate duration and/or symptom count for DSM-IV hypomania) was an important predictor of subsequent progression to full syndromal manic, hypomanic, or mixed episodes [25•]. Therefore, shortening the duration criteria for hypomania could potentially allow such high-risk individuals to be identified earlier and receive appropriate treatment.

On the other hand, including those with shorter-duration hypomania into the existing diagnosis of bipolar II disorder may be associated with important risks, such as increasing intra-diagnostic heterogeneity and diluting the clinical meaningfulness of bipolar II disorder, which has historically been mistakenly viewed as a less severe manifestation of bipolarity [26, 27]. Moreover, diagnosing patients with shorter-duration hypomania with bipolar II disorder increases the likelihood they will be exposed to treatment with mood stabilizers/antipsychotics and their associated harms, despite the lack of controlled data to support the efficacy of such agents for this subthreshold group.

In DSM-5, individuals with major depressive episodes and shorter-duration hypomanic episodes are included under the diagnosis of Other Specified Bipolar and Related Disorders. This is described within DSM-5 as follows: "Short-duration hypomanic episodes (2-3 days) and major depressive episodes: A lifetime history of one or more major depressive episodes in individuals whose presentation has never met full criteria for a manic or hypomanic episode but who have experienced two or more episodes of short-duration hypomania that meet the full symptomatic criteria for a hypomanic episode but that only last for 2-3 days. The symptoms do not overlap in time with the major depressive episodes, so the disturbance does not meet criteria for major depressive episode, with mixed features" [2]. The categorization of shorter-duration hypomania as a separate bipolar variant reflects the consensus of the DSM-5 task force that this clinical presentation could represent a phenotype that is distinct from both unipolar MDD and bipolar II disorder. Indeed, Section 3 of DSM-5 includes the diagnosis of Depressive Episodes with Short-Duration Hypomania as a condition for further study,

noting that individuals who meet criteria for this condition "more closely resemble individuals with bipolar disorder than those with major depressive disorder," yet "may exhibit less severity than individuals with syndromal hypomanic episodes" [2]. It is clear that further investigation with large, well-designed, controlled studies is necessary to improve our understanding of how shorter-duration hypomania fits within the nosology of unipolar and bipolar mood disorders.

Conclusions

Controlled studies examining the construct of depression with shorter-duration hypomania are sparse and demonstrate considerable methodological variability. Nevertheless, certain findings emerge from these investigations. First, in the majority of studies examining individuals with histories of hypomanic symptoms, patients with longer-duration hypomanic episodes were 2–3 times more common than those with only shorter-duration hypomanic episodes. This finding suggests that the current duration criterion for hypomanic episodes may in fact yield adequate sensitivity to capture the majority of individuals experiencing hypomania. Second, the most robust evidence to date regarding the diagnostic validity of shorter-duration hypomania, based on the only multi-site, large-scale, international study examining bipolar validators across patients with differing durations of hypomanic episodes (including no hypomania), supports the conclusion that shorter-duration hypomania represents a distinct intermediate-severity phenotype between unipolar MDD (i.e., no hypomania) and DSM-based bipolar II disorder (i.e., ≥4-day duration hypomania). Third, prospective studies comparing patients with shorter- and longer-duration hypomanic episodes are limited in number and have yielded mixed results, leaving us with little information regarding potential differences and similarities in longitudinal illness course between these two groups. Finally, individuals with shorter-duration hypomanic episodes are generally excluded from bipolar treatment studies, such that the therapeutic implications of identifying such patients remain to be understood.

Individuals who experience shorter-duration hypomania appear to represent a unique clinical subgroup that is distinct from individuals who experience depression with longer-duration hypomanic episodes (i.e., those who meet current DSM-5 criteria for bipolar II disorder), yet also distinct from those with unipolar MDD. As noted above, DSM-5 has acknowledged this phenotypic presentation under the diagnosis of Other Specified Bipolar and Related Disorders, indicated with the specifier "short-duration hypomanic episodes (2-3 days) and major depressive episodes" [2]. The recognition in DSM-5 of this subgroup of mood disorder patients is noteworthy and calls upon clinicians and researchers to obtain careful clinical histories that attend to subthreshold phenomenology. Moving forward, larger, methodologically rigorous studies are needed to improve our understanding of shorter-duration hypomania with respect to its status as a diagnostic entity and, more importantly, its implications for the approach to treatment.

Compliance with Ethical Standards

Conflict of Interest Shefali Miller has received research grants from Merck and Sunovion.

Ellen B. Dennehy is employed by Eli Lilly and Company.

Trisha Suppes reports sources of funding or medications for clinical grants from the National Institute of Health, Sunovion Pharmaceuticals, Inc., Elan Pharma International Limited, and VA Cooperative Studies Program as well as fees for consulting agreements/advisory boards/speaking engagements from Sunovion Pharmaceuticals, Inc., A/S H. Lundbeck, Merck, and Astra Zeneca. Dr. Suppes has also received honoraria payments from the International Society of Bipolar Disorders (ISBD) Columbia, Continuing Medical Education, Healthmatters CME, Omnia-Prova Education Collaborative, Inc., Medscape, and the American Academy of Clinical Psychiatrists. She has also received royalties from Jones and Bartlett and UpToDate and paid travel expenses from Sunovion Pharmaceuticals, Inc., A/S H. Lundbeck, Omnia-Prova Education Collaborative, Inc., the American Psychiatric Association, the International Society of Bipolar Disorders (ISBD) Columbia, Astra Zeneca, and Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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