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Preliminary communication

Hypersomnia in inter-episode bipolar disorder: Does it have prognostic significance?

Katherine A. Kaplan [a], June Gruber [b], Polina Eidelman [a], Lisa S. Talbot [a], Allison G. Harvey [a,*]

[a] Department of Psychology, University of California, Berkeley, Berkeley, CA, United States
[b] Department of Psychology, Yale University, New Haven, CT, United States

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ABSTRACT

Background: Hypersomnia in inter-episode bipolar disorder has been minimally researched. The current study sought to document the prevalence of hypersomnia in a sample of inter-episode patients with bipolar disorder and to examine the relationship between hypersomnia and future bipolar depressive symptoms.
Methods: A total of 56 individuals with bipolar disorder (51 type I + 5 type II) who were currently inter-episode, along with 55 non-psychiatric controls, completed a baseline assessment, including semi-structured interviews for psychiatric diagnoses, sleep disorders, and a battery of indices that included assessment of hypersomnia. Approximately 6 months later, participants were recontacted by telephone and mood was re-evaluated.
Results: Three of six indices suggested that approximately 25% of participants with bipolar disorder endorsed symptoms of hypersomnia in the inter-episode period. Within the bipolar group, hypersomnia in the inter-episode period was associated with future depressive symptoms. This finding was independent of baseline depressive symptoms and medication use.
Limitations: Small sample size and concurrent psychopharmacology in the bipolar sample.
Discussion: Though no gold standard measure for hypersomnia currently exists, this research takes a step towards identifying a clinically and empirically useful hypersomnia assessment. This study demonstrates that hypersomnia in the inter-episode period of bipolar disorder relates to future depressive symptoms, and adds to the growing body of evidence on the importance of inter-episode symptoms predicting bipolar relapse.

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1. Introduction

Bipolar disorder is a serious and chronic psychiatric illness. One of the most important findings to emerge over the last decade is the significance of the inter-episode period. Individuals in the inter-episode period spend roughly 50% of their time unwell (Joffe et al., 2004; Judd et al., 2002), and these symptoms predict relapse into mania or depression (MacQueen et al., 2003). Hence, there is a critical need to identify aspects of the illness that contribute to inter-episode dysfunction and to relapse.

Hypersomnia may be one candidate contributing to inter-episode dysfunction and to relapse but is understudied in bipolar disorder. In unipolar depression, hypersomnia is present in approximately 30% of individuals (Kaplan and Harvey, 2009) and associated with longer, more severe and more treatment-resistant depressions (Matza et al., 2003). Furthermore, individuals with hypersomnia are 2.4 to 2.9 times more likely to develop a subsequent unipolar depressive episode (Breslau et al., 1996; Ford and Cooper-Patrick, 2001). Comparative studies show that hypersomnia is more prevalent in bipolar depression than in unipolar depression (Akiskal and Benazzi, 2005; Benazzi, 2006; Bowden, 2005), and also that hypersomnia is highly recurrent across separate

* Corresponding author at: Psychology Department, Golden Bear Sleep and Mood Research Clinic, University of California, Berkeley, 3210 Tolman Hall #1650, Berkeley, CA 94720-1650, United States. Tel.: +1 510 642 7138; fax: +1 510 642 5293.
E-mail address: aharvey@berkeley.edu (A.G. Harvey).

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episodes of bipolar depression (Leibenluft et al., 1995). Despite its prevalence, four gaps remain in our understanding of hypersomnia in bipolar disorder.

First, although estimates of hypersomnia in bipolar depression range from 38% (Akiskal and Benazzi, 2005) to 78% (Detre et al., 1972), the prevalence of hypersomnia during the inter-episode period is unknown. Hence, one aim of the current study was to estimate the prevalence of hypersomnia in an inter-episode sample of individuals with bipolar disorder.

Second, there is no gold standard measure for hypersomnia. Due to the heterogeneity across diagnostic systems (Kaplan and Harvey, 2009), indices of hypersomnia probe for such disparate features as sleeping 'more than 8 h a day' to 'falling asleep while standing' to the ambiguous 'too much sleep'. Hence, a second aim was to evaluate indices of hypersomnia by including a multi-method assessment (i.e. self-report, clinical interview, and sleep diary) and prospectively examining the relationship between these indices and future depressive symptoms.

Third, though hypersomnia is traditionally viewed as a disorder of self-reported sleep time, all research utilizing objective measures of sleep suggests that sleep latencies and sleep durations of individuals with psychiatric hypersomnia *do not differ* from those of control participants (e.g., Billiard et al., 1994; Nofzinger et al., 1991). This raises an interesting empirical question: is hypersomnia better characterized as a disorder of increased time in bed (TIB), rather than increased total sleep time (TST) (Kaplan and Harvey, 2009)? The third aim tested the prediction that TIB, prospectively calculated via sleep diaries, would correlate more highly with other indices of hypersomnia than TST.

The fourth aim of the current study was to evaluate the relationship between inter-episode hypersomnia and future depressive symptoms. Given the high rate of relapse in bipolar disorder (Perlis et al., 2006), identifying contributors to future depression is essential. As hypersomnia robustly predicts the onset of a unipolar depressive episode (Breslau et al., 1996; Ford and Cooper-Patrick, 2001), and is especially prevalent (Detre et al., 1972) and frequently recurring (Leibenluft et al., 1995) in bipolar disorder, we predicted that hypersomnia in the inter-episode period would be associated with future depressive symptoms in our sample, even after controlling for baseline symptomotology.

2. Methods

2.1. Participants

A total of 56 individuals with bipolar disorder type I ($N=51$) or type II ($N=5$), along with 55 age- and sex-matched control individuals without a history of psychiatric or sleep disorder, were included in analyses. Sample demographics are presented in Table 1. A diagnosis of bipolar disorder type I or II was determined using the Structured Clinical Interview for the DSM-IV (SCID-NP; First et al., 1995), and inter-episode status was defined using established cutoff scores of ≤ 11 on the Inventory of Depressive Symptomotology, Clinician Version (IDS-C; Rush et al., 1996) and ≤ 7 the Young Mania Rating Scale (YMRS; Young et al., 1978). Bipolar participants were excluded if they met criteria for current substance abuse and/or dependence, given their myriad effects on sleep, and also excluded if they met criteria for sleep apnea or restless leg syndrome according to the Duke Structured Interview for Sleep Disorders (DSISD) based on research diagnostic criteria (Edinger et al., 2004). Bipolar participants were not excluded on the basis of comorbidities or pharmacological treatments, given that both are common features of the illness. Control participants were excluded if they met criteria for any current or lifetime Axis I disorder from the SCID-NP, or major sleep disorders on the DSISD. All participants were excluded for unstable major illnesses and severe neurological injuries.

Table 1
Participant characteristics at baseline assessment.

Demographic variable	Bipolar ($N=56$)	Control ($N=55$)	χ^2 or t
Age			0.378
Mean (SD)	35.6 (12.35)	36.5 (11.06)	
Gender			0.92
Male	15	19	
Female	55	34	
Race/ethnicity			3.16
African American	6	4	
Asian American	3	7	
Caucasian	37	35	
Hispanic	4	3	
Other/biracial	5	4	
Employment status			3.41
Full time/part time	36	43	
Unemployed/retired	19	10	
Marital status			2.16
Married/partnered	17	13	
Separated/divorced/ widowed	9	9	
Single	30	31	
Annual income			2.99
Less than $50,000	27	31	
Greater than $50,000	18	9	
IDS-C total score			−7.27***
Mean (SD)	7.92 (3.87)	3.02 (2.69)	
YMRS total score			−4.43***
Mean (SD)	2.63 (2.33)	0.96 (1.37)	
Psychotropic medications			
None	6	55	91.28***
Monotherapy	9	0	9.62**
Polytherapy	41	0	63.85***

** $p<0.01$.
*** $p<0.001$.

2.2. Diagnostic measures

Four semi-structured clinical interviews were administered: the SCID-NP, the DSISD, the IDS-C and the YMRS. To assess diagnostic inter-rater reliability, interviewers blind to diagnostic group evaluated a randomly-selected sample of SCID interviews ($n=13$); diagnoses matched those made by the original interviewer in all cases ($k=1.00$).

2.3. Hypersomnia Indices

The precise wording of five potential indices of hypersomnia is presented in Table 2. Indices included diagnosis based on the DSISD, items from the IDS-C, the Inventory of Depressive Symptomotology, Self Report (IDS-SR; Rush et al., 1996), the Beck Depression Inventory, Second Edition (BDI-II; Beck et al., 1996), and standard sleep diaries kept for 7 days. Participants

Table 2
Definitions and prevalence of hypersomnia symptoms at baseline by potential index.There were no values in Table 2 which will correspond to the footnote detail indicated by the single asterisk. Thus, the values of 2.96 and 2.08 under the column 'χ2 test value' have been initially assigned to correspond to the footnote detail. Please check, and correct if necessary.

Index	Precise wording of question(s)	Hypersomnia prevalence				χ^2 test value
		Bipolar ($N=56$)		Control ($N=55$)		
		n	%	*n*	%	
DSISD [a]	Do you often fall asleep or do you have to struggle to stay awake when you are in any of the following situations? (talking with others, driving, talking on phone, standing, performing your work, other activities?). Do you sleep for long periods of time? [if yes] Has your sleepiness caused you any problems in the daytime such as poor concentration, poor memory, reduced work performance, or irritability? or Has your sleepiness ever interfered in any way with your family or social activities?	6	11.5	0	0	6.74**
IDS-SR [b]	1 I sleep no longer than 10 h in a 24-hour period including naps.	17	28.6	11	20	
	2 I sleep no longer than 12 h in a 24-hour period including naps.	11	21.4	2	3.6	
	3 I sleep longer than 12 h in a 24-hour period including naps.	0	0	0	0	
	Total	*28*	*50*	*13*	*23.6*	7.11**
IDS-C [c]	How many hours on average have you been sleeping in a 24-hour period in the past week, including naps? What is the longest you've slept in a 24-hour period last week?					
	1 I sleep no longer than 10 h in a 24-hour period including naps.	11	20.8	5	9.3	
	2 I sleep no longer than 12 h in a 24-hour period including naps.	2	3.8	1	1.9	
	3 I sleep longer than 12 h in a 24-hour period including naps.	0	0	0	0	
	Total	*13*	*24.6*	*6*	*11.2*	2.96
BDI-II [d]	1 I sleep somewhat more than usual.	11	19.6	2	3.6	
	2 I sleep a lot more than usual.	4	7.1	1	1.8	
	3 I sleep most of the day.	0	0	0	0	
	Total	*15*	*26.7*	*3*	*5.4*	9.29**
Sleep diary	Last night, I think I slept a total of ___ hours and ___ min.					
Total sleep time [e]	9–9.99 h	2	4.1	0	0	
	10–10.99 h	0	0	0	0	
	11+ hours	0	0	0	0	
	Total	*2*	*4.1*	*0*	*0*	2.08
Sleep diary	Last night, I got in to bed at _____. This morning, I got out of bed at _____.					
Time in bed [e]	9–9.99 h	14	28.6	4	7.7	
	10–10.99 h	2	4.1	0	3.8	
	11+ hours	1	2	0	0	
	Total	*17*	*34.7*	*6*	*11.5*	7.69**

[a] DSISD = Duke Structured Interview for Sleep Disorders.
[b] IDS-SR = Inventory of Depressive Symptomotology, Self Report Version, Question 4.
[c] IDS-C = Inventory of Depressive Symptomotology, Clinician Version, Question 4.
[d] BDI-II = Beck Depression Inventory, Second Edition, Question 16.
[e] Average taken from seven nights of sleep diary.
** $p<0.01$.

completed the log prior to sleep and upon waking, and all participants were required to call a voicemail twice daily with their answers to ensure compliance. TST was calculated by subtracting all time spent awake from all time spent in bed nightly. TIB was scored by summing all intended sleep periods, excluding periods of reading or television watching in bed. Inter-rater reliability between interviewers and a trained rater blind to diagnostic status on the hypersomnia section of the DSISD was excellent ($n=15$; $k=1.00$). Inter-rater reliability was acceptable on the hypersomnia item of the IDS-C ($n=14$; ICC absolute agreement = 0.65, 93% agreement).

2.4. Procedure

Adult participants between the ages of 18 and 65 were recruited from advertisements, online bulletins and referrals. Following a telephone screen, participants were sent a copy of the sleep diary with detailed instructions and asked to keep the

diary for 7 days (6.76 ± 0.65 days completed). Once diaries were complete, participants were invited to UC Berkeley for the baseline assessment. Trained doctoral candidates and a postdoctoral fellow conducted all semi-structured interviews. Approximately 6 months after the baseline visit (216 ± 47 days), bipolar participants were re-contacted via telephone and a trained interviewer reassessed depressive and manic symptomotology.

2.5. Statistical analysis

Between groups comparisons were evaluated using two-tailed χ^2 or independent sample *t* tests. Fisher's exact test was used to compare categorical data with expected cell counts of less than five. Bivariate correlations evaluated coherence across hypersomnia indices, and signal detection statistics assessed the predictive values of hypersomnia indices. Partial correlations evaluated associations between hypersomnia at baseline and depressive symptoms at 6-month follow-up, controlling for baseline depressive symptoms.

Participants listed the name, dose, and length of use for all medications taken at baseline assessment. Each medication was subsequently re-categorized into medication classes, and post-hoc χ^2 tests compared the number of individuals endorsing and not endorsing hypersomnia within each medication class. Because class-level analyses are limited by reduced sample size and an inability to consider dosing, we also calculated the medication load for each participant (Almeida et al., 2009; Phillips et al., 2008). Each medication's dose was classified as 'low' or 'high', and assigned a corresponding score of 1 or 2, based on published parameters and chlorpromazine-equivalent mean effective daily doses (ED_{50}; Sackeim, 2001; Davis and Chen, 2004). A composite measure of medication load was created for each participant by summing across medication codes and classes, reflecting both dose and diversity of medications taken by each participant (Almeida et al., 2009). The medication load scores of individuals endorsing and not endorsing hypersomnia were compared using Student's *t* tests.

3. Results

3.1. Participant characteristics

Participant characteristics are presented in Table 1. There were no significant differences between the groups on age, gender, race/ethnicity, employment status, marital status, or annual income level. Although established to be interepisode, the bipolar group reported a greater number of both manic (YMRS) and depressed (IDS-C) symptoms than control participants at baseline ($p<0.001$ for both).

A total of 42 individuals in the bipolar group (75%) completed the follow-up assessment. Reasons for non-participation in the follow-up included: declined to participate ($n=2$), unable to contact ($n=8$), and unable to schedule before conclusion of the study ($n=4$). Completers and non-completers did not differ with respect to baseline IDS-C and YMRS scores, age, gender, ethnicity, employment status, or marital status ($p>0.10$ for all). Mean depression (IDS-C) score at follow-up was 11.3 ± 9.4, and mean mania (YMRS) score at follow-up was 2.6 ± 3.9.

3.2. Inter-episode hypersomnia prevalence

Table 2 lists the definitions and symptom prevalence rates of inter-episode hypersomnia by hypersomnia index. Inter-episode prevalence estimates of hypersomnia varied from 4% to 50% in the bipolar group depending on the index. Hypersomnia was more common in the bipolar group than in the control group on the DSISD, IDS-SR, BDI-II and Sleep Diary TIB ($p<0.05$ for all). No differences were found between groups on the IDS-C ($\chi^2=2.96$, $p=0.09$) or on Sleep Diary TST ($\chi^2=2.08$, $p>0.10$).

3.3. Comparing hypersomnia indices

Intercorrelations were first calculated to understand the degree to which the six indices relate to one another. Zero-order correlations between the IDS-SR, IDS-C, BDI-II, Sleep Diary TIB and Sleep Diary TST were all statistically significant ($r\geq 0.41$, $p\leq 0.05$); only the DSISD did not correlate with any other index. Second, standard signal detection statistics were used to establish the predictive power of various hypersomnia indices to detect depressive symptoms at follow-up. Following standard cutoffs, we defined symptomatic depression as a score of ≥12 on the IDS-C at 6-month follow-up, excluding the hypersomnia item from follow-up score tabulation. Of individuals meeting criteria for depressive symptomotology at follow-up, mean score after excluding the hypersomnia item was 20.5 ± 8.9 (range 14–41); for those not meeting criteria, mean score was 5.6 ± 3.0 (range 0–11).

Table 3 lists signal detection statistics for each potential hypersomnia index. Sensitivity refers to how well a hypersomnia index identifies persons with depressive symptoms. The sensitivity of the DSISD, Sleep Diary TST and Sleep Diary TIB for future depressive symptoms was low (21%, 9% and 36%, respectively). Specificity refers to how well a hypersomnia index identifies persons without depressive symptoms. Given their low false-positive rates, the DSISD and the Sleep Diary TST had the highest specificity (93% and 98%); the IDS-SR exhibited the poorest specificity (44%). Positive predictive value (PPV) refers to the probability that a person with hypersomnia will have depressive symptoms at follow-up, and negative predictive value (NPV) refers to the probability that a person without hypersomnia will not have depressive symptoms at follow-up. The IDS-C and the BDI-II suggest that roughly seven of ten individuals with inter-episode hypersomnia will have depressive symptoms at follow-up (PPV = 67% and 73%, respectively). Likewise, these indices suggest that seven or eight of ten individuals without inter-episode hypersomnia will not have depressive symptoms at follow-up (NPV = 83% and 68%, respectively). The discriminability statistic d' is a measure of test responsiveness, and the area under d' (AUC) is an overall measure of test accuracy with chance equal to 0.5. The IDS-SR and the Sleep Diary TIB have low PPV and AUC statistics, showing limited predictive ability. The IDS-C and the BDI-II have the most favorable balance of test statistics.

3.4. Association between hypersomnia and future depression

To examine the relationship between inter-episode hypersomnia and future depressive symptoms, bivariate partial correlations between hypersomnia indices at baseline and follow-up depressive symptoms were calculated, controlling

Table 3
Predictive power of hypersomnia indices at baseline for IDS-C depressive symptoms at follow-up in the bipolar group ($N = 42$).

Hypersomnia index	Sensitivity	Specificity	Positive predictive value	Negative predictive value	d'	Area under curve
DSISD [a]	0.21	0.93	0.60	0.69	0.65	0.68
IDS-SR [b]	0.47	0.44	0.32	0.60	−0.22	0.43
IDS-C [c]	0.46	0.86	0.67	0.83	0.92	0.74
BDI-II [d]	0.43	0.81	0.73	0.68	0.71	0.69
Sleep diary						
Total sleep time	0.09	0.98	0.67	0.71	.073	0.70
Sleep diary						
Time in bed	0.36	0.64	0.31	0.70	0.01	0.50

[a] DSISD = Duke University Structured Interview for Sleep Disorders.
[b] IDS-SR = Inventory of Depressive Symptomotology, Self Report Version.
[c] IDS-C = Inventory of Depressive Symptomotology, Clinician Version.
[d] BDI-II = Beck Depression Inventory, Second Edition.

for initial level of depression severity and excluding the hypersomnia item from follow-up symptom tabulation. Two of six hypersomnia indices were associated with future depressive symptoms, the IDS-C ($r = 0.32$, $p < 0.05$) and the BDI-II ($r = 0.38$, $p < 0.05$).

3.5. Confounding effects of medications

We carefully evaluated medications as a potential confound. Fifty participants in the bipolar group reported taking at least one medication, and 41 reported taking more than one medication. Chi square tests compared the number of bipolar individuals who did and did not report hypersomnia within each medication class. Hypersomnia presence was evaluated using the IDS-C and BDI-II, as these two indices demonstrated the most favorable balance of test statistics. There were no differences between individuals reporting and not reporting hypersomnia by medication class ($p > 0.05$ for all). Chi square tests of hypersomnia rates between individuals who were not medicated, taking one medication, and taking more than one medication were not significant. Comparisons of medication load between individuals endorsing and not endorsing hypersomnia revealed no differences between groups ($p > 0.05$).

4. Discussion

The first aim of the current study was to document the prevalence of hypersomnia in the inter-episode period. Three of six indices converged on a rate of around 25%. This rate is less than the prevalence of hypersomnia in bipolar depression (Akiskal and Benazzi, 2005; Detre et al., 1972). Even so, the fact that one in four participants reported experiencing hypersomnia is notable, given that the functional consequences of hypersomnia include interpersonal impairment, substance use and decreased productivity (Kaplan and Harvey, 2009). This finding adds to previous research documenting considerable symptomotology in the inter-episode period, including depressive symptoms (Judd et al., 2002), comorbid anxiety (MacQueen et al., 2003), and insomnia (Harvey et al., 2005).

Our second aim was to make progress towards identifying indices of hypersomnia. We did this by evaluating concordance between five hypersomnia indices. Despite considerable differences in wording, administration format (self-report, semi-structured clinical interview, prospective daily diary), and number of persons identified as having hypersomnia, correlations between the indices were medium-to-large (0.42 to 0.57). One interpretation of this finding is that each index shares an underlying construct (Campbell and Fiske, 1959). The only exception to this concordance was the semi-structured DSISD. This may be explained by a difference in emphasis; unlike the other four indices which emphasize prolonged nighttime sleep, the DSISD focuses on excessive daytime sleepiness.

We further evaluated the ability of each index to predict future depressive symptoms. Two indices, the BDI-II and the IDS-C, displayed the best balance of detection statistics. We offer two possible accounts for this finding. First, whereas all other indices asked only about the quantity of time slept or sleepiness, the BDI-II asked about *change* from the usual time slept — thereby differentiating individuals experiencing hypersomnia from mere long sleepers. Second, the IDS-C yielded a much lower rate of hypersomnia than the IDS-SR (24.6% vs. 50%) and also displayed considerably higher predictive power relative to the self-report version (PPV = 0.67 vs. 0.32). Perhaps the prompts included in this clinician-administered measure more carefully discerned patients with hypersomnia. Taken together, these results raise the possibility that an improved assessment for hypersomnia might take the form of a clinician-administered interview and include an emphasis on change from habitual sleep time.

Previous research has raised the possibility that hypersomnia may be better characterized by *TIB* rather than by *TST* (Billiard et al., 1994; Nofzinger et al., 1991). Hence, our third aim was to investigate this distinction. Interestingly, only two individuals with bipolar disorder slept on average greater than 9 h across 7 days of sleep measurement. In contrast, 17 individuals with bipolar disorder spent greater than 9 h in bed. TIB was more highly correlated with all other indices of hypersomnia than TST. These results, consistent with our hypothesis (Kaplan and Harvey, 2009) and the findings from previous researchers (Billiard et al., 1994; Nofzinger et al., 1991), point to the importance of TIB in understanding hypersomnia.

Our fourth and final aim was to evaluate the relationship between hypersomnia in the inter-episode period and future depressive symptoms. Partially supporting our hypothesis, we found that hypersomnia, determined via indices with the best balance of predictive statistics (the BDI-II and the IDS-C), was correlated with future depressive symptoms. This relationship held even after controlling for baseline depression symptoms

and omitting the hypersomnia item from the total depression symptom score at follow-up. This finding is consistent with prospective research on sleep disturbance and unipolar depression (Breslau et al., 1996; Ford and Cooper-Patrick, 2001), and extends it by raising the possibility that hypersomnia also plays a role in bipolar depression. Even so, we emphasize the association may not be interpreted causally.

Several limitations should be noted. First, several of the hypersomnia indices were items taken from depression symptom questionnaires. Though any one individual item from a measure is less reliable than the measure as a whole, these items were included as a first step in indexing hypersomnia. Second, prospective studies on hypersomnia and unipolar depression have utilized a 1-year follow-up (Breslau et al., 1996; Ford and Cooper-Patrick, 2001), although studies suggest bipolar depression can last anywhere from 2 to 4 months (Frankle et al., 2002; Furukawa et al., 2000). Hence, future research should consider multiple assessment points and/or the use of retrospective charting techniques (e.g. Denicoff et al., 2000) to fully elucidate temporal relationships. Third, we emphasize the need for replication in larger samples. Fourth, we acknowledge that this study was based entirely on subjective estimates of sleep. Though sleep diaries are the current gold standard in insomnia research (Buysse et al., 2006) and patient estimates of sleep are typically the only information clinicians can draw upon, future research should use a multi-method approach utilizing both subjective (self-report) and objective (actigraphy and polysomnography) estimates of sleep. Finally and regrettably, we did not re-assess medication use at follow-up. Medication adjustment or discontinuation may have influenced depression symptoms. This limitation should be corrected in future studies.

Interestingly, in the present study there were no differences in medication class, number of medications taken, or overall medication load scores between individuals who did and did not report hypersomnia at baseline. However, we note that medications present a dilemma in research on serious mental illness. As we have reviewed elsewhere (Harvey et al., 2009), sleep-related medication side effects are present in 4% to 37% of patients with bipolar disorder (Glaxo Smith Kline, 2005; PDR Staff, 2007), and atypical antipsychotics in particular are known for their sedative properties (e.g. Kane and Sharif, 2008). However, several medications commonly prescribed for bipolar disorder can be associated with either sedating or alerting side effects (e.g., ariprazole, venlafaxine, sertraline; Glaxo Smith Kline, 2005; PDR Staff, 2007), and it is not uncommon for individuals to experience side effects only early in treatment (Ketter and Wang, 2002). As research in medication-free bipolar samples is unrepresentative and lacks generalizability, we did not pursue this approach here.

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Conflict of interest

All authors report no competing interests.

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