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Authors

Sylvia, Louisa G Salcedo, Stephanie Peters, Amy T <u>et al.</u>

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Do Sleep Disturbances Predict or Moderate the Response to Psychotherapy in Bipolar Disorder?

Louisa Sylvia, PhD^{1,2}, Stephanie Salcedo, BA³, Amy Peters, MA⁴, Pedro Vieira da Silva Magalhães, MD, MSc⁵, Ellen Frank, PhD⁶, David Miklowitz, PhD⁷, Michael W. Otto, PhD⁸, Michael Berk, PhD^{9,10}, Andrew A. Nierenberg, MD^{1,2}, and Thilo Deckersbach, PhD^{1,2} ¹Massachusetts General Hospital, 50 Staniford Street, Suite 580 Boston, MA, 02114

²Harvard Medical School, Boston, MA

³The University of North Carolina at Chapel Hill, Department of Psychology and Neuroscience, 235 E. Cameron Ave, CB 3270, Chapel Hill, NC 27519

⁴University of Illinois at Chicago, Department of Psychology, 1747 W Roosevelt Rd, MC 747, Chicago, IL 60608

⁵National Institute for Translational Medicine, Hospital de Clínicas de Porto Alegre, Universidade Federal de Rio Grande de Sul, Rua Ramiro Barcelos - de 2002 ao fim - lado par Rio Branco 90035003 - Porto Alegre, RS - Brazil

⁶University of Pittsburgh, Department of Psychiatry, 3811 O'Hara St. Pittsburgh, PA15213

⁷UCLA School of Medicine, 760 Westwood Plaza Rm A8-256, Los Angeles, CA 90024-1759

⁸Boston University, Department of Psychological & Brain Sciences, 64 Cummington Mall, Boston, MA 02215

⁹Deakin University, Department of Psychiatry, Victoria, Australia

¹⁰University of Melbourne, Department of Psychiatry, Level 5, 161 Barry Street, Parkville 3010 VIC Australia

Abstract

This study examined whether sleep disturbance predicted or moderated responses to psychotherapy in participants who participated in STEP-BD, a national, multi-site study that examined the effectiveness of different treatment combinations for bipolar disorder. Participants received either a brief psychosocial intervention called collaborative care (CC; n=130), or intensive psychotherapy (IP; n=163), with study-based pharmacotherapy. Participants (N=243) were defined as current (past week) short sleepers (<6 hours/night), normal sleepers (6.5-8.5 hours/night), and long sleepers (9 hours/night), according to reported average nightly sleep duration the week before randomization. Sleep disturbances did not predict the likelihood of recovery nor time until recovery from a depressive episode. There was no difference in recovery

Corresponding Author: Thilo Deckersbach, PhD, Department of Psychiatry, Massachusetts General Hospital, 50 Staniford St, Suite 580, Boston, MA 02114, Phone: 617-724-6300, tdeckersbach@partners.org.

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rates between IP versus CC for normal sleepers, and medium effect sizes were observed for differences in short and long sleepers. In this study, sleep did not play a major role in predicting or moderating response to psychotherapy in bipolar disorder.

Keywords

sleep disturbance; insomnia; hypersomnia

Introduction

Bipolar disorder is a severe psychiatric illness characterized by episodes of mood elevation and depression. Individuals with this disorder have significant functional impairment, reduced quality of life, and a high risk of suicidality (Kilbourne et al., 2004; Novick, Swartz, & Frank, 2010). Pharmacotherapy is considered the foundation of treatment for this chronic disorder (Geddes & Miklowitz, 2013); however, use of medications alone often fails to bring patients to full and sustained remission (Frank, Swartz, & Kupfer, 2000). The limited efficacy of pharmacotherapy alone highlights the need for adjunctive psychosocial interventions (Lauder, Berk, Castle, Dodd, & Berk, 2010).

When psychotherapy is paired with pharmacotherapy, participants experience reduced rates of relapse, improved medication adherence, reduced residual mood symptoms, and improved overall psychosocial functioning (Miklowitz, George, Richards, Simoneau, & Suddath, 2003; Miklowitz, 2008; Otto & Miklowitz, 2004). However, there is considerable variability in response rates in clinical trials of psychotherapy, pointing to the need to identify moderators of treatment response.

Sleep disturbance is a common prodromal feature of bipolar disorder and a precipitant of mood episodes (Jackson, Cavanagh, & Scott, 2003). Sleep disturbance often precedes the onset of both manic and depression symptoms, and it worsens after episode onset (Bauer et al., 2006; Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999; Harvey, Schmidt, Scarnà, Semler, & Goodwin, 2005; Jackson et al., 2003). Moreover, during mood episodes, short sleep duration, which is indicative of insomnia, is associated with more severe symptoms, and both short and long sleep duration are associated with poorer functioning and quality of life. Sleep disturbance is also present during periods of relative remission (Harvey et al., 2005). Psychotherapy (e.g. cognitive behavioral therapy, interpersonal psychotherapy) is associated with decreased rapid eye movement (REM) density in individuals with unipolar depression (Buysse, Frank, Lowe, Cherry, & Kupfer, 1997; Nofzinger et al., 1994). During remission, instability in sleep and biological rhythms are correlated with levels of the disability in bipolar disorder (Giglio, Magalhaes, Kapczinski, Walz, & Kapczinski, 2010).

To better understand the role of sleep in treatment outcomes for bipolar disorder, the current study investigated whether sleep disturbance (defined as shorter or longer sleepers) mediates or moderates the likelihood that patients recover from depression in response to intensive psychotherapy or collaborative care in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). STEP-BD, a National Institute of Mental Health-sponsored

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study of the effectiveness of treatments for bipolar disorder, found that adjunctive, intensive psychotherapy, as compared to brief psychoeducation (collaborative care), was more beneficial in achieving and reducing time to recovery from a depressive episode (Miklowitz et al., 2007). We hypothesized that 1) STEP-BD participants who are normal sleepers will have higher recovery rates from mood episodes and will recover in less time compared to short or long sleepers; and 2) individuals with sleep disturbance (i.e., short or long sleepers) would be more likely to achieve recovery with intensive psychotherapy than with collaborative care.

Method

Study Design

STEP-BD was a national, multi-site study that examined the effectiveness of different treatment combinations for symptoms of bipolar disorder, including various pharmacotherapy and psychosocial interventions. STEP-BD was the largest longitudinal treatment outcome study in bipolar disorder, enrolling 4,361 subjects across 21 sites (Sachs et al., 2003). Ethical approval was obtained by each site's respective human research committee (Sachs et al, 2003). Individuals in STEP-BD, who were currently in a depressive episode, were offered to participate a randomized control trial comparing adjunctive intensive psychotherapy to a control group in 15 clinics (Miklowitz et al., 2007). In this trial, participants, after giving additional written informed consent, were randomly assigned to either 6 weeks of treatment (up to 3 sessions) with collaborative care (CC; N=130) or 9 months of weekly treatment (up to 30 sessions) with intensive psychotherapy (cognitive behavioral therapy [CBT; N=75], family focused therapy [FFT; N=26], or interpersonal social rhythm therapy [IPSRT; N=62]) (Miklowitz et al., 2007).

Collaborative care was a brief intervention that focused on psychoeducation about bipolar disorder and employed some of the most common psychosocial strategies shown to be beneficial for bipolar disorder (Miklowitz et al., 2007). CBT emphasized challenging negative thoughts and dysfunctional beliefs, cognitive restructuring, and problem solving training (Lam, Hayward, Watkins, Wright, & Sham, 2005). FFT focused on educating the participants' family members about bipolar disorder and the family unit's impact on the illness course. It also emphasized improving communication and problem solving in the home environment (Miklowitz et al., 2000). IPSRT stressed the importance of social rhythm stability for prevention of mood disruptions by developing plans for mood and social rhythm stability, and learning strategies to manage interpersonal conflicts such as grief, relationship difficulties, or role disputes (Frank et al., 2000; Frank et al., 2005).

Participants

Participants (n = 293) were eligible for the study if they met DSM-IV criteria for bipolar I or II disorders and a current major depressive episode, and were currently being treated or willing to be treated with a mood stabilizer. If participants were currently undergoing psychotherapy, they could enroll in the study if they discontinued non-study related psychotherapy or reduce the sessions to one or fewer per month. Participants were excluded if they needed treatment for substance/alcohol abuse or dependence, were pregnant, had a

history of nonresponse or intolerance to the antidepressant study drugs, or required initial use or changes to their antipsychotic medications (For a more detailed summary of inclusion/exclusion criteria, see Miklowitz et al., 2007). Depending on what arm of the main study they were in, participants were randomly assigned to double-blind pharmacotherapy with mood stabilizers (lithium, valproate, or carbamazepine), placebo plus adjunctive antidepressants (buproprion or fluoxetine), or a combination of mood stabilizer and antipsychotic medications according to patient-physician agreement and guidelines outlined in STEP-BD for best practice evidence-based pharmacotherapy (Sachs et al., 2003) Included in these analyses is a subset (n = 243; 83%) of randomized participants (n = 293), who provided information both at study entry and throughout study participation regarding their minimum and maximum sleep duration from the past week on the Clinical Monitoring Form (CMF; Sachs et al., 2003). Trained clinicians, specializing in the assessment of bipolar symptoms, would use weekly milestones, such as work, seeing friends and family, or the day of the week to help them remember the most and least amount of sleep that they had over the past week.

Sleep Functioning Measures

Sleep duration was operationally defined as the average number of hours of sleep in the past week. This average was calculated using the minimum and maximum sleep duration values from the prior week reported on the CMF (Gruber et al., 2009). Participants were divided into three groups based on their average nightly sleep duration the week prior to baseline: short sleepers, normal sleepers, and long sleepers. Short sleepers were defined as those with an average of < 6 hours of sleep per night, normal sleepers as those with an average 6.5 - 8.5 hours per night, and long sleepers as those with 9 hours of sleep per night. These cutoffs have been validated in other studies based on their distinct clinical correlates (Edinger et al., 2000; Gruber et al., 2007).

Assessment of Treatment Outcomes

Diagnoses and Psychiatric History—Diagnoses of bipolar disorder relied on the consensus of two trained clinicians: a clinical specialist (a psychologist or social worker) who administered the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and a psychiatrist who administered a standardized affective disorder evaluation (ADE; Sachs, 1990). Diagnosis of anxiety disorders relied on the MINI, and psychiatric history (e.g., number of previous bipolar episodes) were captured on the ADE.

Mood Symptoms—During each treatment visit, participants' mood symptoms were assessed using the CMF. Participants reporting 2 moderate mood symptoms (depression and mania/hypomania) for 8 consecutive weeks were given a clinical status designation of "recovered." Participants were considered "not recovered" if they reported 3 depressive or manic/hypomanic symptoms (Sachs et al., 2003). Interrater reliability coefficients (according to gold standard ratings for depression and mania ratings in the CMF) ranged from 0.83 to 0.99 (intraclass correlations).

Overall Functioning—The Global Assessment of Functioning (GAF) scale is scored on a numeric scale (range: 0=inadequate information to 100=superior functioning) and is widely

used to rate the social, occupational, and psychological functioning of adults (Hall, 1995). The modified Global Assessment of Functioning (GAF) scale has more detailed criteria and a more structured scoring system than the original GAF. Scores were based on the judgment of trained study research staff after completing their clinical interview.

Data Analyses

To evaluate whether sleep group (short, normal, or long sleepers) predicted recovery rates and time until recovery, we conducted logistic regression and Cox proportional hazard (survival) models. Participants were included until their final assessment point, which was a maximum of 365 days (*M*=166.48, *SD*=102.58; Sachs et al., 2003). To evaluate the ability of sleep group to predict recovery status after adjusting for treatment effects, treatment condition (intensive psychotherapy or collaborative care) was included in the model as an independent variable, and participants who were normal sleepers were compared to short and long sleepers in terms of recovery status. Demographic, mood, and medication variables that differed across sleep groups were entered as predictors into the regression models.

To examine whether sleep disturbance moderated treatment outcome, we added an interaction term with treatment condition to our models predicting recovery rates and time until recovery. We followed Kraemer and Kupfer's (2006) recommendations for examining exploratory moderators of treatment outcome in randomized controlled trials, using effect sizes. We examined the magnitude of the treatment effects at each proposed moderator level (Kraemer & Kupfer, 2006) and 95% confidence intervals, as indicated by the Newcombe-Wilson score method without continuity correction (Newcombe, 1998).

To illustrate the magnitude of effect sizes, we used the Number Needed to Treat (NNT) effect size, which is most robust for examining the clinical significance of binary outcomes (Altman & Andersen, 1999; Cook & Sackett, 1995; Cook & Sackett, 1995). NNT is the number of patients one would expect to treat with the investigational treatment, or intensive psychotherapy, in order to have one more patient respond to the treatment than if the same number was treated with the control treatment (Deckersbach et al., 2014). An NNT value of 2 is considered large, 3.5 is medium, and effect sizes greater than 9 are small (Kraemer & Kupfer, 2006). We compared short sleepers, normal sleepers, and long sleepers on the magnitude of the between group (collaborative care vs. psychotherapy) effect size. NNT for "recovered" status was examined separately for participants in each sleep group and treatment condition according to the average number of hours they reported sleeping per night at their baseline visit.

Additionally, for each sleep group, a $3 \times 2 \times 2$ mixed model analysis of variance (MANOVA) was used to examine the change in sleep duration within subjects and across sleep groups and treatment arms, with sleep group (short sleepers, normal sleepers, and long sleepers) and treatment group (intensive psychotherapy, collaborative care) as the between subjects factors and study visit (pre-, post- intervention) as the within subjects factor.

Results

Study Sample

Table 1 shows the demographic and clinical characteristics of the 243 depressed bipolar participants. The average age was 40.32 (SD = 11.47), 60% (n = 146) were female, and 61% (n=136) had bipolar I disorder. There were no significant differences in demographic and clinical characteristics between our sample and the 50 participants with no CMF sleep data (data not shown).

Psychosocial Treatment Outcome

Participants demonstrated significantly higher year end recovery rates if they were randomly assigned to intensive psychotherapy than collaborative care, $\chi^2(1, n = 243) = 4.00$, p < .05. These findings are consistent with the results found in the full sample (n = 293; Miklowitz et al., 2007).

Clinical and Demographic Variables by Sleep Group

Out of the 243 participants with baseline sleep data available, 67 were identified as short sleepers, 99 as long sleepers, and 77 as normal sleepers. The subgroups did not differ in sex, education, marital status, bipolar subtype, depressive symptom severity, or having a lifetime anxiety disorder (all *p*'s > .18; see Table 1). There were differences among the three groups in baseline manic symptom severity, F(2, 242) = 2.95, p = .05, and mood stabilizer usage, $\chi^2(2, n = 238) = 7.61$, p < .05. There were statistical trends towards differences in global functioning (GAF) scores, F(2, 235) = 2.69, p = .07, atypical antipsychotic usage, $\chi^2(2, n = 238) = 4.00$, p = .07, and anticonvulsant usage, $\chi^2(2, n = 238) = 5.43$, p = .06 (Table 1).

Pairwise comparisons showed that short sleepers had greater mania severity than long sleepers, t(240, n = 236) = 2.35, p < .05. Compared to normal sleepers, short sleepers were significantly more likely to be taking mood stabilizers $\chi^2(1, n = 141) = 6.96$, p < .05, but less likely to be taking atypical antipsychotics $\chi^2(1, n = 141) = 4.58$, p < .05. Normal sleepers were significantly less likely than long sleepers to be taking mood stabilizers $\chi^2(1, n = 171) = 5.15$, p < .05, and anticonvulsants $\chi^2(1, n = 171) = 4.96$, p < .05. Short sleepers were also significantly less likely to take atypical antipsychotics than long sleepers $\chi^2(1, n = 164) = 4.04$, p < .05. Note the varying degrees of freedom are due to missing values. Binary logistical regressions showed that baseline mania severity did not significantly predict recovery rates in any of the sleep groups (all p's > .12).

Does Sleep Type Predict Recovery or Time to Recovery?

Logistic and Cox regressions were used to examine predictors of recovery and time to recovery. Treatment group, sleep group, baseline GAF, and medication use (anticonvulsants, atypical antipsychotics, other mood stabilizers) were entered as additional predictors in the models. Results of the modeling sequence are shown in Table 2. Sleep group (short, long, normal) did not predict likelihood of recovery (p's > .41; see Table 2) nor time until recovery (p's > .57). Higher baseline GAF scores and increased mood stabilizer use (not Lithium) significantly predicted recovery (p's < .05) but not time until recovery (p's > .16; see Table 2).

Moderator Analyses

The treatment interaction terms for sleep group did not reach significance for either model, so sleep group did not moderate recovery or time to recovery (p's > .20). Sixty-three percent (n = 25) of short sleepers recovered with intensive psychotherapy, whereas only 41% (n = 11) recovered with collaborative care. This treatment response rate difference resulted in a medium effect size (NNT = 4.55; see Table 3). Thus, we would need to treat 4.55 short sleepers with IP rather than collaborative care to have an additional short sleeper recovering with IP. A similar pattern of effects was observed for long sleepers. Seventy percent (n = 35) of long sleepers recovered with psychotherapy, whereas only 51% (n = 25) recovered with collaborative care. This treatment difference resulted in a medium effect size (NNT = 5.26; see Table 2). That is, we would need to treat 5.26 long sleepers with IP compared to collaborative care to have an additional long sleeper recovered with collaborative care. These recovery and 58% (n = 18) recovered with collaborative care. These recovery rates corresponded to a very small effect size (NNT = 100; see Table 3).

Changes in Sleep with Treatment

Table 4 shows the changes in average sleep duration post-treatment for each sleep group. The $3 \times 2 \times 2$ MANOVA assessing sleep change as function of baseline sleep group and treatment indicated a significant main effect of sleep group, R(2, 237) = 192.7, p < .001, and study visit, R(1, 237) = 8.10, p < .01. There was no main effect of treatment group, R(1, 237)= 0.69, p = .41, indicating that sleep duration did not differ for intensive psychotherapy and collaborative care. There was a significant study visit by sleep group interaction, R(2, 237) =87.92, p < .001, indicating that change in sleep duration varied according to sleep group over the treatment phase. Sleep duration pre- to post-intervention increased for short sleepers ($M_{Pre-} = 4.94$, $M_{Post-} = 6.72$), decreased for long sleepers ($M_{Pre-} = 10.84$, $M_{Post-} = 8.24$), and did not change for normal sleepers. There was no study visit by treatment group interaction, indicating that change in sleep duration over treatment did not vary according to treatment condition. There was also no study visit by treatment group by sleep group interaction, or sleep group by treatment group interaction.

Discussion

The present study investigated whether sleep disturbance serves as a predictor and/or a moderator of psychotherapy response in depressed individuals with bipolar disorder. Sleep neither predicted the likelihood of recovery nor the time to recovery in our analyses. Contrary to our hypothesis, receiving intensive psychotherapy as opposed to collaborative care did not offer a major advantage in terms of recovery rates. This is somewhat surprising, as individuals with bipolar disorder who are poor sleepers may experience more stressors in their lives or have less ability to manage the stressors, which would be addressed in intensive psychotherapy, but not collaborative care. This hypothesis is consistent with prior studies indicating that stressful life events can have a negative impact on sleep quality (Bernert, Merrill, Braithwaite, Van Orden, & Joiner, 2007; Frank et al., 2000; Haynes, McQuaid, Ancoli-Israel, & Martin, 2006). Noteworthy shortcomings of the present study included that sleep duration was assessed by self-report which is vulnerable to recall bias, and we the

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study did not include objective measures of sleep quantity or quality such as polysomnography or actigraphy (Fernandez-Mendoza et al., 2011; Mercer, Bootzin, & Lack, 2002). Therefore, it is not possible to formally diagnose individuals with insomnia or hypersomnia. Future research should utilize objective measures or daily sleep diaries to provide more data on weekly sleep patterns. Randomization to treatment group was not stratified according to sleep-type, possibly confounding our finding of sleep on recovery. Of note, this study also does not examine the role of sleep on mania or hypomania on treatment response as participants were only enrolled if depressed at baseline. Further, due to sample size restrictions, we did not investigate the differential effects of the type of psychotherapy, which consisted of three treatments. Therefore, it is possible that the extent to which sleep was emphasized differed depending on the treatment modality received. Future research should more closely examine whether sleep patterns influence response to psychotherapy differentially depending on type of services. Lastly, the measure of sleep only covered the prior past week, and it would be useful to know if habitual long-term sleep patterns had a similar relationship. Furthermore, it is possible that sleep variability, rather than sleep duration alone may have a greater impact on treatment response. With these caveats in mind, in summary, our findings indicate that sleep during the past week does not seem to play a major role in predicting or moderating response to psychotherapy in bipolar disorder, suggesting that examining current sleep may not be a necessary factor that clinicians need to consider when determining the most appropriate type of psychosocial intervention for their patients.

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References

- Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ (Clinical Research Ed). 1999; 319(7223):1492–1495.
- Bauer M, Grof P, Rasgon N, Bschor T, Glenn T, Whybrow PC. Temporal relation between sleep and mood in patients with bipolar disorder. Bipolar Disorders. 2006; 8(2):160–167. DOI: 10.1111/j. 1399-5618.2006.00294.x [PubMed: 16542186]
- Bernert RA, Merrill KA, Braithwaite SR, Van Orden KA, Joiner TEJ. Family life stress and insomnia symptoms in a prospective evaluation of young adults. Journal of Family Psychology. 2007; 21(1): 58–66. DOI: 10.1037/0893-3200.21.1.58 [PubMed: 17371110]
- Buysse DJ, Frank E, Lowe KK, Cherry CR, Kupfer DJ. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. Biological Psychiatry. 1997; 41(4):406–418. DOI: 10.1016/S0006-3223(96)00041-8 [PubMed: 9034535]
- Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Research. 1999; 86(3): 267–270. DOI: 10.1016/S0165-1781(99)00036-0 [PubMed: 10482346]
- Cook RJ, Sackett DL. The number needed to treat: A clinically useful measure of treatment effect. BMJ (Clinical Research Ed). 1995; 310(6977):452–454.
- Deckersbach T, Peters AT, Sylvia L, Urdahl A, Magalhães PV, Otto MW, Kinrys G. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? results from STEP-BD. American Journal of Psychiatry. 2014; 171(2):178–186. [PubMed: 24077657]
- Edinger JD, Fins AI, Glenn DM, Sullivan RJJ, Bastian LA, Marsh GR, Vasilas D. Insomnia and the eye of the beholder: Are there clinical markers of objective sleep disturbances among adults with and without insomnia complaints? Journal of Consulting and Clinical Psychology. 2000; 68(4):586– 593. DOI: 10.1037/0022-006X.68.4.586 [PubMed: 10965634]
- Fernandez-Mendoza J, Calhoun SL, Bixler EO, Karataraki M, Liao D, Vela-Bueno A, Vgontzas AN. Sleep misperception and chronic insomnia in the general population: Role of objective sleep duration and psychological profiles. Psychosomatic Medicine. 2011; 73(1):88–97. DOI: 10.1097/ PSY.0b013e3181fe365a [PubMed: 20978224]
- Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Eagiolini AM, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Archives of General Psychiatry. 2005; 62(9):996–1004. DOI: 10.1001/archpsyc.62.9.996 [PubMed: 16143731]
- Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: Managing the chaos of bipolar disorder. Biological Psychiatry. 2000; 48(6):593–604. DOI: 10.1016/ S0006-3223(00)00969-0 [PubMed: 11018230]
- Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013; 381(9878):1672–1682. DOI: 10.1016/S0140-6736(13)60857-0 [PubMed: 23663953]

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- Giglio LM, Magalhaes PV, Kapczinski NS, Walz JC, Kapczinski F. Functional impact of biological rhythm disturbance in bipolar disorder. Journal of Psychiatric Research. 2010; 44(4):220–223. DOI: 10.1016/j.jpsychires.2009.08.003 [PubMed: 19758600]
- Gruber J, Harvey AG, Wang PW, Brooks JO I,II, Thase ME, Sachs GS, Ketter TA. Sleep functioning in relation to mood, function, and quality of life at entry to the systematic treatment enhancement program for bipolar disorder (STEP-BD). Journal of Affective Disorders. 2009; 114(1-3):41–49. DOI: 10.1016/j.jad.2008.06.028 [PubMed: 18707765]
- Hall RC. Global assessment of functioning: A modified scale. Psychosomatics. 1995; 36(3):267–275. [PubMed: 7638314]
- Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. The American Journal of Psychiatry. 2005; 162(1):50–59. DOI: 10.1176/appi.ajp.162.1.50 [PubMed: 15625201]
- Haynes, PL., McQuaid, JR., Ancoli-Israel, S., Martin, JL. Disrupting life events and the sleep-wake cycle in depression. United Kingdom: Cambridge University Press; 2006.
- Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. Journal of Affective Disorders. 2003; 74(3):209–217. doi:S0165-0327(02)00266-5. [PubMed: 12738039]
- Kaneita Y, Ohida T, Osaki Y, Tanihata T, Minowa M, Suzuki K, Hayashi K. Association between mental health status and sleep status among adolescents in japan: A nationwide cross-sectional survey. The Journal of Clinical Psychiatry. 2007; 68(9):1426–1435. [PubMed: 17915984]
- Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Haas GL. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disorders. 2004; 6(5):368– 373. DOI: 10.1111/j.1399-5618.2004.00138.x [PubMed: 15383128]
- Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. Biological Psychiatry. 2006; 59(11):990–996. DOI: 10.1016/j.biopsych.2005.09.014 [PubMed: 16368078]
- Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in patients with bipolar disorder: Cognitive therapy outcome after 2 years. The American Journal of Psychiatry. 2005; 162(2):324–329. DOI: 10.1176/appi.ajp.162.2.324 [PubMed: 15677598]
- Lauder SD, Berk M, Castle DJ, Dodd S, Berk L. The role of psychotherapy in bipolar disorder. The Medical Journal of Australia. 2010; 193(4 Suppl):S31–5. [PubMed: 20712559]
- Mercer JD, Bootzin RR, Lack LC. Insomniacs' perception of wake instead of sleep. Sleep: Journal of Sleep and Sleep Disorders Research. 2002; 25(5):559–566.
- Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: State of the evidence. The American Journal of Psychiatry. 2008; 165(11):1408–1419. DOI: 10.1176/appi.ajp.2008.08040488 [PubMed: 18794208]
- Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of familyfocused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Archives of General Psychiatry. 2003; 60(9):904–912. DOI: 10.1001/archpsyc.60.9.904 [PubMed: 12963672]
- Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington N, Wisniewski SR, Kogan JN, Sachs GS. Psychosocial treatments for bipolar depression: A 1-year randomized trial from the systematic treatment enhancement program. Archives of General Psychiatry. 2007; 64(4):419–427. DOI: 10.1001/archpsyc.64.4.419 [PubMed: 17404119]
- Miklowitz DJ, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, Suddath R. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry. 2000; 48(6):582–592. DOI: 10.1016/ S0006-3223(00)00931-8 [PubMed: 11018229]
- Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine. 1998; 17(8):873–890. [PubMed: 9595617]
- Nofzinger EA, Schwartz RM, Reynolds CF, Thase ME, Jennings JR, Frank E, Kupfer DJ. Affect intensity and phasic REM sleep in depressed men before and after treatment with cognitivebehavioral therapy. Journal of Consulting and Clinical Psychology. 1994; 62(1):83–91. DOI: 10.1037/0022-006X.62.1.83 [PubMed: 8034834]

- Novick DM, Swartz HA, Frank E. Suicide attempts in bipolar I and bipolar II disorder: A review and meta-analysis of the evidence. Bipolar Disorders. 2010; 12(1):1–9. DOI: 10.1111/j. 1399-5618.2009.00786.x
- Otto MW, Miklowitz DJ. The role and impact of psychotherapy in the management of bipolar disorder. CNS Spectrums. 2004; 9(11):27–32. [PubMed: 15529090]

Sachs GS. Use of clonazepam for bipolar affective disorder. Journal of Clinical Psychiatry. 1990

- Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Rosenbaum JF. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder. Biological Psychiatry. 2003; 53(11):1028–1042. DOI: 10.1016/S0006-3223(03)00165-3 [PubMed: 12788248]
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Dunbar GC. The miniinternational neuropsychiatric interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry. 1998; 59(Suppl 20):22–33.

Table 1Demographic and Illness Characteristics of 243 Depressed Bipolar Patients By SleepGroup

	Short Sleepers (SS)	Normal Sleepers (NS)	Long Sleepers (LS)	Overall
	$M \pm SD$	$\mathbf{M} \pm \mathbf{S}\mathbf{D}$	$\mathbf{M} \pm \mathbf{S}\mathbf{D}$	$M \pm SD$
Age	41.06 ± 9.98	40.43 ± 12.98	39.71 ± 11.27	40.32 ± 11.47
Depressive Severity	6.68 ± 2.20	6.31 ± 2.36	6.28 ± 1.85	6.40 ± 2.12
Mania Severity ^a	1.35 ± 1.04	1.21 ± 1.14	0.96 ± 0.96	1.15 ± 1.05
Number of Therapy Sessions	$8.61{\pm}9.79$	9.23 ± 11.06	$8.47{\pm}9.91$	8.75 ± 10.22
Baseline GAF	57.84 ± 8.70	54.93 ± 9.51	57.95 ± 9.20	56.96 ± 9.23
	N (%)	N (%)	N (%)	N (%)
Female Sex	44 (67)	42 (55)	60 (61)	146 (60)
Education >1 year college	52 (80)	57 (78)	75 (82)	184 (80)
Married	23 (34)	24 (32)	29 (30)	76 (32)
Diagnosis				
Bipolar I	33 (52)	42 (58)	61 (67)	136 (61)
Bipolar II	30 (48)	30 (42)	30 (33)	90 (40)
Lifetime Anxiety Disorder	40 (63)	45 (63)	62 (68)	147 (65)
Age at illness onset				
< 15	17 (29)	17 (25)	25 (30)	59 (28)
> 15	42 (71)	52 (75)	58 (70)	152 (72)
Number Lifetime Manic Episodes				
1-9	17 (30)	25 (38)	30 (37)	72 (36)
10-20	15 (27)	6 (9)	11 (14)	32 (16)
20+	24 (43)	34 (52)	40 (49)	98 (49)
Number Lifetime Depressive Episodes				
1-9	23 (41)	23 (35)	21 (26)	67 (33)
10-20	6 (11)	8 (12)	12 (15)	26 (13)
20+	27 (48)	34 (52)	48 (59)	109 (54)
# Anxiety Disorders				
0	23 (36)	28 (38)	29 (32)	80 (35)
1	20 (32)	18 (25)	26 (29)	64 (29)
2	11 (17)	16 (22)	16 (18)	43 (19)
3	6 (10)	7 (10)	10 (11)	23 (10)
4	1 (2)	3 (4)	9 (10)	13 (6)
5	2 (3)	1 (1)	1 (1)	4 (2)
# Comorbid Conditions				
0	14 (21)	18 (23)	21 (21)	53 (22)
1	19 (28)	11 (14)	18 (18)	48 (20)
2	14 (21)	23 (30)	19 (19)	56 (23)
3	20 (30)	25 (33)	41 (41)	86 (35)

	Short Sleepers (SS)	Normal Sleepers (NS)	Long Sleepers (LS)	Overall
	$\mathbf{M} \pm \mathbf{S}\mathbf{D}$	$\mathbf{M} \pm \mathbf{S}\mathbf{D}$	$\mathbf{M} \pm \mathbf{S}\mathbf{D}$	$M \pm SD$
Baseline Medications				
Antidepressants	31 (46)	30 (41)	40 (41)	101 (42)
Atypical Antipsychotics ^{a,b}	12 (18)	25 (34)	31 (32)	68 (29)
Anxiolytics	19 (28)	19 (26)	27 (28)	65 (27)
Anticonvulsants ^C	37 (55)	30 (41)	56 (58)	123 (52)
Lithium	21 (31)	27 (37)	30 (40)	78 (33)
Other Mood Stabilizers ^{b,c}	25 (37)	13 (18)	32 (33)	70 (30)

Abbreviations: GAF (Global Assessment of Functioning), Depressive Severity (refers to summary score of depression symptoms [excluding sleep variables] from the Clinical Monitoring Form recorded within 1 week of the date of randomization to treatment), Mania Severity (refers to summary score of mania symptoms [excluding sleep variables] from the Clinical Monitoring Form recorded within 1 week of the date of randomization to treatment)

Notes: Where data points were missing, percentages are calculated out of total number of available cases. Diagnoses were determined using the Affective Disorders Evaluation.

^{*a*}Difference between short sleepers and long sleepers (p < .05)

 $b_{\mbox{Difference}}$ between short sleepers and normal sleepers $(p\,{<}\,.05)$

^CDifference between normal sleepers and long sleepers (p < .05)

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Predictor	p	Wald	OR	(95% CI)	d	\mathbf{R}^{2*}
Logistic regression: predicting recovery						760.
Treatment group **	-0.49	3.06	0.62	(0.36-1.06)	.08	
Short sleepers ***	-0.24	0.50	0.79	(0.41-1.52)	.48	
Long sleepers	-0.28	0.68	0.76	(0.39-1.47)	.41	
Baseline GAF	0.04	0.02	1.04	(1.01 - 1.07)	.01	
Anticonvulsants	0.05	0.02	1.05	(0.52-2.11)	80.	
Atypical Antipsychotics	-0.27	0.74	0.76	(0.41 - 1.41)	.39	
Other Mood Stabilizers	0.77	3.92	2.16	(1.01 - 4.63)	.05	
Cox regression: predicting time until recovery						076
Treatment group **	-0.22	1.59	0.80	(0.57 - 1.13)	.21	
Short sleepers ***	-0.10	0.25	06.0	(0.60-1.36)	.62	
Long sleepers ***	-0.12	0.33	0.88	(0.58 - 1.35)	.57	
Baseline GAF	0.01	1.18	1.01	(0.99-1.03)	.28	
Anticonvulsants	0.12	0.33	1.13	(0.74-1.73)	.57	
Atypical Antipsychotics	0.04	0.04	1.04	(0.71-1.52)	.85	
Other Mood Stabilizers	0.36	2.02	1.43	(0.87 - 2.36)	.16	

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Notes:

For logistic regressions, R² represents Nagelkerke R², an estimate of the increment in variance in the probability of recovery accounted for by the predictors tested. For Cox regressions, R² represents Cox-Snell R², an estimate of the relative association between survival and the predictors tested.

 ** Treatment group: intensive psychotherapy (1) versus collaborative care (0).

*** Sleep group: dummy coded with the normal sleepers group coded as the reference group, so only coefficients relative to the reference group are shown.

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Moderator Effects of Sleep Group on Recovery Rates with Collaborative Care and Psychotherapy for Bipolar Depression

		Psychotherap	y		Collaborati	ve Care		95% Confide	nce Intervals
Sleep Group	Z	Number Recovered	% Recovered	Z	Number Recovered	% Recovered	INN	Lower	Higher
Short Sleepers	40	25	63%	27	11	41%	4.55	-42	2
Normal Sleepers	46	26	57%	31	18	58%	100	-4	5
Long Sleepers	50	35	70%	49	25	51%	5.26	-448	3

Abbreviations: NNT, Number needed to treat; CI, Confidence interval.

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Table 4

	Psychol	therapy	Collabora	tive Care	A	Π
Sleep Group	Pre-M (SD)	Post-M (SD)	Pre-M (SD)	Post-M (SD)	Pre-M (SD)	Post-M (SD)
Short Sleepers	$4.81_{\rm a}(1.03)$	6.91 _b (2.03)	$5.14_{\rm a} (0.68)$	$6.43_{\rm b}$ (2.13)	$4.94_{\rm a}$ (0.92)	6.72 _b (2.07)
Normal Sleepers	$7.54_{\rm a}$ (0.66)	$7.17_{\rm a}$ (1.60)	$7.71_{ m a}(0.67)$	$7.57_{\rm a}(1.40)$	$7.61_{\rm a}$ (0.66)	$7.33_{\rm a}(1.53)$
Long Sleepers	$10.91_{\rm a}(1.85)$	7.99 _b (1.55)	$10.77_{\rm a}(1.58)$	$8.5_{\rm b}$ (2.22)	$10.84_{\rm a}~(1.72)$	8.24 _b (1.92)

Abbreviations: Pre- (Baseline visit), Post- (Post-intervention)

Note: Values with differing subscripts are significantly different at the p < .05 level.