Published in final edited form as:

J Affect Disord. 2012 December 10; 141(0): 484–487. doi:10.1016/j.jad.2012.01.046.

Sleep duration is associated with dyslipidemia in patients with bipolar disorder in clinical remission

I Soreca¹, ML Wallace², E Frank¹, BP Hasler¹, JC Levenson^{1,3}, and DJ Kupfer¹

¹University of Pittsburgh School of Medicine, Department of Psychiatry

²University of Pittsburgh, Department of Statistics

³University of Pittsburgh, Department of Psychology

Abstract

Background—The pathways to increased cardiovascular risk in bipolar disorder include health behaviors, psychosocial stress and long-term medication exposure. However, the evidence that the association between cardiovascular risk factors and bipolar disorder remains significant after controlling for these co-factors suggests that additional important risk factors have yet to be identified. Our hypothesis is that disturbances in the sleep-wake cycle are an important and under-recognized pathway through which affective disorders lead to increased cardiovascular risk.

Methods—In patients with bipolar disorder type 1 in clinical remission, we: 1) explored whether sleep disturbance predicted the endorsement of NCEP ATP-III criteria for dyslipidemia, independent of other lifestyle factors and 2) tested the association between low HDL (NCEP-ATP III) and sleep duration measured with actigraphy over an eight-day period.

Results—Median sleep duration is significantly associated with low HDL. The risk of having low HDL increases by 1.23 with every 30 minutes of reduced sleep time.

Limitations—Since sleep patterns in patients with bipolar disorder are variable and irregular, it is possible that other sleep characteristics, not present during the span of our study, or the variability itself may be what drives the increased cardiovascular risk

Conclusions—Sleep characteristics of patients with bipolar disorder in clinical remission are associated with cardiovascular risk. More specifically, sleep duration was associated with low HDL. Clinicians should pay special attention to sleep hygiene in treating individuals with bipolar disorder, even when they are in clinical remission.

© 2012 Elsevier B.V. All rights reserved.

Corresponding Author; Isabella Soreca Western Psychiatric Institute and Clinic-BT room 807A 3811 O'Hara Street Pittsburgh, PA 15213 USA Phone: 412 2465400 Fax: 412 2465533 sorecai@upmc.edu.

Contributors Author I.S. designed the study managed the literature searches and wrote the first draft of the manuscript. Author M.L.W. managed the analyses. Author EF and DJK designed the study and wrote the protocol. Authors J.C.L. and B.P.H. managed the literature searches and contributed to writing the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest Drs I.S., M.L.W., B.P.H., J.C.L. and D.J.K. have no potential conflict of interest to disclose. Dr EF is in the Servier International Advisory Board and owns Guilford Press and American Psychological Association Press Royalties.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

bipolar disorder; sleep; cardiovascular risk; HDL

Introduction

The pathways through which bipolar disorder is thought to increase CV risk include health behaviors (e.g., smoking, physical inactivity, poor diet, obesity), psychosocial stress (e.g., low occupational status, low income, poor educational attainment) and long-term medication exposure. However, the evidence that the association between cardiovascular risk factors and bipolar disorder remains significant after controlling for these co-factors (Murray et al., 2009, Goldstein et al., 2009, Fiedorowicz et al., 2009) suggests that additional important risk factors have yet to be identified.

Our hypothesis is that disturbances in the sleep-wake cycle are an important and under-recognized pathway through which affective disorders lead to increased CV risk. Bipolar disorder is characterized by a high frequency of subsyndromal inter-episode symptom excursions (Sachs, 2003), including sleep disturbances. While a limited number of studies have described PSG sleep staging in euthymic patients with conflicting results (Knowles et al., 1986, Sitaram et al., 1982), recent findings from sleep diaries and actigraphy indicate that the remitted patients with bipolar disorder have a substantial degree of sleep disturbance (Millar et al., 2004, Jones et al., 2005, Harvey et al., 2005).

A wealth of research over the past decade has linked sleep disturbances and short sleep duration with an increased risk of metabolic syndrome (Hall et al., 2008, Arora et al., 2011) and, more specifically, to altered serum lipid profile (Gangwisch et al., 2010, Kaneita et al., 2008). Even though patients with bipolar disorder are especially vulnerable to cardiovascular morbidity and mortality, to the best of our knowledge no study has explored sleep as a potential link to cardiovascular risk. We therefore sought to explore whether sleep duration would predict the endorsement of NCEP ATP-III (Grundy et al., 2005) criteria for dyslipidemia, independent of other lifestyle factors, in a sample of patients with bipolar disorder type 1 in clinical remission.

Methods

General Procedures

The Institutional Review Board at the University of Pittsburgh reviewed and approved all of the study procedures. Participants in this study were taking part in a larger NIMH funded treatment study (MH081003) comparing standard of care with an integrated model of care for patients with bipolar 1 disorder in maintenance treatment. As part of the inclusion criteria for the parent study, participants were required to meet lifetime criteria for bipolar disorder, type I (ascertained with the SCID-IV), be free of unstable or untreated medical conditions, have a BMI 25 and be in remission, defined as an HAM-D and YMRS scores 10 and 8, respectively, for at least two weeks and have not been hospitalized in the previous year. At study entry participants were also asked to complete fasting blood work to measure lipid profile and wear an actigraphy on their non-dominant wrist for eight consecutive days in their naturalistic environment. The baseline assessments were used for the current analysis. All the participants were on standard of care medications for bipolar disorder.

Dyslipidemia was defined, according to the NCEP ATP-III criteria, as having HDL-C < 40 mg/dL (male), < 50 mg/dL (female) or being on medications to correct dyslipidemia (Grundy et al., 2005).

Statistical analyses

To determine the best way to calculate the central tendency of sleep duration over one week of actigraphy, we first created a histogram of the week of sleep duration observations. Because the sleep duration data were skewed, we chose to use the median to summarize the week of observed sleep durations for each individual.

Non-parametric tests were used to compare patients with and without low HDL and the other components of the metabolic syndrome on age, HAMD, YMRS, psychotropic medications, sleep duration, and fragmentation index due to their skewed distributions. Since there was no differences in these parameters based on other components of metabolic syndrome than low HDL, a logistic regression model was then built to evaluate the contribution of median sleep duration to the likelihood of having low HDL after controlling for age, sex, BMI, and current smoking (yes/no). These covariates were selected based on univariate association with the outcome variable in this sample and also based on a priori knowledge of risk factors for low HDL.

Results

Patients that met the low HDL criterion had significantly shorter median and mean sleep duration, but did not differ on any of the other measures (including HAM-D and YMRS) (Table 1). No differences in sleep parameters or symptom severity were found when patient were compared according to the other components of the metabolic syndrome (results not shown, available upon request)

Median sleep duration is significantly associated with the low HDL. As shown in Table 2, individuals with one minute shorter median sleep duration are $1/\exp(-.007*1) = 1.007$ times more likely to have low HDL. In other words, the risk of having low HDL increases by $1/\exp(-.007*30) = 1.23$ with every 30 minutes of reduced median sleep time (Table 2).

Discussion

Sleep characteristics during the inter-episode interval in bipolar disorder are an important and yet under-recognized feature of this phase of the illness and are associated with impaired functioning and quality of life (Gruber et al., 2009) (Ehlers et al., 1988, Harvey et al., 2005). Moreover, ongoing sleep disturbances are a risk factor for syndromal recurrence (Jackson et al., 2003, Colombo et al., 1999, Kasper and Wehr, 1992, Wu and Bunney, 1990). In this study, we show that sleep characteristics of patients with bipolar disorder in clinical remission are associated with cardiovascular risk. More specifically, sleep duration was associated with increased risk of having low HDL according to the ATP III definition. Of note, while the median sleep duration of patients with low HDL and normal HDL differed by roughly one hour, overall sleep duration was comparable to normative values for the healthy subjects in both groups (Monk et al., 2000).

The association between sleep duration and dyslipidemia in the general population has been shown to have a bimodal distribution, with both shortest and longest reported sleep duration being associated with CVD risk (van den Berg et al., 2008, Bjorvatn et al., 2007). Mechanisms linking short sleep duration (roughly 4 hours per night) with increased cardiovascular risk involve increased markers of inflammation and autonomic dysregulation (van Leeuwen et al., 2009, Novati et al., 2008, Meier-Ewert et al., 2004). Animal models of sleep restriction suggest that insufficient sleep, by acting on stress systems, may predispose individuals to further mood and neuroendocrine dysregulation (van Leeuwen et al., 2009). This is consistent with epidemiological evidence that sleep restriction is an important risk

factor for stress-related conditions, including cardiovascular diseases and mood disorders (Hoevenaer-Blom et al., 2011, Murray and Harvey, 2010).

Longer *reported* sleep, on the other hand, may simply represent longer time in bed (versus longer time of actual consolidated sleep) and thus reflect worse general health or simply lower level of daily activity. In our sample, the overall median sleep duration was roughly 8 hours, with approximately 1 hour difference in sleep duration between the low and the normal HDL group, suggesting that the parameters for “healthy” sleep duration in patients with bipolar disorder may be different than those for the general adult population. Alternatively, one could argue that mechanisms linking sleep duration to cardiovascular risk may be different in patients with mood disorders, making them more vulnerable to changes in sleep duration even within values that are considered normal for adult individuals.

The present study is not free of limitations: the cross-sectional design prevents us from inferring causal relationships; since sleep patterns in patients with bipolar disorder are variable and irregular, it is possible that other sleep characteristics or mood symptoms, not present during the span of our study, or the variability itself may be what drives the increased cardiovascular risk. We tried to minimize uncaptured variability by recruiting patients who had been in clinical remission for at least 2 weeks and by assessing their sleep over an eight-day period. Even though current medications did not have an effect on the results, we can’t rule out that prior medications used may still confound the association between sleep parameters and HDL.

This is the first study to show that in patients with bipolar disorder in clinical remission, sleep duration is associated with a worse cardiovascular profile. Further studies to elucidate mechanisms for sleep-related cardiovascular risk in mood disorder are needed. At the same time, this report suggest that clinicians should pay special attention to sleep hygiene in treating individuals with bipolar disorder, even when they are in clinical remission.

Acknowledgments

We thank Victoria J. Grochocinski and David E. Curet for data management, Joan Battenfield and the DMDPP clinicians for completing the assessments. We finally thank all our study participants.

Funding This work was funded by MH081003 (DJK) and DA027508-03 (IS)

References

- ARORA T, JIANG CQ, THOMAS GN, LAM KB, ZHANG WS, CHENG KK, LAM TH, TAHERI S. Self-reported long total sleep duration is associated with metabolic syndrome: the Guangzhou Biobank Cohort Study. *Diabetes Care*. 2011; 34:2317–9. [PubMed: 21873559]
- Bjorvatn B, Sagen IM, Oyane N, Waage S, Fetveit A, Pallesen S, Ursin R. The association between sleep duration, body mass index and metabolic measures in the Hordaland Health Study. *J. Sleep Res.* 2007; 16:66–76. [PubMed: 17309765]
- 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 Res.* 1999; 86:267–70. [PubMed: 10482346]
- Ehlers CL, Frank E, Kupfer DJ. Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. *Arch. Gen. Psychiatry.* 1988; 45:948–52. [PubMed: 3048226]
- Fiedorowicz JG, Solomon DA, Endicott J, Leon AC, Li C, Rice JP, Coryell WH. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. *Psychosom. Med.* 2009; 71:598–606. [PubMed: 19561163]

- Gangwisch JE, Malaspina D, Babiss LA, Opler MG, Posner K, Shen S, Turner JB, Zammit GK, Ginsberg HN. Short sleep duration as a risk factor for hypercholesterolemia: analyses of the National Longitudinal Study of Adolescent Health. *Sleep*. 2010; 33:956–61. [PubMed: 20614855]
- Goldstein BI, Fagioli A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord*. 2009; 11:657–62. [PubMed: 19689508]
- Gruber J, Harvey AG, Wang PW, Brooks JO 3RD, 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). *J. Affect. Disord*. 2009; 114:41–9. [PubMed: 18707765]
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC JR, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005; 112:2735–52. [PubMed: 16157765]
- Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. *Sleep*. 2008; 31:635–43. [PubMed: 18517034]
- Harvey AG, Schmidt DA, Scrna A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *Am. J. Psychiatry*. 2005; 162:50–7. [PubMed: 15625201]
- Hoevenaer-Blom MP, Spijkerman AM, Kromhout D, Van Den Berg JF, Verschuren WM. Sleep Duration and Sleep Quality in Relation to 12-Year Cardiovascular Disease Incidence: The MORGEN Study. *Sleep*. 2011; 34:1487–92. [PubMed: 22043119]
- Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. *J. Affect. Disord*. 2003; 74:209–17. [PubMed: 12738039]
- Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disord*. 2005; 7:176–86. [PubMed: 15762859]
- Kaneita Y, Uchiyama M, Yoshiike N, Ohida T. Associations of usual sleep duration with serum lipid and lipoprotein levels. *Sleep*. 2008; 31:645–52. [PubMed: 18517035]
- Kasper S, Wehr TA. The role of sleep and wakefulness in the genesis of depression and mania. *Encephale*. 1992; 18(Spec No 1):45–50. [PubMed: 1600904]
- Knowles JB, Cairns J, MacLean AW, Delva N, Prowse A, Waldron J, Letemendia FJ. The sleep of remitted bipolar depressives: comparison with sex and age-matched controls. *Can. J. Psychiatry*. 1986; 31:295–8. [PubMed: 3708522]
- Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J. Am. Coll. Cardiol*. 2004; 43:678–83. [PubMed: 14975482]
- Millar A, Espie CA, Scott J. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. *J. Affect. Disord*. 2004; 80:145–53. [PubMed: 15207927]
- Monk TH, Buysse DJ, Rose LR, Hall JA, Kupfer DJ. The sleep of healthy people--a diary study. *Chronobiol. Int*. 2000; 17:49–60. [PubMed: 10672433]
- Murray DP, Weiner M, Prabhakar M, Fiedorowicz JG. Mania and mortality: why the excess cardiovascular risk in bipolar disorder? *Curr. Psychiatry Rep*. 2009; 11:475–80. [PubMed: 19909670]
- Murray G, Harvey A. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord*. 2010; 12:459–72. [PubMed: 20712747]
- Novati A, Roman V, Cetin T, Hagewoud R, Den Boer JA, Luiten PG, Meerlo P. Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. *Sleep*. 2008; 31:1579–85. [PubMed: 19014078]
- Sachs GS. Unmet clinical needs in bipolar disorder. *J. Clin. Psychopharmacol*. 2003; 23:S2–8. [PubMed: 12832943]
- Sitaram N, Nurnberger JI JR, Gershon ES, Gillin JC. Cholinergic regulation of mood and REM sleep: potential model and marker of vulnerability to affective disorder. *Am. J. Psychiatry*. 1982; 139:571–6. [PubMed: 7072840]

- Van Der Berg JF, Miedema HM, Tulen JH, Neven AK, Hofman A, Witteman JC, Tiemeier H. Long sleep duration is associated with serum cholesterol in the elderly: the Rotterdam Study. *Psychosom. Med.* 2008; 70:1005–11. [PubMed: 18842743]
- Van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, Sallinen M, Harma M, Porkka-Heiskanen T, Alenius H. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PLoS One.* 2009; 4:e4589. [PubMed: 19240794]
- Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am. J. Psychiatry.* 1990; 147:14–21. [PubMed: 2403471]

Table 1

Subjects characteristics

	Low HDL	N	Median (Variance)
Age	No	35	43.11(95.1)
	Yes	51	47.59(84.17)
BMI	No	33	31.04(34.69)
	Yes	48	34.49(40.23)
HRS-25	No	42	7.00(26.26)
	Yes	60	7.00(11.46)
YMRS	No	42	1.00(4.7)
	Yes	60	1.00(5.28)
Nicotine use	No	34	N/A
	Yes	50	
Sleep duration (hours)	No	29	8.63 (101.53)
	Yes	39	7.40(123.7)

Table 2

Logistic regression model testing the association between median sleep duration and low HDL rate.

	B	SE	Wald	Sig	Exp(B)
Age	.027	.030	.804	.370	1.027
Sex	-.072	.596	.014	.904	.931
BMI	.028	.045	.385	.535	1.029
Nicotine use	.825	.707	1.362	.243	2.283
Sleep duration	-.007	.003	4.368	.037	.993