The nature of sleep disturbance in bipolar disorder and the role of circadian dysrhythmia

Bradley AJ[1,2], Webb-Mitchell R[1], Hazu A[1], Slater N[1], Middleton B[3], Gallagher P[1], McAllister-Williams H[1,4], Anderson KN[5]*

1. Institute of Neuroscience, Newcastle University, Wolfson Research Centre, Campus for Aging and Vitality, Westgate Road, Newcastle Upon Tyne, NE4 5LP
2. Eli Lilly and Company Limited, Lilly House, Priestly Road, Basingstoke RG24 9NL.
3. Centre for Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7TE.
4. Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle, UK
5. Regional Sleep Service, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

*corresponding author. Email kirstie.anderson@nuth.nhs.uk

Word count (excluding abstract and references): 3500

Tables 2 (and 1 supplemental table)

Figures 2

References 38

Abstract

Background

Subjective reports of insomnia and hypersomnia are common in bipolar disorder (BD). It is unclear to what extent these relate to underlying circadian rhythm disorder (CRD).

Aims

To objectively assess sleep and CRD in a cohort of patients with BD.

Methods

46 patients with BD and 42 controls had comprehensive sleep/circadian rhythm assessment with respiratory sleep studies, prolonged accelerometry, sleep diaries, melatonin levels, alongside mood, psychosocial functioning and quality of life (QoL) questionnaires.

Results

23 (50%) of patients with BD had abnormal sleep, of who 12 (52%) had a CRD. Patients with abnormal sleep had lower 24 hour melatonin secretion compared to controls and patients with normal sleep. Abnormal sleep/CRD in BD was associated with impaired functioning and worse QoL.

Conclusions

BD is associated with high rates of abnormal sleep and CRD. The association between these disorders, mood and functioning, and the direction of causality, warrants further investigation.

Declaration of Interests

None.

Introduction

Subjective reports of sleep disturbance – both insomnia and hypersomnia – are described in all phases of bipolar disorder (BD), including remission (1-3) but with substantial variability in prevalence between studies. A recent meta-analysis of studies objectively estimating sleep variables in remitted BD patients demonstrated prolonged total sleep time (TST), increased wakenings after sleep onset and reduced sleep efficiency (4). This meta-analysis highlighted that there has also been little consistency in the way sleep and circadian rhythm has been measured and assessed. Studies have used a range of actiwatches and algorithms for calculating sleep and wake estimates and utilised variable recording periods making comparisons across studies challenging. There is a need for methodological improvements, including longer recordings to allow improved analysis of circadian rhythm measures. Thus it is currently unknown what proportion of sleep disorder relates to a circadian rhythm disorder (CRD). Further, none of the published actigraphy studies in BD have performed respiratory sleep studies to screen for primary sleep disorders, such as obstructive sleep apnoea (OSA), that may additionally contribute to hypersomnia and sleep fragmentation. The aim of this study was to describe the different sleep/wake phenotypes in an opportunistic cohort of patients with BD and age matched healthy controls with a comprehensive battery of objective and subjective assessments of sleep and circadian variables, including urinary melatonin levels and respiratory sleep studies analysis.

Method

Participants

The study was approved by the National Research Ethics Service Committee North East - Newcastle & North Tyneside. Outpatients with BD type I or II, in any mood state, were recruited from a research database, patient support groups, and NHS services in the North East of England. Healthy controls, matched by age and gender, were recruited from Newcastle University, local volunteer

databases and hospital staff and their families. All participants provided written informed consent before taking part in the research. Participants were 18 to 65 years, fluent in English and able to provide consent. Exclusion criteria were; Verbal IQ < 90 assessed with National Adult Reading Test (NART)(5), any significant medical or neurological disorder that might interfere with sleep or cognition, current alcohol or substance misuse disorder (defined with DSM IV criteria(6), current shift work and previous significant head injury. A BD diagnosis meeting DSM-IV criteria was confirmed using the Mini International Neuropsychological Interview (MINI)(7). Patients with BD were excluded if they had had any changes to their psychotropic medication in the previous 4 weeks. Exclusion criteria for controls were personal or first degree relative history of a DSM IV Axis I disorder, prescribed psychotropic medications and any known sleep disorder. Additionally controls had to be psychiatrically well, confirmed by MINI interview, have a Hamilton Depression rating scale score (HAMD[17]) score <7, a Young Mania Rating Scale score (YMRS) <5, a Pittsburgh sleep quality index (PSQI) <5 and Epworth sleepiness scale (ESS) score <10.

Overall study design

The study was cross-sectional, with participants assessed over a three week period.

Psychiatric Symptoms and Subjective Sleep Assessments

Participants were assessed on days 1 and 21. A comprehensive battery of questionnaires and rating scales were used to assess mood, anxiety and functioning. These included: the 17 item GRID-HAMD (8), Beck Depression Inventory (BDI) (9), YMRS (10), the State and Trait Anxiety Inventory (STAI) (11), the Functioning Assessment Short Test (FAST) (12). Quality of life (QoL) was assessed with the BD specific scale, the QoL.BD (13). Subjective sleep and circadian rhythm was assessed using: the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (14), the PSQI (15) and the ESS (16). A short version of the morningness/eveningness questionnaire (17) was also used on day 1 of the study to assess chronotype. All medications used by the patients in the BD group were recorded.

Assessment for sleep apnoea

A single night of home partial polysomnography, using the Embletta Gold Polygraphy System (Embla Systems, Bloomfield, USA), was used to screen for sleep apnoea. Respiratory events were scored according to the standard criteria of the American Association of Sleep Medicine (AASM) (18) and the apnoea hypopnoea index (AHI) and oxygen desaturation index (ODI) derived. An AHI of > 5/hr was considered abnormal and indicative of sleep apnoea. Severity was defined as mild (AHI 5-15), moderate (AHI 15 – 30) or severe (AHI >30).

Assessment for Restless Leg Syndrome (RLS).

Participants completed the Restless Legs Syndrome Rating Scale to assess for the presence and severity of RLS (19).

Assessment of sleep wake cycle

Subjects wore a triaxial wrist accelerometer (GENEActiv; Activinsights) on their non-dominant wrist for all 21 days of the study and completed a daily sleep log recording lights out, out of bed time and any daytime naps. The raw accelerometer data was analysed using an open source R package sleep detection algorithm GGIR that has demonstrated a high sensitivity and specificity to detect periods of sleep (20). The algorithm also utilises the sleep log to distinguish nocturnal sleep from daytime naps. As this algorithm is non-proprietary, open access and able to analyse raw accelerometer data recorded on any brand of accelerometer its use should facilitate direct comparisons of sleep estimates from future studies. The following variables were derived: sleep onset time, sleep offset time, TST, time in bed (TIB), sleep efficiency (defined as TST/TIB) and mean 24 hour sleep duration (defined as nocturnal sleep plus daytime naps). Intra-individual variability in sleep variables was defined by the between night standard deviation over the assessment period for individual participants. Correlation analysis was performed to check agreement between sleep logs and accelerometer derived sleep variables. The relative amplitude between day and night activity was calculated from mean acceleration during the least active 5 hours (L5) and most active 10 hours

(M10) according to previously published methods (21). Using both accelerometry derived sleep estimates and the visual sleep wake actograms produced by the algorithm participants were then identified as normal sleepers (6-10 hours sleep within 24 hours with a regular sleep wake cycle), short sleepers (<6 hours nocturnal sleep), long sleep (>10 hours sleep within 24 hours) and circadian rhythm disorder evidenced by either a delayed sleep phase, advanced sleep phase, an irregular sleep wake pattern or a non24 hour pattern in keeping with the circadian rhythm types within the International Classification of Sleep Disorder – 3rd edition (ICSD-3) (22).

Melatonin Measurement

To further explore possible mechanisms of circadian dysfunction 6-sulphatoxymelatonin (aMT6S) was measured. This metabolite of melatonin, was measured in urine over a 48 hour period, once during the first week of the study period and once during the third week of the study period with analysis as per previous published protocols (23).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistical package version 22. Normality of distribution of data was tested using the Shapiro-Wilk test. Log10 or square root transformations were used where necessary to normalise the data. Parametric tests were used unless the data remained non-normally distributed despite transformation when equivalent non-parametric tests were used. A significance threshold of $p< 0.05$ was used for all analyses.

Results

Participants

Eighty eight participants, 46 with BD (16 BD I and 30 BDII) and 42 controls, completed the study protocol and provided accelerometer data (mean 19.7 (SD 3.0) days). Table 1 shows the participant characteristics. Groups did not differ significantly with regard to age or gender but participants with BD had a greater body mass index (BMI), were more likely to be unemployed, and scored more

highly on mood and anxiety ratings and lower on quality of life. Twenty one participants with BD scored $\geq$ 8 on the HAMD[17] (range 8 -35), but none of the patients were considered clinically to be manic or hypomanic for the duration of the study (YMRS range 0-10).

Subjective description of sleep

On the PSQI, which is validated for identifying clinically significant sleep disturbance, patients with BD scored on average 6.4 points higher than the healthy controls (Table 1), with 30 (65.2%) scoring ≥5, indicative of some form of sleep disturbance (Note that a PSQI of ≥5 was an exclusion criteria for healthy controls). Many patients with BD described subjective problems with their sleep. Their average score across the three HAMD[17] sleep items was 2.13 (SD 1.9), with 12 (26.1%) of patients scoring ≥4. Nine BD patients scored $\geq$ 10 on the ESS indicating some excessive daytime sleepiness. In terms of chronotype, the BD group contained more participants with an evening preference than the control group but the difference was not statistically significant (chi squared; 4.449, p=0.108).

Sleep Apnoea

Forty one of 46 participants with BD and 40 of the 42 controls completed the overnight partial polysomnography providing good quality respiratory data. Significantly more participants with BD than controls had OSA (BD n=12 (29%), controls n=4 (10%), chi squared; 4.742, p=0.029). Four participants with BD had moderately severe OSA (AHI 15-30) but no participant in either group had severe sleep apnoea (AHI > 30). One participant with BD was already on continuous positive airways pressure (CPAP) treatment for known OSA and was therefore counted as AHI < 5 and hence with 'normal' sleep.

Restless Leg Syndrome

Two participants with BD, but no controls, reported moderate or severe restless legs symptoms.

Accelerometry defined sleep/wake cycles

Compliance with the accelerometry was very good with the mean number of nights of data collected being 20.1 for controls and 19.2 for the BD group. Accelerometry measures showed participants with BD to spend significantly longer time in bed, have significantly longer nocturnal sleep time and also more unstable and variable sleep wake patterns, alongside longer daytime napping periods, than those in the control group (see supplementary Table 1). Compared to controls participants with BD spent around 51 minutes per night longer in bed, spent 24 mins longer asleep at night and had lower sleep efficiency. Daytime napping/sedentary behaviour was also on average significantly longer by 29 mins/day in participants with BD. The relative amplitude between the most active 10 hours and least active 5 hours was significantly lower in the participants with BD than the controls driven primarily by significantly lower M10 activity. The intra-subject variability in all sleep variables was significantly greater in the participants with BD, indicating instability in sleep/wake patterns compared to controls.

Visual representations of typical actograms are shown in figure 1. Using the definitions as described above 23 of the BD patients had normal sleep and 23 had abnormal sleep length or CRD. Four (2.2%) were short nocturnal sleepers and 14 (30.4%) were long sleepers over each 24 hour period. It is however important to note that if naps and sedentary behaviour during the day are included, no patient with BD 'slept' for less than 6 hours per 24 hours period. Similarly, of the long sleepers none slept for more than 10 hours in a 24 hour period when daytime naps and sedentary behaviour were excluded i.e. no BD patient had > 10 hours nocturnal sleep. Twelve (26.1%) had CRD including delayed sleep phase pattern (n=3), advanced sleep phase pattern (n=1), irregular sleep/wake phase (n=3) non-24 hour sleep/wake phase disorder (n=4) and circadian sleep-wake disorder not otherwise specified (n=1). This compared with just four control participants with CRD, one with an advanced

sleep phase and three with delayed sleep phase. There was significant overlap between the various sleep and circadian disorders as shown in figure 2. Two of the four BD patients who were short sleepers and 6 of the 14 long sleepers had evidence of CRD. OSA was also a potential explanation of long sleep in 5 patients with BD but an additional 3 long sleepers did not complete the partial oximetry so their sleep apnoea status was unknown.

Melatonin assays

To further evaluate whether the sleep/wake cycles were synchronised to the body clock phase, we measured 48 hour melatonin rhythms on two occasions. Thirty nine controls and 38 BD participants provided at least one urine collection that had a clear melatonin rhythm assessed with cosinor analysis. An additional 2 participants with BD provided good samples but had a 24 hour aMT6s output that was too low to detect a rhythm (<3μg/24 hours). Fifty seven (n=30 controls; n=27 BD) participants provided 2 urine samples allowing a period to be calculated. Two participants in the control group and 5 BD participants had a non-24 hour melatonin period (defined as $\geq$ 24.2 hours or $\leq$ 23.8 hours). Controls demonstrated a significantly greater aMT6s secretion(μg/24 hours) than the BD group (18.0 (SD=9.1) vs 12.8 (SD=8.5); Mann-Whitney; 476.0; p=0.003), a greater mesor (μg) (rhythm adjusted mean), controls 12.1 (SD 6.1) vs BD 9.0 (SD 6.0); t=2.56 (75), p=0.012 and amplitude (μg), controls 14.5 (SD 8.0) vs. BD 9.8 (SD 7.7); t= 3.03 (75), p=0.003. Control participants also differed from BD participants in that they demonstrated a significantly earlier mean acrophase (hours)(time of peak aMT6s concentration) which was on average 1 hour 26 minutes earlier, controls 3.24 (SD=1.88) vs BD 4.67 (SD=2.23); Mann-Whitney U; 476.0, p=0.004). The later acrophase in the BD group is indicative of a delayed biological rhythm compared to the controls, which was in keeping with the numerically greater proportion of evening chronotypes in the BD group (see Table 1).

Comparison of mood, sleep, function, QoL and melatonin in normal and abnormal sleeping BD patients.

Differences in mood, anxiety, psychosocial function and QoL were explored within the BD group comparing those with accelerometer defined normal (n=23) and abnormal sleep (n=23) (table 2). There were no statistically significant differences in age, BMI, numbers with OSA or mean AHI, mood or anxiety between the groups. Abnormal sleepers subjectively rated their sleep as lower quality than normal sleepers on the PSQI although it is noteworthy that normal sleeping BD participants still scored in the clinically significant range for poor sleep quality(>5). BRIAN scores were also significantly greater in abnormal compared to normal sleepers indicating greater difficulty maintaining good 24 hour rhythms. However, there was no significant difference in daytime sleepiness scores measured on the ESS with both groups scoring in the normal range (ESS < 10). While mood ratings did not differ between normal and abnormal sleeping groups, there was a significant correlation between both HAMD[17] and BDI scores and PSQI total score in the BD group (Spearmans rank order correlation $r^2(45) = 0.564$, $p<0.001$ $r^2(45) = 0.598$, $p<0.001$ respectively), though no correlation between objective actigraphy measures and mood. There was, however, significantly poorer psychosocial functioning (t-test; 3.033; $p<0.004$) and lower QoL (t-test; -2.495; $p=0.016$) in abnormal versus normal sleeping patients with BD. These differences remained when covarying for either HAMD[17] (FAST, $F=6.502$ df = 1,43, $p=0.014$; QoL.BD, $F=6.436$ df= 1, 43, $p=0.015$) or BDI (FAST, $F = 7.527$, $p=0.009$; QoL.BD, $F=8.839$, $p=0.005$). The aMT6s 24 hour secretion also differed significantly within the BD group. BD participants with normal sleeping patterns demonstrated significantly greater 24 hour aMT6s secretion than abnormal sleeping participants (table 2), but did not differ from normal sleeping controls (BD 15.8 (SD 9.1) vs controls 17.5 (8.3) (Mann-Whitney U 266.0; $p=0.367$).

Discussion

This is the most comprehensive study to date to assess sleep and CRD in patients with BD compared to controls. Of the patients with abnormal sleep, a high proportion had CRD (26.1%) and there was considerable overlap between different sleep and circadian rhythm disorders. Abnormality in circadian rhythm in BD was further demonstrated in the BD group by significant differences in melatonin secretion compared to healthy controls, particularly a decreased 24 hour output that was seen in the patients with abnormal sleep patterns. Those BD patients with abnormal sleep had similar mood symptoms to those with normal sleep but less stable biological rhythms, worse psychosocial functioning and reduced QoL.

The patients with BD in our study spent longer in bed, had more fragmented sleep and had more unstable and irregular sleep wake patterns. However we were also able to show different sleep phenotypes within individual participants. It was possible to determine that within the BD group, 23 retained normal sleep wake patterns with a stable sleep wake pattern and total sleep time between 6 and 10 hours. However 23 had clearly abnormal sleep with striking circadian dysrhythmia in 12 of the patients. Although a number of previous studies have reported different patterns of sleep disturbance in BD, these have usually relied on only short periods of sleep diary or accelerometry data to assess the sleep/wake cycle. Two different studies, each with just 19 BD patients compared group actigraphy variables over periods of 5 and 7 days respectively with controls, but did not define different sleep phenotypes between individual BD subjects but simply reported mean activity levels (24, 25). One problem with the detection of CRDs is that patients may appear to have either an insomnia or hypersomnia pattern if the period of recording is too short and this is particularly true of a non-24 hour period disorder. The recently revised ICSD-3 diagnostic criteria for this disorder stipulate at least 2 weeks of sleep logs and accelerometry should be performed to make the diagnosis (22). Our data also supports this view given the high rate of patients with subjective descriptions of insomnia (as captured by the HAMD sleep items) while objective accelerometry data showed a low rate of short sleepers. Nine of the 12 patients who had a CRD scored the maximum of

2 on at least one of the HAMD sleep items suggesting many of the patients complaining of 'insomnia' actually have a CRD.

There is increasing evidence for an intrinsic circadian rhythm dysfunction within a number of psychiatric disorders and some previous studies of melatonin levels in BD patients have shown reduced melatonin compared to controls as well as a later onset, however others have not shown any difference in light suppression response compared to controls(26-32). Repeated measurements are required to look at the period to estimate whether it is near 24 or longer and previous studies have not reported this. In our study, between group comparison of patients and controls showed both reduced melatonin output and a delayed acrophase (time of peak melatonin concentration) within BD compared to controls. However the differences were most marked in those with abnormal sleep and/or circadian rhythm where total amount of melatonin was significantly lower than those BD patients with normal sleep wake rhythms. There could be a number of potential reasons. Those with fragmented sleep may have abnormal light exposure, be in rooms with increased light levels or have light on during the night that suppresses melatonin output. Alternatively, a subset of BD patients could have an intrinsic circadian rhythm abnormality although all the controls and the majority of patients with BD had a normal pattern and timing of melatonin secretion, even some with abnormal accelerometry data. Some of those who reported fragmented night sleep had very low melatonin levels of <3ug/ml and this may provide a mechanistic explanation for the failure to consolidate night sleep for some and this may provide a therapeutic target.

Overnight respiratory sleep studies analysis showed mild or moderately severe OSA in 29% of patients with BD compared to 10% of controls. There is increasing recognition that secondary consequences of inactivity, weight gain and metabolic syndrome possibly related to medication all increase the risk of conditions such as OSA in those with psychiatric disease. As expected the BD group had an increased BMI compared to the control group. OSA will fragment night sleep and contribute to daytime sleepiness, sedentary behaviour and potentially hypersomnia. Indeed nearly

half of the patients with OSA were also rated as long sleepers. While the sample of patients with BD was not an epidemiological one, the prevalence of OSA of 29% in our sample, is consistent with previous research (33, 34) and highlights the need for screening and treatment of OSA in this patient group given the association between OSA and serious cardiovascular morbidity (35).

Those participants with BD with any cause of abnormal sleep had significantly worse psychosocial functioning and quality of life compared to those with normal sleep. The differences between groups remained after covarying for HAMD[17] and BDI suggesting that accelerometry defined abnormal sleep was associated with lower function and QoL independently of mood. It is noteworthy that although we found a moderate correlation between mood and subjective sleep quality measured on the PSQI we found no differences in mood scores between the groups of normal and abnormal BD sleepers defined by accelerometry. This may be because subjective and objective assessments measure different dimensions of sleep. Other studies have found associations between disturbed sleep and mood (36, 37) but both these studies used subjective sleep diaries to assess sleep function. The impact of targeting specific sleep problems therapeutically on the course of BD needs to be examined further. A preliminary randomised controlled trial assessed the effects of cognitive behavioural therapy for insomnia in patients with BD and shown that not only was it possible to improve sleep efficiency and decrease the severity of insomnia, but time in episode of mood disturbance decreased (38).

Strengths of the study include a well characterised group, multiple measures of mood and comprehensive measures of sleep and circadian rhythm across 21 days. The raw accelerometry data was analysed on an open access algorithm meaning future data sets can use identical analysis methodology thereby making different datasets directly comparable.

Weaknesses of the study include a lack of the gold standard measure of sleep using video polysomnography. However this was a field study and it was felt that studying patients with partial polysomnography in their own homes would increase compliance and the main aim of the home

sleep study was to screen for all forms of sleep disordered breathing. The sample was also opportunistic with a potential bias for over-representation of patients with BD and sleep disorders, while controls were screened out if they suffered significant sleep problems. A larger, more representative, sample size would have allowed more accurate assessment of the prevalence of sleep and circadian disorders as well as greater sub group analysis of the differential effect of the different disorders.

In conclusion we have found that many patients with BD that have sleep disorders have a CRD and/or OSA. BD participants with abnormal sleep had lower function and quality of life which was not accounted for by lower mood. Abnormal sleep in BD is also characterised by reduced 24 hour melatonin secretion compared to both healthy controls and those with BD and normal sleep. There is a need for the use of objective markers of the sleep wake cycle and respiratory function to accurately determine different sleep patterns within clinical populations and assess the impact of specific therapies targeted at these sleep and circadian disorders on long term outcomes of the psychiatric disorders.

Acknowledgements

We would like to thank all of the participants for taking part in the study. The study was sponsored by Northumberland, Tyne and Wear NHS Foundation Trust. Some funding to cover running costs was received from Eli Lilly as an unrestricted investigator initiated and led award. The design, conduct and analysis of the study was entirely under the control of the authors.

References

1. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. The American journal of psychiatry. 2008;165(7):820-9. Epub 2008/06/04.
2. Harvey AG, Schmidt DA, Scarna 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):50-7. Epub 2004/12/31.
3. Kaplan KA, Gruber J, Eidelman P, Talbot LS, Harvey AG. Hypersomnia in inter-episode bipolar disorder: does it have prognostic significance? Journal of affective disorders. 2011;132(3):438-44. Epub 2011/04/15.
4. Geoffroy PA, Scott J, Boudebesse C, Lajnef M, Henry C, Leboyer M, et al. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. Acta psychiatrica Scandinavica. 2014. Epub 2014/11/29.
5. Nelson HE. National Adult Reading Test (NART): Test Manual1982.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition., Text Revision ed. Washington, DC: American Psychiatric Association; 2000.
7. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 1998;59 Suppl 20:22-33;quiz 4-57. Epub 1999/01/09.
8. Williams JB, Kobak KA, Bech P, Engelhardt N, Evans K, Lipsitz J, et al. The GRID-HAMD: standardization of the Hamilton Depression Rating Scale. International clinical psychopharmacology. 2008;23(3):120-9. Epub 2008/04/15.
9. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of general psychiatry. 1961;4:561-71. Epub 1961/06/01.
10. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. The British journal of psychiatry : the journal of mental science. 1978;133:429-35. Epub 1978/11/01.
11. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA Consulting Psychologists Press; 1983.
12. Rosa AR, Sanchez-Moreno J, Martinez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clinical practice and epidemiology in mental health : CP & EMH. 2007;3:5. Epub 2007/06/09.
13. Michalak EE, Murray G. Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. Bipolar disorders. 2010;12(7):727-40. Epub 2010/11/03.
14. Giglio LM, Magalhaes PV, Andreazza AC, Walz JC, Jakobson L, Rucci P, et al. Development and use of a biological rhythm interview. Journal of affective disorders. 2009;118(1-3):161-5. Epub 2009/02/24.
15. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213. Epub 1989/05/01.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. Epub 1991/12/01.
17. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. International journal of chronobiology. 1976;4(2):97-110. Epub 1976/01/01.
18. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J, Jr., et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499-521. Epub 2005/09/21.
19. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless

legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep medicine. 2003;4(2):101-19. Epub 2003/11/01.
20. van Hees VT, Sabia S, Anderson KN, Denton SJ, Oliver J, Catt M, et al. A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. PloS one. 2015;10(11):e0142533. Epub 2015/11/17.
21. Van Someren EJ, Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiology international. 1999;16(4):505-18. Epub 1999/08/12.
22. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, Ilinois: American Academy of Sleep Medicine; 2014.
23. Wulff K, Joyce E, Middleton B, Dijk DJ, Foster RG. The suitability of actigraphy, diary data, and urinary melatonin profiles for quantitative assessment of sleep disturbances in schizophrenia: a case report. Chronobiology international. 2006;23(1-2):485-95. Epub 2006/05/12.
24. Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. Bipolar disorders. 2005;7(2):176-86. Epub 2005/03/15.
25. Millar A, Espie CA, Scott J. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. Journal of affective disorders. 2004;80(2-3):145-53. Epub 2004/06/23.
26. Beck-Friis J, von Rosen D, Kjellman BF, Ljunggren JG, Wetterberg L. Melatonin in relation to body measures, sex, age, season and the use of drugs in patients with major affective disorders and healthy subjects. Psychoneuroendocrinology. 1984;9(3):261-77. Epub 1984/01/01.
27. Souetre E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B, et al. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. Psychiatry research. 1989;28(3):263-78. Epub 1989/06/01.
28. Kennedy SH, Kutcher SP, Ralevski E, Brown GM. Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. Psychiatry research. 1996;63(2-3):219-22. Epub 1996/07/31.
29. Nurnberger JI, Jr., Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, et al. Melatonin suppression by light in euthymic bipolar and unipolar patients. Archives of general psychiatry. 2000;57(6):572-9. Epub 2000/06/06.
30. Lam RW, Berkowitz AL, Berga SL, Clark CM, Kripke DF, Gillin JC. Melatonin suppression in bipolar and unipolar mood disorders. Psychiatry research. 1990;33(2):129-34. Epub 1990/08/01.
31. Robillard R, Naismith SL, Rogers NL, Scott EM, Ip TK, Hermens DF, et al. Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. European psychiatry : the journal of the Association of European Psychiatrists. 2013;28(7):412-6. Epub 2013/06/19.
32. Novakova M, Prasko J, Latalova K, Sladek M, Sumova A. The circadian system of patients with bipolar disorder differs in episodes of mania and depression. Bipolar disorders. 2015;17(3):303-14. Epub 2014/11/02.
33. Kelly T, Douglas L, Denmark L, Brasuell G, Lieberman DZ. The high prevalence of obstructive sleep apnea among patients with bipolar disorders. Journal of affective disorders. 2013;151(1):54-8. Epub 2013/06/19.
34. Soreca I, Buttenfield JA, Hall MH, Kupfer DJ. Screening for obstructive sleep apnea in patients with bipolar I disorder: comparison between subjective and objective measures. Bipolar disorders. 2015;17(3):345-8. Epub 2014/09/05.
35. Butt M, Dwivedi G, Khair O, Lip GY. Obstructive sleep apnea and cardiovascular disease. International journal of cardiology. 2010;139(1):7-16. Epub 2009/06/10.
36. Eidelman P, Talbot LS, Gruber J, Harvey AG. Sleep, illness course, and concurrent symptoms in inter-episode bipolar disorder. Journal of behavior therapy and experimental psychiatry. 2010;41(2):145-9. Epub 2009/12/17.

37. Talbot LS, Stone S, Gruber J, Hairston IS, Eidelman P, Harvey AG. A test of the bidirectional association between sleep and mood in bipolar disorder and insomnia. Journal of abnormal psychology. 2012;121(1):39-50. Epub 2011/08/17.
38. Harvey AG, Soehner AM, Kaplan KA, Hein K, Lee J, Kanady J, et al. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. Journal of consulting and clinical psychology. 2015;83(3):564-77. Epub 2015/01/27.

Table 1. Characteristics of Participants

			Test Statistics		
	Controls (n=42)	**Bipolar Disorder (n=46)**	**X^2 (df)**	**Mann Whitney U**	**p**
Female Gender n (%)	29 (69)	31 (67.4)	0.028 (1)		0.868
Age years: mean (SD) (Range)	42.5 (11.9) (19-64)	46.8 (11.1) (23-64)		768.0	0.098
BMI mean: kg/m^2 (SD) (Range)	25.6 (4.8) (19.5-39.7)	30.0 (6.7) (21.0-52.0)		538.0	0.001
Currently Employed, n (%)	34 (81)	23 (50)	9.218 (1)		0.002
Chronotype n (%)					
Morning	19 (45.2)	14 (30.4)	4.449 (2)		0.108
Evening	3 (7.1)	10 (21.7)			
Neither Type	20 (47.6)	22 (47.8)			
HAM-D^{17} mean (SD) (Range)	0.3 (0.6) (0-2)	9.1 (7.2) (0-35)		49.0	<0.001
BDI (SD) (Range)	0.6 (1.6) (0-9)	12.2 (11.5) (0-49)		127.5	<0.001
YMRS mean (SD) (Range)	0.1 (0.4) (0-2)	0.9 (2.2) (0-10)		839.0	0.075
STAI-S (SD) (Range)	23.6 (4.0) (20-34)	35.1 (12.8) (20-73)		345.5	p<0.001
STAI-T (Range)	24.6 (7.1) (20-54)	44.0 (14.7) (21-77)		206.0	p<0.001
PSQI Global score mean (SD) (Range)	2.2 (1.3) (0-4)	8.6 (4.6) (1-18)		138.5	<0.001
ESS mean (SD) (Range)	3.8 (2.5) (0-9)	6.2 (4.9) (0-21)		680.5	0.016
BRIAN mean (SD) (Range)	20.4 (3.2) (18-30)	40.1 (13.6) (18-65)		122.500	<0.001
FAST mean (SD) (Range)	3.9 (6.2) (0-22)	23.2 (17.4) (0-72)		211.500	<0.001
QoL.BD mean (SD) Range	215.3 (20.2) (162-263)	157.7 (39.5) (50-235)		167.500	<0.001

SD = Standard Deviation, df = degrees of freedom, BMI = body mass index, HAM-D^{17} = 17 item Hamilton Depression Rating Scale, BDI = Beck Depression Inventory, YMRS = Young Mania Rating Scale, STAI- S/T = State and Trait Anxiety Inventory-State/Trait, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry, FAST = Functional Assessment Short Test, Qol.BD = Quality of Life in Bipolar Disorder Questionnaire Morning and evening chronotypes include both definite and moderate subtypes.

Table 2. BD normal vs. abnormal sleepers.

	Bipolar normal sleeper (n=23)	Bipolar abnormal sleeper (n=23)	Normal vs. abnormal test statistics		
	Mean (SD)	Mean (SD)	t (df)	Mann Whitney U	p
Age (years)	45.6 (11.0)	47.9 (11.2)		229.5	0.441
BMI (Kg/m2)	28.4 (4.5)	31.5 (8.1)	1.199 (44)		0.170
AHI	6.3 (8.7)	4.3 (5.0)		198.0	0.754
HAMD[17]	7.8 (7.0)	10.4 (7.3)	1.659 (44)		0.104
BDI	10.0 (11.3)	14.4 (11.6)	1.770 (44)		0.084
YMRS	1.4 (2.8)	0.4 (1.3)		225.5	0.216
STAI-S	33.2 (14.4)	37.0 (10.9)	1.386 (44)		0.173
STAI-T	40.5 (13.8)	47.3 (14.8)	1.611 (44)		0.114
PSQI	6.9 (3.4)	10.4 (5.0)	2.733 (44)		0.009
ESS	5.6 (3.7)	6.9 (5.8)	0.643(44)		0.524
BRIAN	35.7 (13.6)	44.5 (12.3)	2.285 (44)		0.027
FAST	16.7 (15.7)	29.7 (16.8)	3.033 (44)		0.004
QoL.BD	171.4 (37.9)	143.9 (36.9)	-2.495 (44)		0.016
Melatonin (normal sleeper n=19, abnormal sleepers n=21).					
aMT6s (µg/24hr)	15.8 (9.1)	10.0 (7.0)		108.0	0.013

BMI = body mass index, AHI = apnoea hypopnoea index, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry, FAST = Functional Assessment Short Test, Qol.BD = Quality of Life in Bipolar Disorder Questionnaire, HAMD[17] = Hamilton Depression Rating Scale 17 item, BDI = Beck Depression Inventory, YMRS = Young Mania Rating Scale, ASRMS = Altman Self Rating Mania Scale, STAI-S/T = State and Trait Anxiety Inventory – State/trait, aMT6s = 6-sulphatoxymelatonin.

Supplementary Table 1. Summary Accelerometer Data

			Test Statistic		
	Controls (n=42)	**Bipolar Disorder (n=46)**	**t-test (df)**	**Mann Whitney U**	**p**
TIB hours (SD)	7.85 (0.77)	8.69 (1.48)		562.000	0.001
Intra-subject variability in TIB	1.19	1.72	-3.016 (86)		0.003
Nocturnal sleep time (SD)	6.92 (0.70)	7.33 (1.20)		664.000	0.012
Intra-subject variability in nocturnal sleep time	1.01	1.40	-3.386 (86)		0.001
Sleep efficiency (SD)	0.88 (0.04)	0.85 (0.75)		707.000	0.030
Intra-subject variability in sleep efficiency	0.049	0.069	-2.960 (86)		0.004
Daytime naps/sedentary behaviour (SD)	1.47 (0.86)	1.95 (1.05)	-2.246 (86)		0.027
Intra-subject variability in daytime naps/ sedentary behaviour	0.86	1.10	-2.336 (86)		0.022
Intra-subject variability in sleep onset time (hours)	0.99	1.42		730.000	0.056
Intra-subject variability in sleep offset time (hours)	1.29	2.24		694.000	0.023
L5 (SD)	6.0 (2.8)	5.9 (1.9)		923.000	0.719
M10 (SD)	47.8 (14.8)	37.8 (11.6)	3.508 (86)		0.001
Relative amplitude between day and night activity (SD)	0.77 (0.10)	0.71 (0.13)		698.000	0.025
Mean acceleration (milli g) (SD)	30.77 (9.1)	23.77 (6.6)	4.119		<0.001

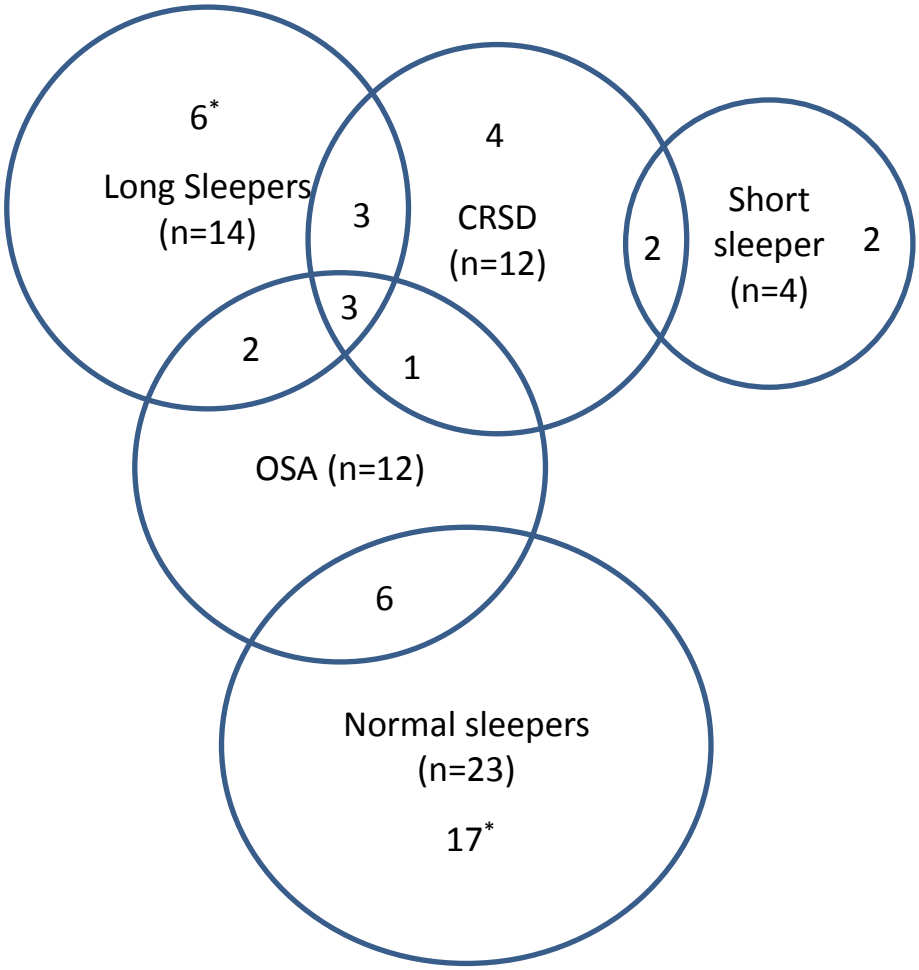
Figure 1.

Figure 1. Actograms demonstrating the sleep wake cycle over 21 days and timing of aMT6s acrophase from 6 different sleep phenotypes.

The blue diamonds represent the timing of the acrophase of aMT6s taken at two different time points over the 21 days of actigraphy.

(a) Normal sleeper with a well entrained circadian rhythm. Mean nocturnal sleep duration = 6.9 hours.
(b) Short sleeper with a well entrained circadian rhythm. Mean sleep duration = 5.76 hours.
(c) Long sleeper mean sleep duration = 10.95 hours. Note mildly irregular sleep/wake times and aMT6s period length =24.40 hours.
(d) Advanced sleep phase with well entrained circadian rhythm. Mean sleep onset time = 20.25, mean nocturnal sleep duration = 7.23 hours.
(e) Delayed sleep phase with well entrained circadian rhythm. Mean sleep onset time = 01:43, mean nocturnal sleep duration = 08:59 hours.
(f) Non 24 hour sleep-wake rhythm. Actogram demonstrated an irregular sleep/wake cycle with evidence of free running sleep onset during the final 8 days. aMT6s period length = 24.40 hours.

Figure 2. Sleep phenotypes and their overlap in the BD group.



Normal sleepers = >6 & < 10 hours nocturnal sleep and no CRSD; Long sleepers = total 24 hour sleep > 10 hours; Short sleepers = nocturnal sleep < 6hours; CRSD = circadian rhythm sleep disorder; OSA = obstructive sleep apnoea.

*3 of the participants in the long sleep only cohort and 2 of the normal sleepers did not complete the test for sleep apnoea.