

## Sleep in bipolar patients

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### Abstract

**Background** Sleep disturbance has been described in bipolar disorder (BPD). Specific complaints may include frequent nighttime awakenings, poor quality of sleep, reduction in total sleep time, and nightmares. Most patients with BPD also report insomnia when in depression, but a significant percentage of patients report hypersomnia symptoms with prolonged nighttime sleep, difficulty in wakening, and excessive daytime sleepiness.

**Objectives** The present study aims to investigate whether bipolar patients with sleep disorders presented impairment in quality of life, disability, and global function.

**Methods** One hundred ninety bipolar patients type-I diagnosed by application of Structured Clinician Interview for DSM-IV Disorders (SCID), were distributed in two groups based on absence or presence of sleep disorders. Quality of life, disability, and global dysfunction were evaluated using the Health Organization's Quality of Life instrument (WHOQOL-Brief), the Sheehan Disability Scale, and the Global Assessment of Functioning (GAF), respectively.

**Results** Sleep complaints have negative influence on general quality of life, observed by decreased scores in WHOQOL and GAF domains and increased Sheehan scores, indicating the importance of maintenance of normal sleep in bipolar patients.

**Conclusion** Our results suggest that sleep complaints impair quality of life and global function. Collectively, further studies are warranted to investigate the impairment of sleep disturbance on others neurotrophic factors and neurochemical pathways.

**Keywords** Bipolar disorder · Sleep · Quality of life · Insomnia · Disability · GAF

### Introduction

Sleep is an active state, critical for our physical, mental and emotional well-being and is favorable for brain plasticity [1–3]. Several studies showed that sleep periods encompass processes ranging from reactivation of neuronal ensembles during post-training sleep to molecular changes [1, 4]. Further, sleep is important for optimal cognitive and overall functioning [5]. However, sleep disorders are very common in the general population, affecting 10–20% of adults [6, 7] with an impact in daytime functioning [8].

Sleep disorder coexists with a number of physical and psychiatric conditions, including psychoses, anxiety disorders, and mood disorders [5–7]. The sleep–wake cycle has been a core component of theoretical conceptualizations of bipolar disorder (BPD) and circadian rhythm instability is a frequent complaint in these patients [9]. Insomnia, as well as hypersomnia, with prolonged nighttime sleep, difficulty in awakening, and excessive daytime sleepiness is often experienced by depressive bipolar patients [10]. Longitudi-

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nal studies have shown that the insomnia is often perceived as a symptom of depression, but it is also associated with a substantial increase in the relative risk of major depression [5, 6]. Moreover, a systematic review showed that sleep disturbance was the most common prodrome of mania [9, 11].

BPD is frequently associated with difficulties with social, interpersonal relationships, and occupational functioning [12]. Bipolar patients showed poor quality of life, particularly in physical and psychological domains when assessed by the WHOQOL [13, 14]. Individuals with both depressive symptoms and sleep complaints showed lower QOL and more difficulties in work activities than patients without mood symptoms [8]. Moreover, sleep disturbance and depressive symptoms are especially related to exhaustion, fatigue, and reports of extra bed time [11].

Thus, we questioned if sleep plays an additional role that contributes to the difficulties persons with BPD experience in physical, psychological, social, and environmental domains. This study was, therefore, conducted to evaluate the influence of sleep disturbance in quality of life assessed by WHOQOL in euthymic bipolar patients.

## Materials and methods

One hundred ninety bipolar patients' type I diagnosed by application of SCID [15] from General Hospital of Porto Alegre, Rio Grande do Sul, Brazil were assessed in a cross-sectional design. The entire evaluation included, besides SCID I, a questionnaire for demographic, social, and clinical information; Hamilton Depression Rating Scale [16]; Young Mania Rating Scale [17]; Global Assessment of Functioning [18]; Sheehan Disability Scale [19] and WHOQOL-Brief [20]. Trained researches made all interviews and the General Hospital of Porto Alegre ethical committee approved this project (07553). After being provided with a complete description of the study, written informed consent to participate was obtained from all participants. The inclusion criteria were patients with bipolar disorder type I, diagnosed by SCID, and in euthymia (HAM-D <7 and YMRS <7).

The patients were separated in two groups, presence and absence of sleep complaints. Patients were present score equal or higher than 17 in questions 4, 5 and 6 of the Hamilton Depression Rating Scale were considered to have sleep problems.

## Data analysis

Histograms and the Kolmogorov–Smirnov test were used to check variables for normality. This sample presented normal distribution. In order to test the hypothesis that

there would be a discrepancy between self-reported QOL and functional (objective) measures in bipolar patients, we used chi-square tests to verify the differences in proportions between the groups, while *t* tests were employed to compare means between groups. Statistical significance was set at  $p < 0.05$ .

## Results

Table 1 describes the patients in terms of demographic and socioeconomic variables. There were more women than men in our sample and half of the patients were aged 40–59 years; 58.42% (111) of bipolar patients presented sleep problems.

Table 2 show alteration in QOL, disability (Sheehan disability) and global assessment function (GAF) in bipolar patients. Patients with sleep problems showed worse quality of life scores in all domains (physical,  $t=5,041$ ,  $df=178$ ,  $p < 0.001$ ; psychological,  $t=467$ ,  $df=178$ ,  $p < 0.001$ ; social,  $t=2,407$ ,  $df=178$ ,  $p=0.017$ ; and environmental  $t=2,843$ ,  $df=178$ ,  $p=0.005$ ). We also observed that the score of physical and psychological domains presented worse impairment than social and environmental domains (14.72%, 14.15%, 8.35%, and 6.68%, respectively). Sheehan disability scales verify impairment in three domains: work social component and familial, since bipolar patients with sleep alteration presented high scores in every domain, indicating functional impairment in these patients (2.46%, 2.05%, 1.63%, respectively). Confirming the results obtained in the Sheehan scale, the GAF presented a diminished score in BP with sleep dysfunction representing 6.66% or worse, representing functional impairment in these patients.

## Discussion

Our aim was to investigate the sleep-related quality of life in euthymic bipolar patients. Although patients experienced symptomatic recovery with low scores of HAM-D and YMRS, the sleep disturbance remained 58.42% of our sample. One reason for high rates of sleep disturbance reported in the current study is the lack of proper routine experienced by bipolar patients. Furthermore, patients with both BPD and sleep disturbance showed lower quality of life than bipolar patients that did not experience insomnia. Bipolar patients with impaired sleep might feel especially exhausted with need for more time in bed which could explain the physical disability. Furthermore, the poor quality of sleep promotes difficulties in concentration, learning, and memory. Although a body of evidence reported that quality of life was inversely correlated with the level of depression, a comparison study between bipolar

**Table 1** Sociodemographic variables among patients

	Sleep dysfunction				Chi-square	<i>t</i> test	Sig
	Absence ( <i>n</i> =69)		Presence ( <i>n</i> =111)				
	Mean	SD	Mean	SD			
Gender							
Female	38.60%		61.40%		0.001		0.974
Male	38.90%		61.10%				
Year of age	40.26	9.75	44.05	12.08		-2.23	0.126
Age of on set	23.32	11.08	26.94	12.29		-2.24	0.044
Years of illness	16.96	11.31	17.15	11.72		-0.11	0.913
NYU	5.04	8.75	7.32	11.61		-1.4	0.16
HAM-D Score	5.36	5.25	12.68	7.04		-7.58	0.001
YMRS	3.88	5.67	5.23	5.76		-1.55	0.122

and unipolar patients suggested that the level of depression did not fully explain the lower quality of life within patients with BPD [21, 22]. We demonstrated here that the sleep alteration was another factor that contributes to low quality of life experienced by bipolar patients. In accordance with our results, Harvey et al. [9] have reported that 70% of bipolar patients experienced sleep alteration and it was associated with low daytime activity levels.

In addition to being associated with quality of life, three lines of evidence point to the importance of sleep in bipolar disorder. First, experimentally induced sleep deprivation is associated with the onset of hypomania and mania in a considerable proportion of patients. Second, in a systematic review of studies of patients with bipolar disorder, sleep disturbance was the most common prodrome of mania and the sixth most common prodrome of bipolar depression. Third, the sleep-wake cycle has been a component of theoretical conceptualizations of bipolar disorder. It has been hypothesized that bipolar disorder patients have a

genetic diatheses that may take the form of circadian rhythm instability [9].

In fact, sleep disturbance has been considered as a cardinal symptom of endogenous depression, and it is known that sleep deprivation exerts an antidepressant effect [23]. It is rare that some form of sleep “change” is not associated with the presence of clinical depression. The essential linkage of sleep disturbance and clinical depression has long been recognized [24]. The relationship between mania and sleep loss is particularly apparent at the beginning of a manic episode, when a typical three-stage escalation has been described [25]. At the beginning of a manic episode, clinicians often observe spontaneous sleep deprivation, due to the hyperactivity of the patient, resulting in an increase in manic symptomatology and then in subsequent sleep loss [26]. Thus, sleep loss appears to act not only as a triggering factor of mania, but also as an augmenting factor during the manic episode, with worse symptomatological outcomes following consistent sleep loss [26].

**Table 2** QOL, disability (Sheehan disability) and global assessment function (GAF) in bipolar patients

	Sleep dysfunction				Levene's test		<i>t</i> test for equality of means		
	Absence ( <i>n</i> =69)		Presence ( <i>n</i> =111)		<i>F</i>	Sig	<i>t</i>	<i>df</i>	Sig (2-tailed)
	Mean	SD	Mean	SD					
WHOQOL									
Physical domain	61.56	19.62	46.84	18.57	0.31	0.578	5.041	178	0.001
Psychological domain	60.24	21.23	46.09	18.79	2.605	0.108	4.67	178	0.001
Social domain	57.97	24.01	49.62	21.7	0.448	0.504	2.407	178	0.017
Environmental domain	58.85	17.2	52.17	14.04	3.712	0.056	2.843	178	0.005
Sheehan disability									
Work domain	3.52	3.64	5.98	3.46	1.717	0.192	-4.595	178	0.001
Social domain	4.01	3.75	6.05	3.45	2.704	0.102	-3.801	178	0.001
Familial domain	3.02	3.49	4.83	3.34	0.56	0.455	-3.523	178	0.001
GAF	66.54	16.22	59.88	12.87	7.262	0.008	3.101	178	0.002

Finally, it has been suggested that sleep periods are favorable for brain plasticity [27]. Recent studies have provided evidence that the expression of genes involved in synaptic plasticity is affected by sleep–wake state. For example, the phosphorylated form of cAMP response element binding protein (CREB), important transcription factor, is present at higher levels after periods of waking than periods of sleep [28]. Down-regulation of phosphorylated CREB was observed in post-mortem brain tissue of affective patients [29]. Furthermore, selective REM sleep deprivation (6 h) suppresses brain derived neurotrophic factor (BDNF) protein levels in the cerebellum and brainstem without producing changes in the hippocampus [30]. Our group has demonstrated that BDNF levels were decreased in manic and depressed BPD patients [31] and this was negatively correlated with manic symptoms [32]. Of note, BDNF has been involved in memory and learning [33], and trophic actions, such as altered neuronal plasticity and cellular morphology while CREB is a transcription factor and one of the genes regulated by the cAMP-CREB cascade is BDNF [34].

Considering that (1) sleep dysfunction leads to alteration in neurotrophic and transcription factors; (2) these factors are very important for maintaining the normal neuronal plasticity; (3) sleep dysfunction has been described in BPD, our results suggest that sleep complaints impair quality of life and global function. Collectively, further studies are warranted to investigate the impairment of sleep disturbance on others neurotrophic factors and neurochemical pathways.

## References

- Maquet P (2001) The role of sleep in learning and memory. *Science* 294:1048–1052 doi:10.1126/science.1062856
- Siegel JM (2001) The REM sleep-memory consolidation hypothesis. *Science* 294:1058–1063 doi:10.1126/science.1063049
- Stickgold R, Fosse R (2001) Sleep, learning and dreams: off-line memory reprocessing. *Science* 294:1052–1057 doi:10.1126/science.1063530
- Benington JH, Frank MG (2003) Cellular and molecular connections between sleep and synaptic plasticity. *Prog Neurobiol* 69:77–101 doi:10.1016/S0301-0082(03)00018-2
- Coleman R (1992) Periodic movements in sleep. In: Guilleminault C (ed) *Sleeping and waking disorders: indications and techniques*. Addison-Wesley, Menlo Park, CA, pp 265–269
- Ancoli-Israel S (2006) The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care* 12:S221–S229
- Walsh JK (2004) Clinical and socioeconomic correlates of insomnia. *J Clin Psychiatry* 65(suppl 8):13–19
- Phillips B (2005) Sleep-disordered breathing and cardiovascular disease. *Sleep Med Rev* 9:131–140 doi:10.1016/j.smr.2004.09.007
- Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM (2005) Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia and subjects without sleep problems. *Am J Psychiatry* 162:50–57 doi:10.1176/appi.ajp.162.1.50
- Harvey AG (2002) A Cognitive model of insomnia. *Behav Res Ther* 40:869–893 doi:10.1016/S0005-7967(01)00061-4
- Theorell HJ, Lindberg E, Janson C (2006) What are important risk factors for daytime sleepiness and fatigue? *Sleep* 29(6):751–757, Jun 1
- Kauer-Sant’Anna M, Tramontina J, Andreazza AC, Cereser K, da Costa S, Santin A, Yatham LN, Kapczinski F (2007) Traumatic life events in bipolar disorder: Impact on BDNF levels and psychopathology. *Bipolar Disord* 9(Suppl 1):128–35
- Gazalle FK, Andreazza AC, Cereser KM, Hallal PC, Santin A (2005) Kapczinski. Clinical impact of late diagnose of bipolar disorder. *J Affect Disord* 86(2–3):313–316 doi:10.1016/j.jad.2005.01.003
- Gazalle FK, Hallal PC, Andreazza AC, Frey BN, Kauer-Sant’Anna M, Weyne F, da Costa SC, Santin A, Kapczinski F (2007) Manic symptoms and quality of life in bipolar disorder. *Psychiatry Res* 153(1):33–38 doi:10.1016/j.psychres.2006.07.007
- Spitzer RL, Williams JB, Gibbon M, First MB (1992) 1996. The Structured Clinical Interview for DSM-III-R (SCID) I: History, rationale, and description. *Arch Gen Psychiatry* 49(8):624–649
- Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62
- Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 133:429–35, Nov
- Jones SH, Thornicroft G, Coffey M, Dunn G (1995) A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* 166(5):654–659
- Sheehan TJ (1996) Creating a psychosocial measurement model from stressful life events. *Soc Sci Med* 43(2):265–271 Jul
- Fleck MP, Chachamovich E, Trentini C (2006) Development and validation of the Portuguese version of the WHOQOL-OLD module. *Rev Saude Publica* 40(5):785–791 doi:10.1590/S0034-89102006000600007
- Berlim MT, Pangendler J, Caldieraro MA, Almeida EA, Fleck MP, Joiner TE (2004) Quality of life in unipolar and bipolar depression: are there significant differences? *J Nerv Ment Dis* 192(11):792–795, Nov
- Yatham LN, Lecrubier Y, Fieve RR, Davis KH, Harria SD, Krishnan AA (2004) Quality of life in patients with bipolar I depression: data from 920 patients. *Bipolar Disord* 6(5):379–385, Oct
- Adrien J (2002) Neurobiological bases for the relation between sleep and depression. *Sleep Med Rev* 6(5):341–51, Oct, Review
- Kupfer DJ (2006) Depression and associated sleep disturbance. *Eur Neuropsychopharmacol* 16:S639–S643 doi:10.1016/S0924-977X(06)70010-4
- Carlson GA, Goodwin FK (1973) The stages of mania: a longitudinal analysis of the manic episode. *Arch Gen Psychiatry* 28:221–228
- Barbini B, Bertelli S, Colombo C, Smeraldi E (1996) Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Res* 65(2):121–125, 1996 Nov 15
- Guzman-Marin R, Ying Z, Sunstova N, Methippara M, Bashir T, Szymusiak R, Gomez-Pinilla F, McGinty D (2006) Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. *J Physiol* 575(Pt 3):807–819 doi:10.1113/jphysiol.2006.115287
- Cirelli C, Tononi G (2000) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J. Neurosci* 20(24):9187–9194, December 15

29. Young LT, Bezchilbnyk YB, Chen B, Wang JF, MacQueen GM (2004) Amygdala cycling adenosine monophosphate response element binding protein phosphorylated in patients with mood disorder: effect of diagnosis, suicide and drug treatment. *Biol Psychiatry* 55:570–577
30. Sei H, Saitoh D, Yamamoto K, Morita K, Morita Y (2000) Differential effect of short-term REM sleep deprivation on NGF and BDNF protein levels in the rat brain. *Brain Res* 877(2):387–390 doi:10.1016/S0006-8993(00)02708-6
31. Cunha BM, Frey BN, Andreazza AC, Goi JD, Rosa AR, Gonçalves CA et al (2006) Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and maniac episodes. *Neurosci Lett* 398:215–219 doi:10.1016/j.neulet.2005.12.085
32. Machado-Vieira R, Dietrich MO, Leke R, Cereser K, Zanatto V, Kapczinski F et al (2007) Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. *Biol Psychiatry* 61(2):142–144, Epub 2006 Aug 7, Jan 15
33. Tramontina J, Frey BN, Andreazza AC, Zandona M, Santim A, Kapczinski K (2007) Val66met polymorphism and serum brain-derived neurotrophic factor levels in bipolar disorder. *Mol Psychiatry* 12(3):230–231 doi:10.1038/sj.mp.4001941
34. Duman H, Zival IM, Campolat A (2002) Spontaneous subfascial transcallosal migration of a missile to the contralateral hemisphere causing deterioration in neurological status—case report. *Neurol Med Chir (Tokyo)* 42(8):332–333 doi:10.2176/nmc.42.332