



ORIGINAL ARTICLE

Personal and social functioning and satisfaction with life in schizophrenia outpatients with and without sleep disturbances

PEDRO AFONSO^{1*}, SOFIA BRISSOS², JULIO BOBES³, FERNANDO CAÑAS⁴, IVAN BERNARDO FERNANDEZ⁵

¹ Faculty of Medicine, University of Lisbon, (FMUL), Lisbon, Portugal

² Centro Hospitalar Psiquiátrico de Lisboa, Lisbon, Portugal

³ Departamento de Psiquiatria, Universidad de Oviedo, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Oviedo-Asturias, España

⁴ Hospital Dr. R. Lafora. Madrid. Spain

⁵ Janssen Pharmaceutical, Madrid, Spain

Abstract

Background: Patients with schizophrenia often present sleep complaints which have been related to poor patient quality of life. Physiologic sleep, compatible with work routines is necessary, and may translate into better social functioning, engagement in rehabilitation strategies, and satisfaction with life.

Methods: In this cross-sectional, non-interventional study, 811 adult outpatients with a diagnosis of schizophrenia were divided into two groups according to the presence (or absence) of sleep disturbances, and assessed using measures of symptom severity, quality and patterns of sleep (Pittsburgh Sleep Quality Index - PSQI), personal and social functioning, and satisfaction with life.

Results: Patients with sleep disturbances were significantly more symptomatic, and revealed worse quality of sleep on all components of the PSQI ($p < 0.0001$), as compared to patients without sleep disturbances. Patients with sleep disturbances presented significantly worse personal and social functioning and satisfaction with life in all domains. Satisfaction with life of patients with sleep disturbances' caregivers was also significantly worse in all domains.

Personal and social functioning was significantly correlated with sleep quality ($r = -0.23328, p < 0.0001$), indicating that patients with worse quality of sleep have lower levels of functioning in every domain of functioning ($p < 0.01$). Quality of sleep was also significantly correlated with patients' and caregivers' satisfaction in all domains ($p < 0.01$).

Conclusions: Our findings show that schizophrenia patients reporting sleep disturbances present greater symptom severity and worse personal and social functioning. Moreover, both patients with sleep disturbances and their caregivers, report worse satisfaction with life.

Keywords: Caregiver satisfaction; patient satisfaction; personal and social functioning; positive and negative symptoms; schizophrenia; sleep.

1. Introduction

Sleep problems are commonplace in patients with schizophrenia (SZ) [1-5], the most prevalent disturbances being sleep conciliation and maintenance insomnia [6] which, although rarely the predominant complaint, can often be severe enough to require separate clinical care.

Research reports on polysomnography in SZ patients have revealed: difficulty to fall asleep, early awakening and inability to fall asleep again, which reduces the depth of slow-

wave sleep and shortens rapid eye movement (REM) latency [1,3,7,8]. Reduced sleep efficiency and total sleep time, increased sleep latency, and alterations of stage 2 sleep, slow wave sleep (SWS) and REM sleep variables have been reported in most patients with SZ [5]. This is especially true during psychotic episodes [9], but difficulties initiating or maintaining sleep are common in the prodromal phase [5,11], and recurring episodes. And although sleep architecture may improve with antipsychotic treatment, sleep remains mostly fragmented and doesn't recede to its normal pattern [9].

Additionally, studies with actigraphy have revealed that there are indeed abnormalities in a substantial number of patients, with most showing longer sleep times than

Address

Pedro Afonso, Faculty of Medicine, University of Lisbon, (FMUL), Lisbon, Portugal ; E-mail: pedromafonso@netcabo.pt

controls [11]. Positive and negative symptoms may correlate with important sleep variables such as sleep latency, sleep efficiency, SWS, and REM sleep parameters [5,12], although results are contradictory [13].

How abnormal sleep develops in SZ patients is still unknown, and it remains unclear whether sleep problems are secondary to social withdrawal and reclusive behavior, to medication, or whether they are due to an intrinsic abnormality of the neuroendocrine systems regulating sleep and wakefulness [14,15].

Moreover, sleep appears to play an important role in the consolidation of memory [16], and patients with a more normal rhythm perform better on cognitive tasks of visuospatial memory, procedural learning, and frontal lobe function [13]. This has important implications, and a normal rest-activity cycle with relative amplitude of day/night activity may be a prerequisite for adequate cognitive functioning in individuals with SZ [13,16]. This, in turn, may translate into better social functioning, and/or better engagement in rehabilitation strategies.

Poor sleep quality in SZ patients has been related to poor patient quality of life [12,17-19]. Nowadays, the aim of mental health clinicians is not just to ameliorate symptoms, but also to improve functional outcome and satisfaction with life for SZ patients [20]. To accomplish this, physiologic sleep, compatible with work routines and timetables is necessary. However, the relationship between quality of sleep, personal and social functioning, and satisfaction with life in SZ outpatients has been understudied.

The aim of this work was to assess the differences between symptom severity, functioning level, satisfaction with life, and sleep quality perceived by SZ outpatients with and without self-reported sleep disturbances. We hypothesized that worse quality of sleep, would be associated with greater symptom severity, worse personal and social functioning and worse satisfaction with life.

2. Material and methods

Study design

In this multicenter, Iberic, cross-sectional, non-interventional study, outpatients with a diagnosis of SZ aged 18 years or older were screened for the presence of sleep disturbances¹.

¹ In the Spanish version of the study, there was a time-frame of 1 one week when six patients were included in the "case and control" study (three patients reporting sleep disturbances and three patients denying sleep disturbances). In Portugal, investigators included 10 patients in the study: 5 with sleep disorders and 5 without. In case no patients were recruited for the period of 1 week, the investigator was allowed to continue recruitment for the following weeks.

Participants

From a total of 1492 screened patients, 811 patients were recruited from psychiatric departments November 2010 to July 2011 (709 in Spain and 102 in Portugal). Patients were asked to subjectively report whether they had sleep disturbances or not; 401 patients considered themselves to have sleep disorders while 410 did not. Inclusion criteria were as follows: outpatients with a diagnosis of SZ according to DSM-IV criteria [21], ascertained from interview with their psychiatrist and medical chart review, aged 18 years or older, and having been on a stable dose of antipsychotic for at least 6 months prior to interview. Patients with any type of severe sleep disturbances related to disorders other than SZ (e.g. nightmares, nocturnal fears, restless leg syndrome) were excluded. Schizoaffective disorder, organic impairment, or cognitive deficits that could influence patients' self-report were also considered exclusion criteria. Patients were excluded mainly due to unstable antipsychotic treatment, non-consent, lack of cognitive ability or other sleep disorders.

Patients were mainly prescribed atypical antipsychotics: risperidone (37%), olanzapine (21%), paliperidone (20%), quetiapine (13%), aripiprazol (12%), clozapine (11%), haloperidol (9%), amisulpride (6%), levomepromazine (5%), zuclopentixol (5%), flufenazine (4%), ziprasidone (4%) and others (4%). There were no statistical significant differences between patients with sleep disorders as compared to patients without sleep disorders regarding type of antipsychotic treatment (Table 1); however, patients with sleep disorders were prescribed significantly more anxiolytics and hypnotics (Table 1).

The investigators were aware of the patients' diagnosis and overall clinical status.

The local Ethics committees approved the study, and all participants provided written informed consent.

Assessment instruments

Symptom severity was evaluated with the Brief Psychiatric Rating Scale (BPRS) [22].

The quality and patterns of sleep were measured with the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) [23]. This self-report questionnaire rates sleep quality and patterns during the previous month, and evaluates 7 components of sleep: subjective quality, latency, duration, usual efficiency, sleep disturbances, medication use, and daytime dysfunction. The score is given through a Likert-like scale, between 0 and 3, with a cut-off value of 5, higher scores meaning worse sleep quality.

Social functioning was evaluated with the Portuguese and Spanish versions of the Personal and Social Performance (PSP) scale [24,25]. The PSP is a brief instrument that assesses four domains of functioning. The ratings are based on the assessment of four objective indicators: 1) socially useful activities, including work and study; 2) personal

and social relationships; 3) self-care; and 4) disturbing and aggressive behaviours. These are rated on a six-point severity scale (absent to very severe), according to specific operational definitions. The interviewer assigns a global score on a 100-point scale, based upon information from interview and other valid sources. Although there are no cut-off points, the total score is usually divided into three levels: 71-100, reflecting mild or no functioning difficulties; 31-70, reflecting varying degrees of difficulties; and 0-30, reflecting functioning so poor that the patient needs intensive support and supervision.

Patient and caregiver satisfaction with life (job, family, sexual, social, health and general satisfaction) was evaluated by means of a visual analogue scale.

Statistical analysis

We compared patients reporting sleep disturbances versus a control group of patients without sleep disturbances. Both groups were compared in their sociodemographic, and clinical variables using parametric t-Student or F-Snedcor. The associations between functioning, sleep and patient and caregiver satisfaction were calculated with Pearson’s correlation coefficient. The associations between functioning and quality of sleep were calculated with Pearson’s correlation. We used SAS 9.3. Copyright (c) 2002-2010 by SAS Institute Inc., Cary, NC, USA.

3. Results

Patients were predominantly male (67%), 84% lived accompanied (89% with either their spouse or their parents), and the majority was not working (76%). There were no statistical differences in gender, age, illness duration, age of diagnosis, educational level, and employment status between the groups (Table 2).

Table 1: Medication prescribed to patients with and without sleep disorders.

Treatment until visit day	Patients without		Patients with sleep		All patients	Chi ²	p value
	(N = 410)	(N = 401)	(N = 410)	(N = 401)			
	N (%)	N (%)	N (%)	N (%)	N (%)		
Atypical antipsychotics	384 (93.7)	372 (92.8)	756 (93.2)	0.2543	0.6141		
Typical antipsychotics	88 (21.5)	88 (22.0)	176 (21.7)	0.0277	0.8678		
Antidepressants	101 (24.6)	122 (30.4)	223 (27.5)	3.4087	0.0649		
Anxiolytics	133 (32.4)	162 (40.4)	295 (36.4)	5.5501	0.0185		
Mood stabilizers	34 (8.3)	46 (11.5)	80 (9.9)	2.3037	0.1291		
Anticholinergics	55 (13.4)	65 (16.2)	120 (14.8)	1.2560	0.2624		
Hypnotics/sedatives	51 (12.4)	107 (26.7)	158 (19.5)	26.2216	<0.0001		
Others	15 (3.7)	26 (6.5)	41 (5.1)	3.3712	0.0663		

Table 2: Sociodemographic and clinical characteristics.

Characteristics	Patients without	Patients with sleep	Chi ²	p value
	Sleep disturbances (N = 410)	disturbances (N = 401)		
	N (%)	N (%)	N (%)	
Gender (men:women)	270:140	270:131	1.990	0.925
Educational level				
No education	30	24		
Primary education	166	174	1.939	0.585
Secondary education	147	148		
University education	67	55		
Employment status				
Employed	56	54		
Unemployed	83	86		
Retired	84	88		
Sick leave	134	141	5.600	0.469
Housewife	24	15		
Student	17	9		
Other	12	8		
	mean (SD)	mean (SD)	t-Student	p value
Age	42.7 (11.64)	42.4 (11.72)	0.36	0.716
Age of diagnosis (years)	25.8 (8.67)	25.2 (7.90)	0.90	0.368
Illness duration (years)	16.9 (10.64)	17.2 (11.13)	0.29	0.768
BPRS total score	12.8 (8.27)	16.6 (9.43)	6.05	<0.001
PSQI total score	4.8 (3.30)	11.6 (3.96)	26.72	<0.001
PSP scale total score	60.6 (16.89)	56.2 (17.60)	3.58	<0.001

Legend: BPRS: Brief Psychiatric Rating Scale; PSP: Personal and Social Performance; SD: standard deviation; PSQI: Pittsburgh Sleep Quality Index

63% of patients were current smokers, and more patients with sleep disturbances were smokers (Chi²=9.455, p=0.024). The majority of patients (77%) in our study denied alcohol consumption; however, more patients with alcohol consumption reported sleep disturbances (Chi²=7.509, p=0.023).

Patients with sleep disturbances were significantly more symptomatic (Table 2), and scored significantly higher on all components of the PSQI (p < 0.0001), revealing worse quality of sleep, as compared to patients without sleep disturbances. Finally, patients with sleep disturbances presented significantly worse personal and social functioning in every domain of functioning, as well as significantly worse satisfaction with life in all domains (Table 3). Moreover, the satisfaction with life of patients

Table 3: Personal and social functioning of patients with and without sleep disorders.

PSP domains	Patients without	Patients with sleep	<i>t-Student</i>	<i>p</i> value
	Sleep disturbances (N = 410)	disturbances (N = 401)		
	mean (SD)	mean (SD)		
Social activities	3.00 (1.21)	3.28 (1.22)	3.23	0.0013
Personal and social relationships	3.00 (1.15)	3.26 (1.15)	3.22	0.0014
Self-care	1.89 (0.89)	2.17 (1.08)	3.93	<0.0001
Disturbing and aggressive behavior	1.43 (0.79)	1.65 (0.88)	3.68	0.0003
PSP total score	60.6 (16.89)	56.2 (17.60)	3.58	<0.001

Legend: PSP: Personal and social functioning scale

Table 4: Patients' and caregivers' level of satisfaction with life.

PSP domains	Patients without	Patients with sleep	<i>t-Student</i>	<i>p</i> value
	Sleep disturbances (N = 410)	disturbances (N = 401)		
	mean (SD)	mean (SD)		
Patient satisfaction				
Job satisfaction	4.3 (2.84)	3.4 (2.73)	4.36	<0.0001
Family satisfaction	6.6 (2.34)	5.8 (2.56)	4.86	<0.0001
Sexual satisfaction	3.5 (2.83)	3.0 (2.70)	2.57	0.0105
Social life satisfaction	5.4 (2.28)	4.4 (2.35)	5.97	<0.0001
General satisfaction	6.0 (1.91)	5.0 (2.08)	6.99	<0.0001
Satisfaction with health	6.5 (1.88)	5.6 (2.11)	6.65	<0.0001
Caregiver satisfaction				
Job satisfaction	(N = 212) 4.1 (2.94)	(N = 222) 3.3 (2.57)	4.36	0.0035
Family satisfaction	6.4 (2.33)	5.4 (2.37)	4.86	<0.0001
Sexual satisfaction	3.9 (2.72)	3.1 (2.65)	2.57	0.0013
Social life satisfaction	4.8 (2.10)	3.8 (2.18)	5.97	<0.0001
General satisfaction	5.8 (1.88)	4.7 (1.91)	6.99	<0.0001
Satisfaction with health	6.5 (1.82)	5.5 (2.07)	6.65	<0.0001

with sleep disturbances' caregivers was also significantly worse in all domains (Table 4).

For all patients, personal and social functioning was significantly negatively correlated with sleep quality ($r = -0.233$, $p < 0.0001$), indicating that patients with worse quality of sleep have lower levels of functioning. This was true for every domain of functioning ($p < 0.0001$). Quality of sleep was also significantly correlated with patients' and caregivers' satisfaction in all domains ($p < 0.0001$).

4. Discussion

As hypothesised, patients with worse quality of sleep presented greater symptom severity, worse personal and social functioning, and less satisfaction with several life dimensions.

To the best of our knowledge, ours is the first study showing an association between quality of sleep and several domains of personal and social functioning. This could be mediated by cognitive function, since sleep appears to play an important role in the consolidation of memory [16], and patients with a more normal rhythm perform better on cognitive tasks of, independent of clinical status [13,16]. Therefore, a normal rest-activity cycle with relative amplitude of day/night activity may be a prerequisite for adequate cognitive functioning in individuals with SZ [13,16], which could in turn translate into better personal and social functioning, and/or better engagement in rehabilitation strategies.

Poor sleep quality in SZ patients, has been related to poor patient quality of life [612,17-19], even after correcting for depression and drug effects [17-19]. In our study, both patients with sleep disturbances and their caregivers reported worse satisfaction with life in all domains. We are not aware of studies on this association, but satisfaction with life may be considered as a proxy for quality of life.

Regarding symptomatology, studies have shown insomnia to be associated with increased positive symptoms [26], and that these, namely suspiciousness, hallucinations and hyperactivity, are associated with more disrupted sleep/wake patterns and circadian activity rhythms in SZ patients [12]. It has been purposed that positive symptoms could make it harder for the patients to fall asleep, due to an increased neurophysiologic arousal, explaining the longer sleep latency, and lower total sleep time found in this group. On the other hand, patients with negative syndrome present low motor activity levels [27], possibly facilitating sleep, while improved sleep itself may reduce negative symptoms [28]. Patients with sleep disturbances self-reported worse quality of sleep and more daytime sleepiness. Atypical antipsychotics tend to improve sleep induction and/or sleep maintenance in SZ patients [6], and most atypical antipsychotics demonstrate an increase in total sleep time and/or sleep efficiency in SZ patients [5]. Clozapine has been shown to increase the total sleep time, sleep efficiency, and stage 2 sleep and decrease sleep latency and wake time after sleep onset [5,29,30]. Olanzapine demonstrates comparable influences on sleep variables with an overall improvement in sleep efficiency and an increase of REM sleep and SWS [31,32]. A significant enhancement of SWS has also been noted in risperidone treated patients [33]. Paliperidone has been shown

to reduce persistent sleep latency, sleep onset latency, number of awakenings after sleep onset, time awake in bed, stage 1 sleep duration, and to cause a prolongation in total sleep time, sleep period time, stage 2 and REM sleep duration, and an increase in the sleep efficiency index measured by polysomnography [34]. Concerning quetiapine, ziprasidone, and aripiprazole we are not aware of studies with these antipsychotics on the quality of sleep of SZ patients. Despite that, quetiapine and ziprasidone improve sleep induction and consolidation in healthy individuals [35,36]. Information on the effect of long-acting injectable antipsychotics on sleep is also sparse, although paliperidone palmitate in acutely exacerbated SZ patients has been shown to improve sleep quality compared with placebo [37].

Antipsychotic treatment can produce akathisia, which is characterized by intense motor restlessness and pacing, and restless legs syndrome (RLS) [5]. The prevalence of RLS in antipsychotic-treated schizophrenic patients has been reported to be more than twice that of healthy controls [38]. Clinicians should be aware for these side effects, since they can cause significant sleep disruption.

Daytime somnolence is a relatively common side effect of antipsychotic treatment, ranged from 24% to 31% in SZ patients [39] and may contribute to non-compliance and potentially to a poorer outcome. Somnolence in antipsychotic-treated schizophrenic patients can lead to daytime naps. Consequently, these patients can develop sleep reversals and polyphasic sleep patterns with a negative impact on nighttime sleep. Sleep hygiene and other behavioral treatments are widely available and may have beneficial effects on these patients.

However, to disentangle the effects of SZ itself from the influence of medication on sleep is difficult [5], and although we did not stratify the patients by type and/or dose of medication, it seems unlikely that treatment alone could explain the differences between the groups. Previous studies have shown that these variable sleep patterns are also unlikely to be simply caused by having unstructured days without any routine, since when compared to unemployed individuals who may also not have a pattern to their daily lives, the differences persist [11]. Interestingly, an association between having a daily occupation, and better sleep quality and lower sleep latency has been previously reported [12], indicating that social and professional rehabilitation could reflect positively in the patients' circadian rhythms.

Our study has several limitations: the lack of objective evaluation of sleep (i.e. polysomnography or actigraphy) allowed only for the study of patients' perceptions. We included patients who were taking benzodi-

azepines and other psychotropics and did not control for the effect of type and dose of antipsychotic and/or other medicines. Stimulant use (e.g. coffee, tea, etc) and alcohol use was also not controlled for. Although sleep apnea was an exclusion criterion, we cannot guarantee that some of our sample may have undiagnosed sleep apnea, which may contribute to sleep difficulties. Severe insomnia has been associated with significantly higher body mass indexes [19], which we did not control for. Our patients presented elevated symptom levels, and therefore our results may not be applicable to patients in remission. Finally, our results from an Iberic population may not apply to other countries/cultures, and therefore need further replication. Strengths of the study include the sample size and its naturalistic nature, representing "real-life" patients.

5. Conclusions

Our results show that patients reporting sleep disturbances show greater symptom severity, and worse personal and social functioning. Moreover, both patients with sleep disturbances and their caregivers self-report worse satisfaction with life. These disturbances may reinforce altered sleep patterns, cognitive deficits and social engagement associated with SZ, with a negative impact on rehabilitation strategies.

Although not a diagnostic criterion, sleep disturbance is prevalent in SZ patients, and the identification of sleep complaints is of the utmost importance. Careful history taking, and the use of sleep diaries, will usually lead to a proper characterization of sleep disturbances with practical therapeutic implications. Given the success in improving sleep through behavioral interventions such as sleep hygiene, particularly enforcement of stable sleep and wake times, in various populations [40] it might benefit patients with SZ as well. Improvement in cognition, functioning, as well as satisfaction with life of people with SZ may also depend on improving sleep parameters. Nevertheless, this important area has received lack of attention from SZ researchers, despite the positive impact that treatments should have on these variables.

Conflicts of Interest

The authors report no conflict of interest.

Sofia Brissos and Ivan Bernardo-Fernandez at the time of this study (2011) were full-time employees of Janssen Pharmaceutical in Portugal and Spain respectively, as Medical Affairs Managers.

Funding and Support

This study was supported by Janssen. The sponsor of the study had no role in the collection and analysis of the data, or preparation of the manuscript.

Acknowledgements

The authors thank the following study investigators: Portugal: António Bajouco, Gisela Borges, Pedro Carvalho, Elsa Lara, Luciano Marmelada, Fernanda Rosa; Spain: Alberto Fuentes, Alexandre Pons i Villanueva, Alfonso Rodríguez, Alfredo Cortell, Alfredo Galindo, Ana Isabel González, Andrés González, Andrés Martín, Andrés Porcel, Ángel Royuela, Antonio Agüera, Antonio Carrillo, Antonio Galbis, Antonio Martínez, Blanca Fernández-Abascal, Carlos José Pino, Carlos Riaza, Carmen Moreno, Carmen Pernía, César Antón, Clara Pedrejón, Consuelo de Dios, Cristina García, Desiderio Mejías, Luis Goenechea, Ignacio Zarranz, Patricia Llorens, Elena de las Heras, Elisabet Gorgues i Queralt, Eloísa Gloria Román, Enrique Daniel Vega, Esther García, Eva Fontela, Evaristo Nieto, Francisco Arnau Feiró, Francisco de Vicente, Francisco del Río, Francisco Gázquez, Francisco Javier Fernández, Guillermo Lahera, Guillermo Masana, Horacio Watman, Jaqueline Mayoral, Javier Alberca, Jesús Enrique Mesones, Jesús Salomón, Joan Cadevall, Jorge Domingo Ribas, José Antonio Juan, José Carlos Rodríguez, José Carmona, José Luis Gálvez, José Manuel Crespo, José Manuel Perea, José María Martínez, José Salazar, Juan Carlos García, Juan Carlos Giménez, Juan Carlos Gómez, Juan Carlos López, Juan Carlos Ortigosa, Juan José Fernández, Juan José Gea, Juan Pablo Vedia, Julia Fraga, Julia García-Albea, Ladislao García, Leonardo Moyano, Luis Ignacio Rodríguez, Luis Mínguez, Luis Santa-María, Lydia Gayubo, Maria Carmen García Mahía, Maria Eulalia Jaén, Maria Lourdes Fernández, Maria Rosario Cejas, Manuel Soria, María Aránzazu Sánchez, María Elena Caruezo, María José Márquez, María Peñitas Ríos, Mercè Aubareda, Mercedes Guzmán, Micaela González-Quirós, Miguel Alfonso García, Miguel Hernández, Miguel Lliteras, Miguel Soler, Olga Sobrino, Pablo Álvarez, Pedro A. Sopolana, Pedro Ecénarro, Pedro Vicente Canut, Rafael Fernández G^a-Andrade, Ramón Planet, Raquel Largo, Raúl Vázquez-Noguerol, Rosa Catalán, Rosa González, Rosa Villanueva, Salustiano Campos, Salvador Martínez, Salvador Ros, Santiago Navarro, Santiago Sánchez, Sara González, Sara Sole, Saulo Pérez Gil, Susana Álvarez, Valero Pérez, Vicente Berenguer, Vicente Tordera, Victoria Caramés, Virgilio Traid, Xavier Fluvià.

References

1. Keshavan MS, Reynolds CF 3rd, Miewald MJ, Montrose DM, Sweeney JA, Vasko RC Jr, Kupfer DJ. Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. *Arch Gen Psychiatry* 1998; 55(5):443-8.
2. Taylor SF, Tandon R, Shipley JE, Eiser AS. Effect of neuroleptic treatment on polysomnographic measures in schizophrenia. *Biol Psychiatry* 1991; 30:904-912.
3. Tandon R, Shipley JE, Taylor S, Greden JF, Eiser A, DeQuardo J, Goodson J. Electroencephalographic sleep abnormalities in schizophrenia: Relationship to positive/negative symptoms and prior neuroleptic treatment. *Arch Gen Psychiatry* 1992, 49:185-194.
4. Monti JM, Monti D. Sleep disturbance in schizophrenia. *Int Rev Psychiatry* 2005, 17(4):247-53.
5. Cohrs S. Sleep disturbances in patients with schizophrenia: Impact and effect of antipsychotics. *CNS Drugs* 2008, 22:939-962.
6. Monti JM, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. *Sleep Med Rev* 2004, 8:133-148.
7. Wetter TC, Lauer CJ, Gillich G, Pollmächer T. The electroencephalographic sleep pattern in schizophrenic patients treated with clozapine or classical antipsychotic drugs. *J Psychiatr Res* 1996, 30(6):411-419.
8. Wirz-Justice A, Haug HJ, Cajochen C. Disturbed circadian rest-activity cycles in schizophrenic patients: An effect of drugs? *Schizophrenia Bull* 2001, 27:497-502.
9. Kupfer DJ, Wyatt RJ, Scott J, Syder F. Sleep disturbance in acute schizophrenic patients. *Am J Psychiatry* 1970, 126:1213-1223.
10. Donlon PT, Blacker KH. Clinical recognition of early schizophrenic decompensation. *Dis Nerv Syst* 1975, 36(6):323-327.
11. Wulff K, Dijk DJ, Middleton B, Foster RG, Joyce EM. Sleep and circadian rhythm disruption in schizophrenia. *Br J Psychiatry* 2012, 200(4):308-316.
12. Afonso P, Brissos S, Figueira ML, Paiva T. Schizophrenia patients with predominantly positive symptoms have more disturbed sleep-wake cycles measured by actigraphy. *Psychiatry Res* 2011, 189(1):62-6.
13. Bromundt V, Köster M, Georgiev-Kill A, Opwis K, Wirz-Justice A, Stoppe G, Cajochen C. Sleep-wake cycles and cognitive functioning in schizophrenia. *Br J Psychiatry* 2011, 8(4):269-76.
14. 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. *Chronobiol Int* 2006, 23(1-2):485-495.
15. Afonso P, Figueira ML, Paiva T. Sleep-promoting action of the endogenous melatonin in schizophrenia compared to healthy controls. *Int J Psychiatry Clin Pract* 2011, 15(4):311-315.
16. Wulff K, Joyce E. Circadian rhythms and cognition in schizophrenia. *Br J Psychiatry* 2011, 198(4):250-252.

17. Ritsner M, Kurs R, Ponizovsky A, Hadjez J. Perceived quality of life in schizophrenia: relationships to sleep quality. *Qual Life Res* 2004, 13(4):783-791.
18. Hofstetter JR, Lysaker PH, Mayeda AR. Quality of sleep in patients with schizophrenia is associated with quality of life and coping. *BMC Psychiatry* 2005, 5:13.
19. Palmese LB, DeGeorge PC, Ratliff JC, Srihari VH, Wexler BE, Krystal AD, Tek C. Insomnia is frequent in schizophrenia and associated with night eating and obesity. *Schizophr Res* 2011, 133(1-3):238-243.
20. Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Möller HJ. WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: long-term treatment of schizophrenia. *World J Biol Psychiatry* 2006, 7(1):5-40.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC, 4th ed. (DSM IV-TR), 2000.
22. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS). recent developments in ascertainment and scaling. *Psychopharmacol Bull* 1988, 24:97-99
23. Buisse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989, 28:193-213.
24. Brissos S, Palhavã F, Marques JG, Mexia S, Carmo AL, Carvalho M, Dias C, Franco JD, Mendes R, Zuzarte P, Carita AI, Molodynski A, Figueira ML. The Portuguese version of the Personal and Social Performance Scale (PSP): reliability, validity, and relationship with cognitive measures in hospitalized and community schizophrenia patients. *Soc Psychiatry Psychiatr Epidemiol* 2011 Jul 8. [Epub ahead of print]
25. Garcia-Portilla MP, Saiz PA, Bousoño M, Bascaran MT, Guzmán-Quilo C, Bobes J. Validation of the Spanish Personal and Social Performance scale (PSP) in outpatients with stable and unstable schizophrenia. *Rev Psiquiatr Salud Ment* 2011, 4:9-18
26. Poulin J, Daoust AM, Forest G, Stip E, Godbout R. Sleep architecture and its clinical correlates in first episode and neuroleptic-naïve patients with schizophrenia. *Schizophr Res* 2003, 62(1-2):147-153.
27. Walther S, Koschorke P, Horn H, Strik W. Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. *Psychiatry Res* 2009, 169(3):187-190.
28. Kato M, Kajimura N, Okuma T, Sekimoto M, Watanabe T, Yamadera H, Takahashi K. Association between delta waves during sleep and negative symptoms in schizophrenia. Pharmacoeeg studies by using structurally different hypnotics. *Neuropsychobiology* 1999, 39(3):165-172.
29. Hinze-Selch D, Mullington J, Orth A, Lauer CJ, Pollmächer T. Effects of clozapine on sleep: a longitudinal study. *Biol Psychiatry* 1997, 42:260-266.
30. Lee JH, Woo JI, Meltzer HY. Effects of clozapine on sleep measures and sleep-associated changes in growth hormone and cortisol in patients with schizophrenia. *Psychiatry Res* 2001, 103:157-166.
31. Salin-Pascual RJ, Herrera-Estrella M, Galicia-Polo L, Lurrabaquio MR. Olanzapine acute administration in schizophrenic patients increases delta sleep and sleep efficiency. *Biol Psychiatry* 1999, 46:141-143.
32. Müller MJ, Rossbach W, Mann K, Röschke J, Müller-Siecheneder F, Blümner M, Wetzel H, Russ H, Dittmann RW, Benkert O. Sub chronic effects of olanzapine on sleep EEG in schizophrenic patients with predominantly negative symptoms. *Pharmacopsychiatry* 2004, 37(4):157-162.
33. Yamashita H, Morinobu S, Yamawaki S, Horiguchi J, Nagao M. Effect of risperidone on sleep in schizophrenia: a comparison with haloperidol. *Psychiatry Res* 2002, 109(2):137-142.
34. Luthringer R, Staner L, Noel N, Muzet M, Gassmann-Mayer C, Talluri K, Cleton A, Eerdeken M, Battisti WP, Palumbo JM. A double-blind, placebo-controlled, randomized study evaluating the effect of paliperidone extended-release tablets on sleep architecture in patients with schizophrenia. *Int Clin Psychopharmacol* 2007, 22(5):299-308.
35. Cohrs S, Meier A, Neumann A-C, Jordan W, Rüter E, Rodenbeck A. Improved sleep continuity and increased slow wave sleep and REM latency during ziprasidone treatment: a randomized, controlled, crossover trial of 12 healthy male subjects. *J Clin Psychiatry* 2005, 66(8):989-996.
36. Cohrs S, Rodenbeck A, Guan Z, Pohlmann K, Jordan W, Meier A, Rüter E. Sleep-promoting properties of quetiapine in healthy subjects. *Psychopharmacology* 2004, 174(3):421-429.
37. Pandina GJ, Lindenmayer JP, Lull J, Lim P, Gopal S, Herben V, Kusumakar V, Yuen E, Palumbo J. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacol* 2010, 30(3):235-244.
38. Kang SG, Lee HJ, Jung SW, Cho SN, Han C, Kim YK, Kim SH, Lee MS, Joe SH, Jung IK, Kim L. Characteristics and clinical correlates of restless

- legs syndrome in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007, 31(5):1078-1083.
39. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005, 353(12):1209-1223.
40. Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998-2004). *Sleep* 2006, 29(11):1398-414.