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Quality of sleep in escitalopram-treated female patients with panic disorder

D. Todder[1]* and B. T. Baune[2]

[1]*Department of Psychiatry, University of Ben-Gurion, Israel*
[2]*Department of Psychiatry and Psychiatric Neuroscience, James Cook University, QLD, Australia*

Objective The purpose of this study was to assess the development of the night-activity rhythm and quality of sleep during escitalopram treatment of patients suffering from panic disorder.
Methods Fifteen women with panic disorder were included and followed-up over a 5-week study period during treatment with escitalopram. An age-matched control group of 15 women were also assessed for 1 week. Motor activity was continuously measured with an electronic wrist device (Actiwatch), sleep was assessed with the Pittsburgh sleep quality index (PSQI) and patients were clinically assessed with the panic and agoraphobic scale (P&A), the global assessment of functioning (GAF) score, the Hamilton depression and anxiety scales (HAM-D, HAM-A) and the clinical global impression (CGI) score.
Results There was a statistically significant difference on the self-rated PSQI between the panic disorder patients and the control group. This difference disappeared after 4 weeks of treatment with escitalopram. There was no statistically significant difference of the objective measurements of the Actiwatch between the patients and the control group. In addition, no statistically significant changes were found in the actigraphy measurements at the beginning and the end of the treatment period for patients with panic disorder.
Conclusions Patients with panic disorder rate their sleep worse than healthy controls. Treatment with escitalopram improved the subjective quality of sleep, whereas objective measures remained unchanged during treatment. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — locomotor activity; panic disorder; quality of sleep; subjective; objective

INTRODUCTION

Panic disorder (PD) ranks high in disability, suffering and economic costs (Zaubler and Katon, 1996). PD is a syndrome comprising a variety of symptoms that can be divided into three clusters: behavioural, cognitive and somatic (APA, 2000). Behavioural symptoms include the need for external reassurance, opening windows 'to get air', and more. Cognitive symptoms usually consist of the fear of dying, losing control or going insane, while somatic symptoms include a wide spectrum of sympathetic symptoms, such as sweating and tachycardia. Although sleep complaints do not belong to the diagnostic criteria of PD, they are often encountered as accompanying phenomena/symptoms and are particularly relevant for clinical practice.

Sleep is a complex phenomenon that is composed of cognitive and biological aspects that can be assessed in an objective or subjective manner. The subjective assessment of sleep is usually done with different self-report questionnaires (e.g. the Pittsburgh Sleep Quality Inventory, PSQI) (Buysse *et al*., 1989). The objective assessments are usually carried out by polysomnography, which measures electroencephalographic (EEG) signals. In the last decade, actigraphy emerged as a method for the objective assessment of sleep, which is based on the night-time locomotor activity. The basic idea behind this method is that disturbed sleep-wake cycles are most likely related to alterations of circadian rhythms affecting also circadian locomotor activity (Taphoorn *et al*., 1993). An actigraph is a watch-like device worn on the wrist of the non-dominant hand, capable of measuring and keeping a record of the wrist movements. The 'bigger' the movement, the greater is the amplitude of the signal. The advantage of the actigraph is its ease of use—also in outpatient settings—and the opportunity to continuously measure sleep and activity parameters in a home environment. However, the correlation between subjective and objective measurements varies.

The relationship between sleep and PD is particularly interesting because of arousal regulation problems in

* Correspondence to: D. Todder, Department of Psychiatry, University of Ben-Gurion, Israel. Tel: +972-50-6267688 Fax: +972-8-6401580
E-mail: dtoder@netvision.net.il

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this group of patients (Lepola *et al*., 1994). Another interesting observation is that PD is one of the leading causes of night sweats seen in women in general practice (Mold et al., 2002), which also could be related to sleep problems. Another source of sleep problems could be nocturnal panic attacks (Sloan *et al*., 1999).

The studies on the subjective quality of sleep in patients with PD show varying results. In a review by Sheikh *et al.*, it is concluded that across studies approximately two-third of PD patients complain about bad quality of sleep as measured by questionnaires including the PSQI (Sheikh *et al*., 2003). Similar findings were reported by Overbeek et al. (Overbeek *et al*., 2005) who reported that patients with PD demonstrate a higher prevalence of sleep complaints compared to controls, possibly due to comorbid depression. The authors also concluded that nocturnal panic attacks were not related to sleep quality.

The objective sleep measurements in PD have demonstrated inconsistent results. In a review on objective sleep pattern in patients with PD, Sheikh and colleagues review findings on sleep in PD patients (Sheikh *et al*., 2003). While some studies reported normal sleep patterns in PD, other reports showed a variety of pathological patterns as reduced rapid eye movement (REM) latency, decreased REM density, reduced sleep efficiency and increased sleep latency in this patient group (Sheikh *et al*., 2003).

Another important aspect to be considered is the effect of antidepressants on the connection between anxiety and sleep quality. In an uncontrolled study, Cervena et al. reported small but significant change of the subjective quality of sleep but not on total sleep time, sleep onset latency and refreshment score (Cervena *et al*., 2005). On the other hand there was a statistically significant change of the objective measurement of sleep architecture, especially shorter stage 1 sleep and longer stage 4 sleep. No significant effects of benzodiazepines and antidepressants on the objective or the subjective parameters of quality of sleep in patients with PD was found (Cervena *et al*., 2005). In light of the limited and inconsistent findings on sleep disturbances in PD, further studies are needed.

The purpose of this prospective study was to assess night-activity rhythm and quality of sleep among initially unmedicated and subsequently medicated patients suffering from PD. All patients in this study were initially assessed in an unmedicated state and then for another 4 weeks during treatment with a proven antipanic agent 'escitalopram' (Stahl *et al*., 2003). Furthermore, we compared locomotor-based sleep assessments between patients and healthy controls. We hypothesized that improvement of sleep is closely related to alterations in night-time locomotor activity, and that sleep features in the patient group would 'normalize' by the end of the treatment period compared to controls.

MATERIALS AND METHODS

Design

The study was designed as a prospective controlled study over 5 weeks. The first week, which was a 'drug-free' period, was followed by 4 weeks of escitalopram treatment. A 5-week period allowed weekly assessments of clinical parameters and quality of sleep and continuous assessment of motor activity (see below for details). The study was approved by the ethics committee of the University of Ben-Gurion.

Patients

The inclusion criteria were 18–65-year old female patients with untreated panic disorder. We recruited 15 female patients. Initially we plan to have both male and female, but the first male that was allegeable to the study came after 13 females so we decided to keep the homogeneity of the group and concentrate only on females. Participants were excluded if they met one of the following criteria: suicidal ideation, another axis I disorder (including primary sleep disorders), any endocrinology disorder or organic disorder. Patients who used benzodiazepine were excluded since PD patients on benzodiazepines may require a long-term detoxification and withdrawal period, which was not part of the study design. All patients signed an informed consent according to the local Helsinki committee regulation before participating in the study.

To meet the criteria of a drug-free period during week 1, patients treated by any other antianxiety agent without response were asked to go through a week of wash-out before starting the one drug-free week. Those who were treated with fluoxetine went through 2 weeks wash-out prior to the drug-free week. Our group consisted of seven drug-naive patients, and eight patients needed to go through the washout period. Two of them were using fluoxetine, three used paroxetine and three were medicated with sertraline. Out of the 15 patients 13 were working, one was student and another one was a housewife.

All patients were assessed on a weekly basis with the following set of questionnaires: CGI-S, CGI-I, HAM-A (Hamilton anxiety) (Hamilton, 1959), HAM-D-21 (Hamilton depression scale) (Hamilton, 1960) and

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P&A (panic and agoraphobic scale) (Bandelow *et al*., 1999).

Treatment

Starting on the first day (of the second week) patients received escitalopram 5 mg per day. Doses were adjusted according to clinical response up to escitalopram 10 mg per day. No other psychotropic drug was allowed.

Objective assessment of sleep parameters. Patients wore an Actiwatch-TS on the wrist of the non-dominant hand, a watch-like device that continuously measures skin temperature and motor activity. Activity is measured by the means of a piezo-electric accelerometer that is set up to record the integration of intensity, amount and duration of movement in all directions. The corresponding voltage produced is converted and stored as an activity count in the memory unit of the Actiwatch. The total number of counts is recorded within an epoch selected by the researcher, in this case 30 s. Using these settings, the device can store data for approximately 5.5 days before data is read out by a software program.

Patients were asked to wear the Actiwatch continuously except during showering as the device is not waterproof. Actigraphy recordings over the whole study period were carried out with the same Actiwatch per patient (individual Actiwatches). When data were read out into the database, patients received the same Actiwatch as before to continue the study. A volunteer healthy control group of female persons with similar age and a high level of general functioning (GAF score >80) wore the Actiwatch-TS device for 1 week (although the device measured only for 5.5 days as noted above).

The patients' locomotor activity was measured continuously including weekends. Data were read out in the study centre weekly on the same day of the week. Locomotor activity data of the controls included weekend data in order to make it comparable to the patients.

Controls

Physically and mentally healthy female controls working in administration in the Beer Sheva mental health centre, where the study was performed, were asked to participate in the study. All of them came from the same cultural and neighbourhood background as the enrolled patients. The controls were not shift workers. In order to exclude a neuropsychiatric condition, the structured diagnostic interview (M.I.N.I.) (Sheehan *et al*., 1998) was applied. Only those without a neuropsychiatric condition and a GAF score larger than 80 were included into the study.

Procedures

Psychiatric diagnoses of patients were assessed using a structured diagnostic interview (M.I.N.I.) (Sheehan *et al*., 1998). Patients were clinically assessed on a weekly basis using the panic and agoraphobia scale (P&A) (Bandelow *et al*., 1999), the HAM-A (Hamilton, 1959) and HAM-D (Hamilton, 1960) general functioning was assessed with the global assessment of functioning scale (GAF) (Endicott *et al*., 1976) and clinical global impression scale (CGI). Patients were advised to continue with their usual life styles including work and to function at the same level of activity as they used to. The participants wore the wrist Actiwatch continuously (Actiwatch-TS, Cambridge Neurotechnology Ltd, Cambridge, UK) on their wrist of the non-dominant hand for the full period of approximately 5 weeks.

The Pittsburgh sleep quality index (PSQI) evaluates various aspects of sleep perception retrospectively over a period of 4 weeks. In our study, however, we used the Pittsburgh sleep quality index (PSQI) on a weekly basis referring to past 7 days only. The wording of the commonly used timeframe of 4 weeks was modified in our study to a timeframe of 1 week prior to each assessment. Actigraph measurements and the estimates of sleep time and sleep patterns were calculated according to Sadeh et al. (Sadeh *et al*., 1995).

Activity analysis

Data was analysed using the 'Sleep Analysis version 5' software (Cambridge Neurotechnology Ltd, Cambridge, UK). The analysis of sleep parameters was done according to the algorithms provided by the actigraph software. We choose to focus on actigraphy parameters which have a corresponding parameter on the PSQI. This was the case for actual sleep time and sleep efficiency. We also used the actigraphy measure 'index of the fragmentation of sleep', which has no direct PSQI equivalent. Sleep time in % indicates the percentage of time asleep between sleep onset and end of sleep and sleep efficiency in % is derived from the actual sleep time divided through total time in bed.

In order to ensure that we analysed patient and control data during the same night-time period, we chose the time between 23:00 and 06:00. According to the sleep diaries, which patients and controls were

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Table 1. Clinical characteristics of 15 women with panic disorder

Clinical assessment	Start of drug-free period Mean ± SD	End of treatment Mean ± SD	*p*-value
P&A	33.6 ± 8	17.3 ± 11.4	0.012 *
HAM-A	20.6 ± 7.6	10.3 ± 8.6	0.009 *
HAM-D	12.4 ± 6.7	5.9 ± 7	0.008 *
GAF	55 ± 8.8	75 ± 10.1	0.0028 *
CGI-S	4.8 ± 1.0	3.0 ± 1.1	0.010 *

p-value according to Wilcoxon matched pairs test; * *p*-values < 0.05.
Start: results at the start of the 'drug free' week; End: results at last week of study (after 4 weeks of treatment).

requested to document sleep/wake-up time and quality of sleep including panic attacks, this time period captured full data from all study participants.

Statistical analysis

Statistical analyses were carried out with non-parametric tests. We used the Mann–Whitney *U*-test for comparing patients to controls, and the Wilcoxon-test to compare results of quality of sleep between week 1 and week 4 for each patient.

RESULTS

The overall age of the cohort was 34.5 years with similar age between patients (36.3years) and controls (32.9years; $p > 0.05$). To account for data loss from one patient, who dropped out after 3 weeks of treatment due to severe gastrointestinal side effects of escitalopram, the 'last observation carried forward' procedure was used. During the study, the following clinical measures improved significantly between baseline and 4-week of treatment (mean ± SD between baseline vs. 4 weeks): **P&A** 33.6 ± 8 vs. 17.3 ± 11.4, $p = 0.012$; **HAM-A** 20.6 ± 7.6 vs. 10.3 ± 8.6, $p = 0.009$; **HAM-D** 12.4 ± 6.7 vs. 5.9 ± 7, $p = 0.008$; **GAF** 55 ± 8.8 vs. 75 ± 10.1, $p = 0.0028$; **CGI** 4.8 ± 1.0 vs. 3.0 ± 1.1, $p = 0.01$ (Table 1). The ranges of HAM-A and HAM-D scores were as follows: 12–32 for HAM-A (>6 is considered as clinically relevant symptoms) and 3-22 for HAM-D (>7 is considered as clinically relevant symptoms).

Objective and subjective sleep analysis

Table 2 presents details of the objective and subjective sleep assessment as measured with the Actiwatch and the PSQI, respectively. We found that the total score of the subjective PSQI showed a statistically significant poorer overall quality of sleep of PD patients during the drug-free period compared to control subjects ($p = 0.028$). In addition, a trend ($p = 0.08$) of improved quality of sleep according to the PSQI was observed between the drug-free period and the end of the treatment period in PD patients. In contrast, the actigraphic parameters between the two time periods for patients

Table 2. Quality of sleep by objective and subjective assessment with actiwatch and Pittsburgh sleep quality index (PSQI) among 15 female patients with panic disorder and 15 healthy controls

Sleep parameters	Mean (SD) drug free week 1	Mean (SD) week 4 of treatment	Mean (SD) control	*p*-value[1] drug-free week 1 vs. control	*p*-value[1] week 4 of treatment vs. control	*p*-value[2] drug free week 1 vs. week 4 of treatment
Actigraphy measures						
Actual Sleep (%)	84.2 (±13.6)	86.7 (±5.7)	85.8 (±8.6)	0.71	0.97	0.79
Sleep efficiency (%)	69.9 (±13.5)	81.4 (±12.1)	69.9 (±24.7)	0.29	0.047 *	0.16
Motor activity	18.9 (±25.3)	13.4 (±8.1)	15.6 (±13.9)	0.83	0.97	0.64
Fragmentation index	40.9 (±27.1)	38.4 (±12.3)	35.8 (±20.9)	0.91	0.81	0.57
PSQI measure						
Total score	5.0 (±2.1)	3.6 (±2.5)	2.8 (±0.9)	0.028	0.72	0.08

[1] Mann–Whitney-test; [2] Wilcoxon-test; * *p*-value < 0.05; Mean (SD) of the actigraphy activity during the drug free period and after 4 weeks of treatment with escitalopram, and in the control group.
PSQI: Pittsburgh Sleep Quality Index.
Actual sleep (%) indicates the percentage of time asleep between sleep onset and end of sleep.
Sleep efficiency (%) is derived from the actual sleep time divided through total time in bed.

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with PD as well as between the patient and the control group showed no statistically significant difference.

Association of sleep parameters and clinical improvement

The results of the objective and the subjective assessments of sleep divided according to the clinical improvement status after 4 weeks of treatment are presented in Table 3. Clinical improvement was defined according to the Hamilton anxiety scale (≥50% reduction), P&A scale (≥50% reduction) and GAF scale (≥20% improvement). Participants with a ≥50% reduction on the HAM-A scale showed a trend of increased motor activity and actual sleep time as compared to those with less than 50% reduction on the HAM-A scale after 4 weeks of treatment, whereas the P&A and the GAF scales showed no differences between time points among PD patients.

Table 3. Sleep parameters obtained with Actiwatch or questionnaire (PSQI) compared for subjects * improved on the HAM-A scale, GAF and P&A scales after 4 weeks of treatment with escitalopram

	Improvement of ≥50% on HAM-A between week 1 and 4		
	Yes ($N=8$)	No ($N=7$)	p-value
Sleep parameters at week 4 of treatment	Mean ± SD	Mean ± SD	
Actual sleep time, %	86.4 (±3.1)	81.1 (±21.7)	0.09
Sleep efficiency, %	72.6 (±9.5)	66.2 (±18.3)	0.18
Mean activity score	15.4 (±8.3)	7.3 (±3.8)	0.09
Fragmentation Index	40.8 (±13.5)	31.2 (±4.9)	0.32
PSQI Total score [a]	4.2 (±2.4)	5.8 (±1.4)	0.22
	Improvement of ≥20 points on GAF scale between week 1 and 4		
	Yes ($N=8$)	No ($N=7$)	
Actual sleep time, %	87.9 (±4.3)	84.6 (±8.2)	0.65
Sleep efficiency, %	85.0 (±5.9)	75.3 (±18.9)	0.6
Mean activity score	11.4 (±4.0)	16.7 (±13.1)	0.7
Fragmentation Index	33.9 (±9.9)	45.8 (±14.2)	0.1
PSQI Total score [a]	2.8 (±2.4)	4.8 (±2.2)	0.4
	Improvement of ≥50% on P&A between week 1 and 4		
	Yes ($N=8$)	No ($N=7$)	
Actual sleep time, %	86.3 (±4.7)	86.9 (±7.4)	0.88
Sleep efficiency, %	83.3 (±7.2)	79.4 (±16.8)	0.9
Mean activity score	12.7 (±4.8)	14.1 (±11.4)	0.70
Fragmentation Index	38.9 (±9.9)	38.2 (±11.4)	0.68
PSQI Total score [a]	2.5 (±2.6)	4.8 (±3.1)	0.14

p-value of Mann–Whitney U-test.
[a]PSQI: Pittsburgh Sleep Quality Index; Actual sleep (%) indicates the percentage of time asleep between sleep onset and end of sleep; Sleep efficiency (%) is derived from the actual sleep time divided through total time in bed; * different subjects are in different sections as the means are different.

DISCUSSION

In this study, we examined quality of sleep and motor activity during 4-week treatment with escitalopram in patients with PD. We investigated the relationship between sleep parameters and night-time motor activity. The focus of this study was to compare sleep parameters between 3 groups: panic disorder patients without psychotropic treatment (drug-free period) compared to the same group of patients treated with escitalopram over 4 weeks as compared to a healthy control group.

We found a statistically significant difference in the subjective quality of sleep as measured by the PSQI between patients in the 'drug-free' period and the controls. These results are in agreement with a study by Sheikh et al. reporting that approximately two-third of patients with PD complained of impaired subjective sleep (Sheikh *et al*., 2003) and with research by Overbeek and colleagues reporting that patients with PD suffer from worse quality of sleep compared to controls (Overbeek *et al*., 2005).

After 4 weeks of treatment with escitalopram, there was no longer a statistically significant difference of quality of sleep between patients with PD and controls. When we compared the subjective sleep assessment as measured by the PSQI between the drug-free period and week 4 of treatment, we found a trend towards improvement after 4 weeks of treatment. Therefore, we suggest that the treatment process may have 'normalized' the subjective sleep measure. These findings are in contrast to Cervena's work suggesting that antidepressants failed to change sleep quality (Cervena *et al*., 2005). However, the comparison between the two studies is difficult, since the patients in Cervena's study were given benzodiazepines, while in our study patients received only escitalopram without any concomitant medication. Another important difference between these two studies is that some of the patients in Cervena's research were treated with antidepressants at the beginning of the study, while other patients started the antidepressant therapy later in the study as opposed to our study protocol where patients started and continued escitalopram over the same study period of 4 weeks.

While subjective sleep assessment improved with treatment in our study, the objective assessment of quality of sleep using the Actiwatch failed to show any difference on various sleep parameters between the patient group in the 'drug-free' period and the control group, as well as between the drug-free period and week 4 of treatment. However, such discrepancies between subjective and objective scoring of sleep

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quality have been reported previously. Roy-Byrne et al. raised the possibility that patients with PD may be specifically sensitive to sleep quality subjectively measured while the objectively assessed sleep patterns appear grossly normal (Roy-Byrne *et al*., 1986).

The improvement of sleep quality as captured by the PSQI questionnaire could be attributed to at least two mechanisms. The first could be due to the clinical improvement in PD symptoms, and the second mechanism could related to a beneficial effect of escitalopram treatment without an immediate connection to the status of the panic attacks. If the first suggested mechanism holds true, a statistically significant difference of subjective sleep parameters between the clinically improved group and the non-improved group subjective sleep parameters would have been expected. However, since our study failed to show such a difference, we suggest that the subjective sleep improvement was not due to clinical improvement (Table 1), but possibly due to other non-specific factors, such as placebo effect.

Our study has strengths and limitations. As we used continuously recorded actigraphy measures over several weeks, we may have obtained more accurate measures of motor activity than previous studies in this field. Other strengths are the prospective study design allowing pre- and post-treatment comparison and the comparison with healthy controls. The limitations are the small sample size, the open-label design and the fact that none of the patients were men. Generalization of our results to all patients with PD including men is therefore limited. In fact, we cannot exclude the possibility that sleep patterns in men with PD are distinctly different from women, which warrants further studies. Another limitation might be related to the study procedure that we mixed actigraphy data from weekdays and weekends since habits and motor activity might be differencing between working days and non-working days. However, since actigraphy data from patients as well as from controls both contained mixed weekday and weekend data, the bias might be limited. Furthermore, future actigraphy studies might be improved by matching patients and controls according to weekday when included into the study since at least theoretically varying daily habits during the week could influence actigraphy data. This limitation in our study might serve as an explanation for the large distribution of sleep efficiency in both the patient and control groups. Finally, although polysomnography is the gold standard to assess sleep architecture, the Actiwatch device proves to be useful for the application over an extended period of time, such as our treatment study using a pre-post design in a community setting.

CONCLUSION

We found a discrepancy between objective and subjective assessment of sleep in women with panic disorder. While the subjective measurements of locomotor activity suggest a normalization process of sleep parallel to the improvement of symptomatology with escitalopram treatment, objectively assessed sleep patterns remained unchanged. Long-term studies are needed in order to understand the different time scales for improvement of sleep and motor activity in patients with PD.

CONFLICT OF INTERESTS

Both authors declare no conflict of interest.

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