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Sleep quality in opioid-naive and opioid-dependent patients on methadone maintenance therapy in Malaysia

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Background/aim: Sleep disturbances may contribute to poor treatment outcomes in opioid-dependent patients. The extent to which the sleep profiles of opioid-dependent patients differ from those of the general Malaysian population is not documented. This study compared opioid-naive subjects and opioid-dependent patients on methadone maintenance therapy (MMT) in terms of their sleep quality.

Materials and methods: Participants comprised Malay male opioid-naive subjects (n = 159) and opioid-dependent patients (n = 160) from MMT clinics in Kelantan, Malaysia, between March and October 2013. Sleep quality was evaluated using the translated and validated Malay version of the Pittsburgh Sleep Quality Index (PSQI).

Results: The opioid-dependent patients exhibited higher global PSQI scores [adjusted mean (95% CI) = 5.46 (5.02, 5.90)] than the opioid-naive group [4.71 (4.26, 5.15)] [F (1, 313) = 4.77, P = 0.030].

Conclusion: This study confirmed the poorer sleep quality among opioid-dependent patients on MMT, as manifested by their higher global PSQI scores. The sleep complaints in this patient population are a factor to consider and, when necessary, sleep evaluation and treatment should be undertaken to improve MMT patients' quality of sleep and overall treatment outcome.

Key words: Clinical, insomnia, methadone, outcomes, response, subjective, sleep, sleep quality

1. Introduction

Worldwide, the problem of opioid dependence is growing and has become an important public health concern. This growing group of patients has extensive health care needs and management of opioid dependence represents a great challenge to clinicians. Although methadone is available, discontinuation of methadone maintenance therapy (MMT) and continued use of opiates pose challenges to the treatment of patients with opiate dependence.

In addition to comorbid medical and psychiatric illnesses such as pain and depression, sleep disturbance may also contribute to poor treatment outcome in opioid-dependent patients. Previous studies have shown that sleep disturbances caused premature exit from treatment (1–3), increased use of sleep medications (4–6), and increased chronic depressive symptoms (7,8). Evidence also showed that sleep disturbances affected patients' quality of life and impaired their engagement with treatment, leading to continue illicit drug use (4,7,9). Opioid-dependent patients frequently reported sleep problems during MMT (4–6,8–12). However, physicians often underestimate the sleep complaints in this patient population.

Several papers on sleep quality in opioid-dependent patients during MMT were published previously in the United States and other countries (4–6,12–16). However, sleep disorder data are largely unavailable in Malaysia. A previous study used the Pittsburgh Sleep Quality Index (PSQI) to investigate the effects of electroacupuncture on sleep quality in 20 patients receiving MMT in Kajang, Malaysia (17). Recently, we published our data on the relationship between cold pressor pain-sensitivity and sleep quality in opioid-dependent males on methadone treatment (18); however, the distinct sleep component of patients on MMT in comparison with the data from

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a sample of opioid-naive individuals has not been characterized. In the absence of published data in our local population that document the extent to which the sleep profiles of opioid-dependent patients differ from those of the general population, clinical studies may provide important information regarding sleep quality in these patients. This study sought to fill this gap.

The present study investigated sleep quality using the translated and validated Malay language version of the PSQI in opioid-naive subjects and opioid-dependent patients on MMT to test the hypothesis that there is a significant difference in sleep quality between this patient population and the general population.

2. Materials and methods

2.1. Participants

This observational cross-sectional study involved Malay male subjects ≥18 years of age. Participants comprised opioid-naive subjects (n = 159) and opioid-dependent patients (n = 160) according to the DSM-IV criteria (19). We selected only Malay male subjects in this study, trying to minimize the influence of ethnicity on sleep quality (20,21) and because drug abusers in Malaysia are predominantly males; thus, this reflects our patient population (22). Participants were recruited from March to October 2013 as part of an ongoing clinical study to evaluate the application of personalized methadone therapy among patients on MMT.

Opioid-naive subjects were defined as individuals who had not taken any opioids including morphine and methadone to their best knowledge and were presumed so after two consecutive negative urine screenings for drugs. They were recruited from the local and university communities via word of mouth. Subjects with acute or chronic medical, surgical, and psychiatric illnesses that required medical, surgical, or psychiatric therapy were excluded from the study.

Opioid-dependent patients met the inclusion and exclusion criteria of the national MMT program and were currently enrolled in the national MMT program at Hospital Universiti Sains Malaysia and other MMT clinics in Kelantan. All were stabilized in treatment, defined as having been enrolled in the program for more than 1 month with no change of methadone dosage over the past 1 month. Patients with acute medical, surgical, and psychiatric illnesses and those acutely intoxicated were excluded. Patients who had major psychiatric illness, peripheral vascular disease, chronic or ongoing acute pain, or benzodiazepine, cannabinoid, and barbiturate abuse; those on regular anticonvulsants, neuroleptics, or analgesics; and those who used alcohol regularly were also excluded from the study.

As we found that the number of available opioid-naive subjects and patients receiving MMT who met all inclusion and exclusion criteria were limited, we took all eligible subjects within the study period.

2.2. Data collection

Each subject was informed about the nature and purpose of the study and the usage of data, and was asked if he would participate. If he agreed, written informed consent was obtained. Subjects were then asked to fill out the translated and validated Malay version of the PSQI.

The PSQI is one of the validated self-administered written questionnaires to measure subjective sleep quality and disturbances during the previous month and to discriminate between 'good' and 'poor' sleepers that has been translated into several languages, including Malay. The Malay translation of this questionnaire was performed by the MAPI Research Trust and permission for use the Malay version of the PSQI was obtained from its authors at the University of Pittsburgh (23).

The PSQI contains 19 items that are included in scoring. The 19 individual items are used to generate seven component scores: subjective sleep quality (one item), sleep latency (two items), sleep duration (one item), habitual sleep efficiency (three items), sleep disturbances (nine items), use of sleep medications (one item), and daytime dysfunction (two items). Each of the seven component scores is determined based on scoring guidelines, with the seven component scores each with a potential range of 0–3, where 3 reflects the negative extreme on the Likert scale. The sum of these seven component scores yields one global score of subjective sleep quality with a potential range of 0–21, with higher scores representing poorer subjective sleep quality. A global PSQI score of >5, as we used, indicates that an individual has severe sleep difficulties in at least two areas or moderate difficulties in more than three areas (23). The internal consistency and reliability of the PSQI as estimated by Cronbach's alpha was 0.83 (23).

2.3. Ethics

The study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia in Kelantan, Malaysia, (reference number: USMKK/PPP/JEPeM (253.3 [14]), and the Medical Research & Ethics Committee, Ministry of Health, Malaysia (reference number: NMRR-13-524-16614).

2.4. Statistical analysis

Frequency and percentages were computed for categorical variables, and for numerical variables, mean and standard deviation (SD) were also computed. Comparison of the PSQI data between opioid-naive individuals and the MMT group were evaluated using an independent t-test. We studied sleep disorders as a continuous variable (the global PSQI scores). The independent t-test was used to compare factors that

may affect sleep quality such as age and body mass index (BMI) between opioid-naive and MMT groups. Analysis of covariance (ANCOVA) was carried out to further elucidate the mean difference of the global PSQI scores between the opioid-naive and MMT groups taking other covariates such as age and BMI. All analyses were done using SPSS for Windows (version 20, IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered significant.

3. Results

Opioid-naive subjects averaged 27.6 (SD 10.12) years of age, ranging from 18 to 63 years old. The mean BMI of these subjects was 24.8 (SD 5.31), ranging from 15.0 to 45.0 kg/m^2. Patients averaged 37.2 (SD 6.19) years of age, ranging from 25 to 55 years old. The mean BMI of these patients was 22.2 (SD 3.65), ranging from 14.9 to 36.3 kg/m^2. The mean age and BMI were significantly different between the opioid-naive and MMT groups ($P < 0.001$).

3.1. PSQI data in opioid-naive and opioid-dependent subjects

The PSQI data in opioid-naive and opioid-dependent subjects are presented in Table 1. The mean global PSQI score was 5.43 (SD 2.75), slightly above a cut-off score of 5, thus indicating poor overall sleep quality among patients. The mean global PSQI score of opioid-naive subjects was 4.74 (SD 2.30), indicating good overall sleep quality. The mean global PSQI score was significantly different between the opioid-naive and MMT groups ($P < 0.016$). More specifically, 40.0% (n = 64) of patients were identified as 'poor sleepers' (global PSQI scores >5), and 49 (30.8%) of opioid-naive subjects had PSQI scores of >5, but the difference did not reach statistical significance [χ^2 (df) = 2.94 (1), P = 0.086].

3.2. Comparison of global PSQI scores between opioid-naive and opioid-dependent subjects

The analysis of covariance revealed that opioid-dependent patients had higher global PSQI scores [adjusted mean (95% CI) = 5.46 (5.02, 5.90)] than the opioid-naive group [4.71 (4.26, 5.15)] [F (1, 313) = 4.77, P = 0.030] (Table 2).

4. Discussion

The present study investigated sleep quality in opioid-naive Malay subjects and opioid-dependent Malay patients on MMT. An important finding of this study is that the sleep quality is significantly different between this patient population and opioid-naive subjects. Compared with opioid-naive subjects, opioid-dependent patients had significantly higher sleep latency scores, lower sleep duration scores, higher sleep disturbance scores, higher use of sleep medication scores, and higher daytime dysfunction scores.

Though several reports on the severity and prevalence of sleep disorders in patients receiving MMT were previously published, this study is important because it identifies the sleep problems in patients on MMT in comparison with the data from a sample of opioid-naive individuals, which has largely been unstudied. Furthermore, this study was designed to exclude patients with chronic medical and

Table 1. The PSQI components, global PSQI, and other sleep variables reported by opioid-naive controls and opioid-dependent patients.

Variable	Mean (SD)		Test stat. (df) [a]	P-value
	Opioid-naive (N = 159)	Patient (N = 160)		
Component scores				
1. Subjective sleep quality	0.79 (0.58)	0.86 (0.52)	–1.24 (313)	0.216
2. Sleep latency	0.89 (0.82)	1.14 (0.70)	–2.95 (309)	**0.003**
3. Sleep duration	0.75 (0.94)	0.51 (0.83)	2.37 (312)	**0.018**
4. Habitual sleep efficiency	0.19 (0.56)	0.30 (0.74)	–1.51 (297)	0.133
5. Sleep disturbances	1.11 (0.48)	1.30 (0.63)	–2.98 (296)	**0.003**
6. Use of sleep medication	0.18 (0.46)	0.33 (0.78)	–2.18 (258)	**0.030**
7. Daytime dysfunction	0.84 (0.65)	0.98 (0.61)	–2.06 (316)	**0.040**
Global PSQI	4.74 (2.30)	5.43 (2.75)	–2.43 (308)	**0.016**
Minutes to fall asleep	17.02 (17.33)	21.74 (15.00)	–2.61 (317)	**0.010**
Actual sleep time per night (h)	6.78 (1.63)	7.23 (1.61)	–2.45 (317)	**0.015**

Significant P-values are in bold; [a] t-statistic using independent t-test.

Table 2. Comparison of global PSQI scores between opioid-naive controls and opioid-dependent patients controlling for potential confounders.

Group	Adj. mean[a] (95% CI)	Adj. mean diff. (95% CI)[b]	F stat. (df)	P-value[c]
Opioid-naive (N = 159)	4.71 (4.26, 5.15)	-0.75 (-1.43, -0.08)	4.77 (1, 313)	0.030
Patient (N = 160)	5.46 (5.02, 5.90)			

CI, Confidence interval.
[a] Adjusted mean controlling for age and BMI; [b] Bonferroni adjustment for 95% confidence interval for difference; [c] P-values were obtained using analysis of covariance.

psychiatric illnesses such as chronic pain, depression, and anxiety that are associated with sleep disorders. We think that these findings may provide important information regarding sleep quality in this patient population.

Malay patients have significantly higher global PSQI scores compared with the opioid-naive subjects. Previously, Xiao et al. designed a study to explore the nocturnal sleep structure of patients on early methadone treatment in Beijing, China (24). They evaluated subjective sleep using the PSQI and the Epworth Sleepiness Scale. They also assessed objective sleep patterns with overnight limited polysomnography (PSG). They showed that patients in early methadone treatment had poor sleep quality and abnormal sleep architecture. They similarly found that the PSQI scores among 20 male patients on early methadone treatment (mean (SD) = 10.5 (4.4)) were significantly higher than those of 20 healthy male controls [mean (SD) = 3.6 (1.8)) (t (df) = 6.92 (38), $P \leq 0.001$].

Results of PSG showed that patients had lower sleep efficiency, shorter total sleep time, more awakenings, and shorter slow wave sleep compared with healthy controls. Similarly, we found that the patients had lower sleep duration scores than opioid-naive subjects. In contrast, habitual sleep efficiency score was higher (but not statistically significant) in patients compared to opioid-naive individuals.

Oyefeso et al. investigated subjective sleep parameters and sleep difficulties of opiate addicts undertaking methadone detoxification using the St. Mary's Hospital Sleep Questionnaire (3). They found that the subjective sleep parameters of opiate addicts undertaking in-patient methadone detoxification (n = 27, 16 males and 11 females) were quantitatively and qualitatively different compared with those of drug-free controls (n = 26, 9 males and 17 females).

Compared with healthy controls, patients reported significantly shorter nocturnal sleep, longer sleep onset latency, and greater difficulty falling asleep. Similarly, we found that patients had lower sleep duration scores, higher sleep latency scores, and longer time to fall asleep.

Wang et al. studied sleep problems in patients on MMT. In both studies, MMT patients (n = 50, 25 males and 25 females) and 20 normal subjects underwent PSG (8,25). Patients demonstrated shorter total sleep time, higher sleep efficiency, and lower sleep onset latency compared to age-, sex-, and BMI-matched normal subjects. However, the differences were not statistically significant.

In the study by Wang et al., participants completed standardized questionnaires including the Epworth Sleepiness Scale and Functional Outcome of Sleep Questionnaire (8). They found that patients receiving MMT had significantly worse daytime function and had increased daytime sleepiness when compared with control subjects. Similarly, our patients had higher daytime dysfunction scores compared to opioid-naive subjects.

Almost all previous studies reported significant differences in sleep quality between opioid-dependent patients on MMT and opioid-naive subjects. In terms of the global PSQI, our current study confirmed the results of an earlier study (24) in that it showed the poorer sleep quality among opioid-dependent patients on MMT compared to the general population.

As with all studies, this study has limitations such as the lack of objective sleep evaluation. PSG could have helped as it objectively measures sleep quality, latency, duration, and habitual sleep efficiency that are subjectively covered by the PSQI, in addition to other parameters, such as sleep architecture (15). This was not available for our work. Second, we did not included both sexes in our study and only male subjects were included, as this reflects the cohort population of drug abusers in Malaysia, where more than 90% of them are male (22). Third, the sleep quality data are cross-sectional in nature, and therefore the current study cannot address the effects of MMT on sleep.

Notwithstanding these limitations, this study confirmed the poorer sleep quality among opioid-dependent patients on MMT, as manifested by their higher global PSQI scores. Data on the sleep quality in a sample of patients on MMT will hopefully provide complementary information and allow better prescription of methadone for individual

subjects in close association with drug efficacy and adverse drug reactions observed in each subject. Therefore, the sleep complaints in this patient population should not be underestimated. Sleep evaluation and treatment should be done to improve MMT patients' quality of sleep and overall treatment outcome.

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