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SCIENTIFIC INVESTIGATIONS

Subjective Daytime Sleepiness and Daytime Function in Patients on Stable Methadone Maintenance Treatment: Possible Mechanisms

David Wang, Ph.D.[1,2]; Harry Teichtahl, M.B.B.S. (Hons.)[1]; Cathy Goodman, B.App.Sci.[3]; Olaf Drummer, Ph.D.[4]; Ronald R. Grunstein, M.D., Ph.D.[2]; Ian Kronborg, M.B.B.S.[3]

[1]Department of Respiratory & Sleep Disorders Medicine, Western Hospital and Department of Medicine (RMH & WH), The University of Melbourne, Melbourne, Australia; [2]Woolcock Institute of Medical Research, The University of Sydney and Department of Respiratory & Sleep Medicine, Royal Prince Alfred Hospital, Sydney, Australia; [3]Drug and Alcohol Service, Western Hospital, Melbourne, Australia; [4]Victorian Institute of Forensic Medicine, Melbourne, Australia

Introduction: Subjects using opioids on a chronic basis have been reported to have a high prevalence of abnormal sleep architecture and central sleep apnea (CSA). The severity of CSA is, in part, related to blood opioid concentration. The aim of this study was to investigate subjective daytime sleepiness and daytime function in patients who are on stable methadone maintenance treatment (MMT) and to assess the possible mechanisms involving abnormal sleep architecture, CSA severity, and blood methadone concentration.

Methods: Fifty patients on MMT and 20 normal control subjects matched for age and body mass index were tested using polysomnography, blood toxicology, Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), and Beck Depression Inventory (BDI).

Results: The patients receiving MMT had significantly worse daytime function, were depressed, and had increased daytime sleepiness when compared with the control subjects (FOSQ 15.47 ± 3.19 vs 19.4 ± 0.47, BDI 14.64 ± 10.58 vs 2.05 ± 2.46, ESS 7.1 ± 5 vs 2.05 ± 1.76; all p values < 0.001). Nevertheless, daytime sleepiness in the patients receiving MMT was, on average, within the normal range (ESS ≤ 10). Multiple regression analysis demonstrated that the severity of CSA, blood methadone concentration, and abnormalities in sleep architecture were not significant in predicting the variance of ESS or FOSQ (all p values > 0.05) in these patients receiving MMT. The BDI was the best predictive variable for FOSQ, explaining 16% of the variance (p = 0.004).

Conclusions: Patients on stable MMT have, in general, normal subjective daytime sleepiness but impaired daytime function that partially relates to depression. The changes in sleep architecture, presence of CSA, and blood methadone concentrations do not significantly affect subjective daytime sleepiness and daytime function in these patients.

Keywords: opioid, methadone, sleep apnea, sleepiness, daytime function, daytime performance, sleep architecture, sedation, drowsiness

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Opioid use has increased rapidly in Western societies, with the major increase being in prescribed opioids, illicit or not. Opioids are commonly used for a number of clinical situations, including treatment of acute pain, trauma, cancer, and nonmalignant chronic pain and in methadone maintenance treatment (MMT) programs.[1] The US Congress declared the years 2001-2010 as the Decade of Pain Control and Research (Public Law 106-386-OCT). This declaration was to address and improve the situation that clinically significant chronic pain has not been adequately managed. Of the more than 50 million Americans suffering from chronic pain, only around 40% obtain adequate relief.[2] Meanwhile, illicit opioid use has increased substantially. Recent reports show that there are around 10 million heroin users in the world, with an estimated 2 to 4 million or more in Western Europe and North America alone.[3,4] Methadone, a long-acting μ-opioid agonist, is recognized as the most-effective treatment for heroin addiction.[5]

It has been reported that short-term opioid use can cause depressed consciousness or sedation.[6,7] There is conflicting evidence about tolerance to the sedative effect when opioids are used long term. Although some reports indicate that tolerance develops within a few days on a stable dose of drug and with a return of normal cognitive functioning, other studies suggest that patients continue to experience unpleasant sedative effects and cognitive impairment.[6-8] Although there are a number of studies describing the sedative effects of opioids, few studies have investigated the effects of opioids on sleep architecture and the possible effects on daytime sleepiness and daytime function, even though opioids have been reported to cause disrupted sleep and abnormal sleep architecture.[7,9,10] Furthermore, our previous studies have shown that central sleep apnea (CSA) occurs in

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Address correspondence to: David Wang, Level E11, Department of Respiratory & Sleep Medicine, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW 2050 Australia; Tel: 61 2 9515 5048; Fax: 61 2 9515 7196; E-mail: dwang@med.usyd.edu.au

approximately 30% of patients on stable MMT.[11,12] The severity of CSA has been shown to correlate significantly with increased methadone blood concentration.[12] Similarly, CSA is also reported in long-term users of time-release opioid analgesics, and the appearance of CSA is linked to increased opioid dose.[13-15] Sleep apnea itself can cause significant daytime sleepiness and reduced daytime function.[16] However, no studies to date have addressed the issue of the potential for CSA to cause these changes in subjects who use opioids on a chronic basis. Moreover, given the reported sedative effect of opioids used on a short-term basis and the significant correlation between CSA and opioid blood concentration, it would be of interest to know whether opioid blood concentration directly or indirectly affects daytime sleepiness and daytime function in patients on stable MMT.

The aim of the present study was to investigate the subjective daytime sleepiness (using the Epworth Sleepiness Scale [ESS])[17] and daytime function (using the Functional Outcomes of Sleep Questionnaire [FOSQ])[18] of patients on stable MMT and to compare the data with those from matched control subjects. In addition, we have explored the possible mechanisms for the differences found between the patients on MMT and control subjects in particular with respect to sleep architecture, sleep disordered breathing, and opioid blood concentration.

METHODS

The study was performed in a teaching hospital of The University of Melbourne, Australia. The research protocol was approved by the institutional research and ethics committee. All subjects gave written informed consent prior to participation.

Subject Selection

Patients on MMT and control subjects were recruited through advertisements placed in Melbourne pharmacies licensed to distribute methadone. The research topic was not mentioned in the advertisement. To be eligible for the study, patients on MMT had to be on methadone for 2 months or longer and had to be on a stable dose of methadone. A screening examination was performed to exclude those subjects with severe cardiac, respiratory, neurologic, or liver disease. Patients who had diagnosed psychotic disorders or pregnant patients were also excluded. Normal control subjects were recruited through advertisements placed on public notice boards with no mention of the research topic. They were matched to the included patients on MMT for age and body mass index (BMI). They did not have a current or previous history of substance abuse and did not have significant physical or other illnesses, and none were taking medications at the time of the study. No subject was excluded because of symptoms of sleep disordered breathing. Fifty patients on MMT (25 women, 25 men) and 20 normal control subjects (10 women, 10 men) completed the study.

Subject Assessments

Polysomnography

All subjects completed in-laboratory standard polysomnography (Compumedics E series, Victoria, Australia) on 2 successive nights with the first night used as acclimatization. The polysomnography included 2 channels of electroencephalogram (EEG), 2 channels of electrooculogram (EOG), chin electromyogram (EMG), leg EMG, electrocardiogram (ECG), nasal air pressure, thermistor, percentage oxygen saturation (SpO_2), body position, and snoring. Sleep staging, respiratory events, and arousals were scored in a blinded fashion by DW using standard criteria.[16,19-21] CSA was defined as complete cessation of airflow and lack of respiratory effort for 10 seconds or longer. Obstructive respiratory events were defined as continuing respiratory effort plus (1) no airflow or a clear decrease (> 50%) in airflow for 10 seconds or more, compared with baseline, or (2) if the amplitude reduction of airflow did not reach 50%, there needed to be either an oxygen desaturation of at least 3%, or an arousal. The apnea-hypopnea index was calculated as the number of apneas and hypopneas divided by total sleep time (TST) in hours. The central apnea index (CAI) was defined as the number of central apneas per divided by the TST, and obstructive sleep apnea-hypopnea index (OSAHI) was defined as the total number of obstructive apneas plus hypopneas per hour of sleep divided by the TST. Further details are described elsewhere.[12]

Blood Toxicology

All subjects had blood taken for toxicology before the second night of polysomnography. Tests included a screening for alcohol, amphetamines, benzodiazepines, cocaine, cannabinoids, opioids, 3,4-methylenedioxymethamphetamine ("ecstasy"), methadone, meperidine, benzodiazepines, antidepressants, and other prescription and over-the-counter drugs, using validated methods.[12] Methadone blood concentrations were quantified using high-performance liquid chromatography (HPLC) procedures routinely used in the laboratory of the Victorian Institute of Forensic Medicine. The precision of this assay is ± 5%.

Questionnaire Data

All subjects completed the following questionnaires: (1) ESS[17]; (2) Functional Outcome of Sleep Questionnaire (FOSQ), which includes 5 subscales: general productivity, social outcome, activity level, vigilance, and intimate relationship and sexual activity[18]; (3) the second version of the Beck Depression Inventory (BDI-II), which was employed to assess symptoms of depression[22] and includes 4 items: agitation, worthlessness, concentration difficulty, and loss of energy; and (4) Modified Mini-Mental Status Examination (MMSE), which was employed to detect cognitive impairment or organic mental disorders. The modified MMSE makes interpretation possible on an intuitive level and does not require mathematical calculations.[23]

Statistical Analysis

All values were expressed as mean ± SD unless otherwise stated. Group mean comparisons were assessed using parametric unpaired t-test or nonparametric Mann-Whitney rank sum test where appropriate. Univariate correlations were performed using Pearson correlation coefficient for normally distributed data and Spearman rho for nonnormally distributed data. A

Table 1—Sleep Architecture and Sleep-Disordered Breathing Data Comparison Between Patients on MMT and Control Subjects

Parameter	Patients n = 50	Controls n = 20	p Value
TST, min	380 ± 55.8	382 ± 55.5	0.87
Sleep efficiency, %	88.2 ± 9.8	85.7 ± 8.54	0.14
Sleep latency, min	9.72 ± 9.1	13.9 ± 17.4	0.45
REM latency, min	105 ± 57	92.3 ± 46.7	0.48
Arousal index	13.2 ± 5.02	13.2 ± 4.98	0.99
Sleep stage, min			
1	26.8 ± 17.3	37.7 ± 16.1	0.006[a]
2	243 ± 63.3	209 ± 33.9	0.03[a]
SWS	55.2 ± 40.4	64.7 ± 37.8	0.26
REM	55.2 ± 28.8	70.9 ± 23.0	0.03[a]
OSAHI, /h	10.8 ± 10.3	9.4 ± 9.1	0.59
CAI, /h	6.7 ± 14.2	0.25 ± 0.33	< 0.001[a]

Notes: The table was made based on data from Wang et al and is used with permission from the American Thoracic Society.[12] MMT refers with methadone maintenance therapy; TST, total sleep time; SWS, slow-wave sleep; REM, rapid eye movement sleep; OSAHI, obstructive sleep apnea-hypopnea index; CAI, central apnea index.

[a]Indicates statistical significance at $p < 0.05$ level.

multiple linear regression model (backward deletion) was used to determine the factors associated with the degree of daytime sleepiness and daytime function. ESS and square-transformed overall FOSQ scores were the outcome variables, and the predictive variables were the patients' demographic data, BDI, blood toxicology, sleep architecture, and sleep disordered breathing data. Independent variables were examined for colinearity. Statistical analysis was performed using SPSS 14 software (SPSS, Inc., Chicago, IL). A p value of less than 0.05 was considered significant, and all tests were 2-tailed.

RESULTS

The 50 patients on MMT and 20 control subjects were well matched for age (35 ± 9 vs 35 ± 9 years) and BMI (27 ± 6 vs 27 ± 5 kg/m^2). Detailed sleep architecture, sleep disordered breathing, and blood toxicology data have been published elsewhere.[12] The patients on MMT had an average methadone blood concentration of 0.34 ± 0.34 mg/L (0.09-1.70). Blood toxicology tests detected benzodiazepine, antidepressant, and cannabinoid in 38%, 14%, and 38% of the patients, respectively. Sleep architecture and sleep disordered breathing data in patients on MMT and controls subjects are shown in Table 1. Fifteen patients on MMT (30%) had a CAI greater than 5 (range, 0-93/hour). Ten patients (20%) had a CAI greater than 10. No control subject had CAI greater than 1. OSAHI was similar in the both the patient and normal control groups (Table 1).

As shown in Table 2, patients on MMT had increased daytime sleepiness (as measured by ESS), compared to the control group, although the average ESS was within the clinical normal range (ESS ≤ 10).[17,24] There were 12 patients on MMT (24%) who had excessive daytime sleepiness, with an ESS score greater than 10. No control subject had an ESS score greater than 10. Daytime function in patients on MMT, as measured by the FOSQ, was significantly impaired, compared with the controls. In patients on MMT, all FOSQ domains, including overall score, were significantly lower than in the controls ($p < 0.001$), as well as lower than the reference clinical normal values.[25,26] There were 35 patients on MMT (70%) who had a total FOSQ score less than 17.9, whereas no control subject had a score less than this reference normal value. Cognitive function, as tested by MMSE, was similar between patients on MMT and control subjects ($p = 0.09$), and both groups had averages that were within the clinical normal range (MMSE > 27).[23] There were 3 patients on MMT who had MMSE score less than 27, whereas all control subjects had scores above 27. Patients on MMT were significantly more depressed, with significantly higher BDI scores than control subjects. Only 18 patients (36%) had BDI scores within the normal range (0-9); 13 patients (26%) were in the mild to moderate depression range (BDI 10-16); 13 patients (26%) were in the moderate to severe depression range (BDI 17-29); and 6 patients (12%) had BDI scores in the severe depression range (BDI 30-63). All control subjects had a BDI score within the normal range (0-9).

The data in Table 3 explore whether CSA and methadone blood concentration play a role in subjective daytime sleepiness and daytime function in the patients on MMT. No difference was detected in the comparisons of FOSQ and ESS in patients on MMT with and without CSA, either with lower or higher methadone blood concentration.

Multiple linear regression results show that OSAHI, age, sleep latency, sleep efficiency, and rapid eye movement sleep

Table 2—Subjective Daytime Sleepiness and Psychological Function in Patients on MMT and Control Subjects

Questionnaire	MMT n = 50	Control n = 20	p	Reference normal value/range
ESS score	7.10 ± 5.00	2.05 ± 1.76	< 0.001	≤ 10[17]
FOSQ Overall	15.47 ± 3.19	19.40 ± 0.47	< 0.001	17.89 ± 3.08[25,26]
FOSQ GP	3.19 ± 0.63	3.92 ± 0.12	< 0.001	3.60 ± 0.51
FOSQ SO	3.28 ± 0.74	3.95 ± 0.22	< 0.001	3.80 ± 0.46
FOSQ AL	2.91 ± 0.74	3.76 ± 0.19	< 0.001	3.61 ± 0.54
FOSQ V	3.05 ± 0.81	3.83 ± 0.24	< 0.001	3.51 ± 0.67
FOSQ IR	3.10 ± 1.03	4.00 ± 0.00	< 0.001	3.93 ± 0.17
MMSE	28.66 ± 2.01	29.35 ± 1.04	0.09	≥ 27[23]
BDI	14.64 ± 10.58	2.05 ± 2.46	< 0.001	≤ 9[22]

Notes: MMT refers with methadone maintenance therapy; ESS, Epworth Sleepiness Scale; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory. The 5 subscales of the Functional Outcome of Sleep Questionnaire (FOSQ) are general productivity (GP), social outcome (SO), activity level (AL), vigilance (V) and intimate relationship and sexual activity (IR). Mann-Whitney rank sum tests were tested.

Table 3—Subjective Daytime Sleepiness, Psychological Function, and Daytime Function in Patients on MMT

	Central apnea index		P value	Methadone blood level		P value
	< 5 (n = 35)	> 5 (n = 35)		Low (n = 25)	High (n = 25)	
ESS	6.63 ± 5.02	8.20 ± 4.90	0.31	6.16 ± 4.59	8.04 ± 5.29	0.26
FOSQ						
Overall	15.81 ± 3.10	14.67 ± 3.37	0.19	15.58 ± 2.86	15.37 ± 3.55	0.92
GP	3.25 ± 0.63	3.07 ± 0.63	0.30	3.20 ± 0.59	3.19 ± 0.68	0.79
SO	3.35 ± 0.74	3.13 ± 0.74	0.58	3.32 ± 0.72	3.24 ± 0.78	0.44
AL	2.95 ± 0.74	2.82 ± 0.76	0.58	2.88 ± 0.70	2.95 ± 0.79	0.56
V	3.13 ± 0.78	2.87 ± 0.87	0.37	3.06 ± 0.77	3.04 ± 0.85	0.86
IR	3.21 ± 1.01	2.82 ± 1.08	0.17	3.14 ± 1.11	3.05 ± 0.97	0.36
MMSE	28.71 ± 1.64	28.53 ± 2.75	0.74	28.80 ± 1.68	28.52 ± 2.31	0.82
BDI	14.80 ± 10.25	14.27 ± 11.69	0.70	12.92 ± 10.35	16.36 ± 10.74	0.26

Notes: Comparisons were made between patients with and without central sleep apnea and having lower and higher methadone blood concentrations. Mann-Whitney rank sum tests were tested. No significance reached the < 0.05 level. The 5 subscales of the Functional Outcome of Sleep Questionnaire (FOSQ) are general productivity (GP), social outcome (SO), activity level (AL), vigilance (V) and intimate relationship and sexual activity (IR). MMSE refers with the Mini-mental State Examination; BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale.

Table 4—Multiple Linear Regression Results

	ESS			SqrFOSQ		
		P value	r^2		P value	r^2
Significant Predictors	OSAHI	0.003	0.35	BDI	0.004	0.32
	Age	0.009		TST	0.024	
	Sleep latency	0.011		REM-latency	0.031	
	Sleep efficiency	0.018				
	REM latency	0.028				

Notes: The Epworth Sleepiness Scale (ESS) score and squarely transformed Functional Outcomes of Sleep Questionnaire (FOSQ) data were the outcome variables. Both the central apnea index and the methadone blood concentration were eliminated early in the backward deletion process. None of the concomitant drug use (benzodiazepine, antidepressant, and cannabinoid detection) significantly predicted the variance of ESS and SqrFOSQ. OSAHI refers to obstructive sleep apnea-hypopnea index; TST, total sleep time; BDI, Beck Depression Inventory; REM, rapid eye movement sleep.

latency were significant predictive variables for ESS and, together, explain 35% of the variance in the ESS scores (Table 4). OSAHI is the best predictive variable for ESS (p = 0.003). BDI, total sleep time, and rapid eye movement sleep latency were significant predictive variables and, together, explain 32% of the variance in the SqrFOSQ. The BDI alone explained 16% of the variance of the SqrFOSQ (p = 0.004) (Table 4). The BDI was found to have significant univariate correlation with SqrFOSQ (r = -0.39, p = 0.005) but not with ESS (r = 0.11, p = 0.46). Except for the BDI, the significant predictive variables noted in Table 4 were not different between patients on MMT and control subjects. CAI, blood methadone concentration, and benzodiazepine, antidepressant, and cannabinoid detection in the blood were not significant predictors for ESS or FOSQ (Table 4).

DISCUSSION

Since we first reported the high prevalence of CSA in patients on stable MMT in 2001,[11] other studies have confirmed this finding in various patients using opioids on a chronic basis.[12-14] The present study investigated subjective daytime sleepiness and daytime function in patients on stable MMT and assessed the possible mechanisms related to the abnormalities found. In particular, we assessed whether abnormal sleep architecture, CSA severity, and blood methadone concentration play a significant role in daytime function and subjective daytime sleepiness in patients on stable MMT.

Our patients on MMT have a significantly higher ESS, compared with the control group, but the mean values for both groups are within the range expected in the normal population. This may be partly due to the wide range of normality for ESS scores.[17,24] Our result is consistent with those of the few studies that have tested ESS in chronic opioid users.[14,27] Burke et al studied 113 long-term opioid users and reported an average ESS score of 7.8 ± 5.2 SD.[27] Walker et al evaluated 60 patients taking opioids on a chronic basis and found an average ESS score of 11.6 ± 5.6 SD, compared with 10.2 ± 5.8 SD in controls who were not taking opioids.[14] The higher mean ESS scores in this study may be explained by the patient group being much older (52.7 years) and having more significant sleep apnea (mean apnea-hypopnea index = 43.5) than our patients on MMT.[14]

Daytime functioning in our patients on MMT was significantly worse than that of the subjects in the control group, as assessed by the FOSQ, but only mildly worse than the reference normal value (FOSQ = 17.89)[25,26] and similar to those of patients with mild OSA in Melbourne (FOSQ = 15.6).[28] The patients on stable MMT on average were also mildly or moderately depressed, as measured by the BDI, and had normal cog-

nitive function, as evaluated by the MMSE. Similar to previous reports, the depression level inversely correlated with reduced daytime function.[29]

Opioids affect alertness and cognitive function with acute use and during dose escalation.[6,8] Our patients on MMT had been receiving MMT for at least 2 months, and all of them were on a stable maintenance dose of methadone. Our data indicate that tolerance to the daytime sedative effect is generally well developed in those patients, although there were a small number of individuals who had incomplete tolerance with significant residual daytime sleepiness and reduced cognitive function. A lack of relationship between blood methadone concentration and subjective daytime sleepiness and daytime function in our study further supports this conclusion.

It has been reported that patients with congestive heart failure who develop Cheyne-Stokes respiration experience excessive daytime sleepiness.[30] The mechanism may relate to significantly increased sleep fragmentations, which is associated with Cheyne-Stokes respirations.[30] In contrast, the CSA in our patients on MMT is not associated with increased arousals during sleep.(Table 1) In addition, the CSA in chronic opioid users may have different underlying mechanisms, as compared with the Cheyne-Stokes respirations in patients to congestive heart failure.[12]

Our results show that the severity of CSA, as measured by the CAI, and blood methadone concentrations did not correlate with the ESS and FOSQ scores. However, because we studied only 50 patients, there is the possibility that a type-II statistical error exists and that, with more subjects, a significant correlation may indeed exist between the above. The results of multiple regression analysis revealed that obstructive sleep disordered breathing and sleep architecture parameters play an important role in predicting subjective daytime sleepiness and reduced daytime function. It is important to note that, other than the BDI, none of the significant predictive variables for ESS and FOSQ listed in Table 4 was significantly different between the patients on MMT and control subjects. This may indirectly explain why patients on MMT have, on average, normal subjective daytime sleepiness and implies that the mildly reduced daytime function in patients on MMT is more related to depression than to sleep disordered breathing or minor changes in sleep architecture parameters. The existence of a relationship between opioid use and psychopathology has been well reported.[31,32] Methadone treatment can ameliorate the psychiatric symptoms of the opioid user.[32,33] Rounsaville et al reported a current psychiatric disorder rate of 70.3% (excluding substance dependence) among a sample of in-treatment opioid users and a lifetime prevalence of 86.9%.[32] In our study, 64% of the patients on MMT had an elevated BDI score. It has been reported that mood disorders can independently contribute to impaired daytime performance.[29] Our multiple regression analysis further confirms a close relationship between depression and daytime function but not between depression and increased subjective daytime sleepiness.

As shown in Table 1, Stage 1 sleep, Stage 2 sleep, and rapid eye movement sleep times were significantly different between the patients on stable MMT and control subjects. However, none was a significant predictor for ESS or FOSQ scores. We therefore believe that these sleep architecture findings are not of clinical significance in this context.

One of the limitations of this study is the use of questionnaires and lack of objective measurements for daytime sleepiness and daytime function. We would therefore recommend future studies utilizing objective tests such as the Multiple Sleep Latency Test and Maintenance of Wakefulness Test, driving simulator test, and more subtle cognitive function tests. Nevertheless, it should be noted that those objective daytime sleepiness tests also have their limitations.[34,35] The ESS has been reported to correlate with Multiple Sleep Latency Test score, but not strongly.[35,36] The reason could be that the ESS measures sleepiness in 8 different situations, whereas the Multiple Sleep Latency Test measures only 1.[35,36] In fact, most of the objective sleepiness-related measurements such as the Multiple Sleep Latency Test, Maintenance of Wakefulness Test, and driving simulator test are assessed in 1 low-stimulus situation, whereas, in real life, sleepiness occurs in different situations with multiple stimulators.[34,35] That may be why none of those objective tests could predict real-world sleepiness-related motor vehicle or industrial accidents.[34,35] A recent review suggested that, although questionnaires may not always be reliable, their use is still currently the best way to assess ability to drive.[34]

Another limitation is that we could not exclude the potential confounding effects from the concomitant use of drugs such as benzodiazepines, antidepressants, and cannabis, although they are not significant predictors of daytime sleepiness and daytime function. Nevertheless, our patients may well be a better representative cohort from community MMT clinics than would be patients taking methadone only.

In conclusion, we found that the subjective daytime sleepiness in patients on stable MMT is, on average, within the clinical normal range, although the patients' ESS scores were higher, compared with the normal control subjects. Patients on stable MMT have impaired daytime function, as measured by FOSQ, and this in part relates to depression. Sleep architecture parameters, the presence of CSA, and the level of blood methadone concentration have no significant effect on subjective daytime sleepiness and daytime function in these patients on stable MMT.

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REFERENCES

1. Gutstein H, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw-Hill; 2005.
2. Phillips DM. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. JAMA 2000;284:428-9.
3. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). The state of the drugs problem in europe. Annual report 2005. Lisbon, Portugal: EMCDDA; 2005.
4. United Nations International Drug Control Program (UNDCP). World Drug Report. Vienna, Austria: UNDCP; 2005.
5. NIH Consensus Conference. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. JAMA 1998;280:1936-43.
6. Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, eds. Textbook of pain. Edinburgh, Scotland: Churchill-Livingstone, 1999;1479-522.
7. Young-McCaughan S, Miaskowski C. Definition of and mechanism for opioid-induced sedation. Pain Manag Nurs 2001;2:84-97.
8. Clemons M, Regnard C, Appleton T. Alertness, cognition and morphine in patients with advanced cancer. Cancer Treat Rev 1996;22:451-68.
9. Moore P, Dimsdale JE. Opioids, sleep, and cancer-related fatigue. Med Hypotheses 2002;58:77-82.
10. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev 2007;11:35-46.
11. Teichtahl H, Prodromidis A, Miller B, Cherry G, Kronborg I. Sleep-disordered breathing in stable methadone programme patients: a pilot study. Addiction. 2001;96:395-403.
12. Wang D, Teichtahl H, Drummer OH, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest 2005;128:1348-56.
13. Farney RJ, Walker JM, Cloward TV, Rhondeau, S. Sleep-disordered breathing associated with long-term opioid therapy. Chest 2003;123:632-9.
14. Walker JM, Farney RJ, Rhondeau S, et al. Chronic opioid use is a risk factor for development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007;3:455-61.
15. Berry RB. Central apnea during stage 3,4 sleep. J Clin Sleep Med 2007;3:81-2.
16. AASM Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement technique in clinical research. Sleep 1999;22:667-89.
17. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
18. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 1997;20:835-43.
19. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Washington, DC: Public Health Services, U.S. Government Printing Office; 1968.
20. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173-84.
21. Teichtahl H, Cunnington D, Cherry G, Wang D. Scoring polysomnography respiratory events: the utility of nasal pressure and oro-nasal thermal sensor recordings. Sleep Med 2003;4:419-25.
22. Beck AT, Steer RA, Brown BK. Beck Depression Inventory Manual, 2nd ed. San Antonio, TX: Psychological Corporation; 1996.
23. Patten SB, Fick GH. Clinical interpretation of the mini-mental state. Gen Hosp Psychiatry 1993;15:254-9.
24. Berry RB. Sleep Medicine Pearls, 2nd ed. Philadelphia, PA: Hanley & Belfus; 2003.
25. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep 2007;30:711-9.
26. Weaver TE. Personal communication. 2007.
27. Burke CK, Peirce JM, Kidorf MS, et al. Sleep problems reported by patients entering opioid agonist treatment. J Subst Abuse Treat 2008;[Epub ahead of print].
28. Barnes M, Houston D, Worsnop CJ, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med 2002;165:773-80.
29. Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 1992;152:538-41.
30. Hanly P, Zuberi-Khokhar N. Daytime sleepiness in patients with congestive heart failure and Cheyne-Stokes respiration. Chest 1995;107:952-58.
31. Buckley TC, Parker JD, Heggie J. A psychometric evaluation of the BDI-II in treatment-seeking substance abusers. J Subst Abuse Treat 2001;20:197-204.
32. Rounsaville BJ, Weissman MM, Kleber H, Wilber C. Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch Gen Psychiatry 1982a;39:161-8.
33. Rounsaville BJ, Weissman MM, Crits-Christoph K, Wilber C, Kleber H. Diagnosis and symptoms of depression in opiate addicts. Course and relationship to treatment outcome. Arch Gen Psychiatry 1982b;39:151-6.
34. George CF. Sleep apnea, alertness, and motor vehicle crashes. Am J Respir Crit Care Med 2007;176:954-6.
35. Johns M. Rethinking the assessment of sleepiness. Sleep Med Rev 1998;2:3-15.
36. Chervin RD, Aldrich MS, Pickett R, Guilleminault C. Comparison of the results of the Epworth Sleepiness Scale and the Multiple Sleep Latency Test. J Psychosom Res 1997;42:145-55.