Screening for obstructive sleep apnoea in tramadol users: a case–control study

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Background
Although opioids are known to cause sleep apnoea, to date, the risk for obstructive sleep apnoea (OSA) in individuals abusing tramadol has not been investigated. Therefore, we aimed to investigate the risk for OSA in individuals abusing tramadol.

Patients and methods
We conducted a case–control study comparing 100 patients with tramadol addiction with 100 healthy controls, assessing them for risk for OSA with the STOP-Bang questionnaire and for risk for daytime sleepiness with the Epworth Sleepiness Scale (ESS). We correlated between Severity of Dependence Scale, STOP-bang and ESS scores.

Results
Individuals abusing tramadol had significantly higher scores ($P<0.001$) on both STOP-bang and ESS compared with healthy controls. However, both the patient and control groups scored less than 3 on the STOP-bang, indicating that neither group reached the threshold for being high risk for OSA. Correlation of Severity of Dependence Scale scores with STOP-bang and ESS scores showed a statistically significant negative correlation ($P<0.001$ for both). Correlation between STOP-bang scores and ESS scores showed a statistically significant positive correlation ($P<0.001$).

Conclusion
Our study was the first to specifically examine the risk for OSA in individuals abusing tramadol. We found a significantly higher risk for OSA and more daytime sleepiness compared with healthy controls. However, OSA risk in both the patient and control groups did not reach the threshold for being high risk for OSA. We also found a significant negative correlation for dependence severity with OSA risk and daytime sleepiness, and a significant positive correlation between OSA risk and daytime sleepiness.

Keywords:
daytime sleepiness, opioid, sleep apnoea, STOP-bang, tramadol

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Introduction

The relationship between disturbed sleep and substance misuse is an area of emerging interest, with studies reporting a relation between sleep disorders and substance misuse [1]. In terms of cause and effect, it has been suggested that sleep disturbances can predispose a person to substance misuse [2], and can even be so severe as to reverse the benefits gained from treatment and trigger relapse [3]. Sleep disturbances are therefore an important factor that can predict relapse even when other risk factors for relapse are controlled for (such as comorbid mental illness), and it has been demonstrated that relapse and dependence are greater in those who have than in those who did not have sleep disturbances at baseline [4].

Even though opioid abuse is common, opioids are also frequently prescribed for restless leg syndrome, pain (acute or chronic) and during anaesthesia [5,6]. Evidence shows that there is an increasing prevalence of use of opioids around the world [7]. Although opioids have a sedative effect, they still cause sleep interruption by decreasing total sleep time, reducing rapid eye movement (REM), increasing wakefulness and reducing slow wave sleep [8].

Tramadol is an opioid analgesic that produces its mechanism of action by binding to the μ-opioid receptor and by inhibiting the reuptake of norepinephrine and serotonin [9]. In 1995 it was approved as an analgesic, and at first the manufacturer claimed that it had a weak narcotic effect. Because of this initial lack of established abuse potential, many physicians prescribed tramadol to known drug users and recovering addicts. Consequently, many reports of dependence and abuse emerged over the next few years [10].

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Although the issue of substance misuse is not new in Egypt, tramadol has emerged in recent years as a drug of abuse primarily because of its cheap cost, availability and ease of access despite it legally being a restricted drug [11]. The extensive use and popularity of tramadol, especially among the young and middle-aged, is due to its effects in relieving stress-related symptoms such as anxiety, low mood and headaches, and also because of its alleged sexual effects in increasing sexual pleasure and delaying premature ejaculation [11].

Although the causes are not clearly understood, patients being prescribed opioids for the long term have higher rates of mortality. It may be because of unintentional overdoses as it has been shown that patients receiving opioids experience hypoxaemia associated primarily with sleep apnoea [12]. In addition, opioids alter the response to hypercapnic and hypoxic stimuli, which results in variations in the hypoxic response (depending on whether opioid use is acute or chronic) and a reduction in the hypercapnic ventilation response [13].

The effects of opioids on the respiratory system are numerous and include reductions in the respiratory rate, reductions in gas exchange and tidal volume, and (at high doses) respiratory arrest [14]. It has been shown that opioids disrupt the respiratory rhythm through a general suppression of respiratory network activity [15], which can perhaps be attributed to the presence of μ opioid receptors and endogenous opioids in the respiratory centres of the medulla and pons [14].

It has been established that opioids can cause sleep apnoea. Webster *et al.* [16] reported a high prevalence of central, obstructive and combined sleep apnoea in individuals receiving opioid treatment for chronic pain. Wang *et al.* [17] reported that 30% of individuals receiving methadone maintenance treatment experienced central sleep apnoea. Mogri *et al.* [13] reported a prevalence of 36% for obstructive sleep apnoea (OSA), 24% for central sleep apnoea and 21% for combined obstructive and central sleep apnoea in a sample of 98 individuals on long-term opioid therapy.

To the best of our knowledge no studies have looked at the risk for OSA in individuals abusing tramadol. Therefore, we sought to screen a sample of individuals abusing tramadol for the risk for OSA in comparison with healthy controls, and to correlate between dependence severity, OSA risk and excessive daytime sleepiness.

Patients and methods

A case–control study was carried out to assess the risk for OSA as well as for daytime sleepiness in individuals with opioid dependence who were abusing tramadol, compared with healthy controls.

Participants

Participants were recruited over a 6-month period from January to June 2015. Two hundred participants were included in the study and were divided into a patient and a control group with each consisting of 100 participants. Patients were recruited from the Substance Misuse Outpatient Clinic and Inpatient Unit at the Department of Psychiatry at Mansoura University Hospital, Mansoura, Egypt. All patients fulfilling the inclusion criteria were offered to participate in the study until the sample size was reached.

Controls were apparently healthy with no history of any psychiatric disorders, chronic diseases or substance abuse. They were chosen from the workers at Mansoura University Hospital. All participants were interviewed using the Structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) and urine screening was requested to exclude any use of substance.

Ethical approval for the study was granted by Mansoura University Faculty of Medicine Ethical Committee. The purpose of the study was explained to each participant and informed consent was sought and obtained. Participants refusing to give consent were excluded. Inclusion criteria for the study were as follows: male and female participants; age between 25 and 50 years; meeting DSM-IV criteria for opioid dependence; the main drug of abuse being tramadol according to history; and the use of tramadol regularly for at least 1 year. Exclusion criteria were as follows: presence of any comorbid psychiatric disorder (according to DSM-IV); dependence or misuse of any other substance or any opioid preparation other than tramadol; any history of benzodiazepine use in the previous month; having uncontrolled neurological or medical illnesses or using medications known to affect breathing; and history of head injury resulting in loss of consciousness for more than 10 min.

Tools

Data were collected for each participant's sociodemographic and clinical characteristics. Before further assessment, a urine drug screening was carried out for substances of abuse – opiates, cannabis, benzodiazepines, barbiturates, cocaine, amphetamines and tramadol. Any patient positive for polysubstance abuse was excluded. The following assessment tools were then used.

Structured clinical interview for Diagnostic Statistical Manual of Mental Disorders, 4th ed. (research version) [18]

This is a clinician-administered, semistructured interview that was developed to confirm psychiatric diagnosis according to DSM-IV. This was used to ascertain the diagnosis of dependence and to exclude other Axis-I comorbid psychiatric conditions.

Severity of Dependence Scale [19]

This is a five-item scale that measures the severity of opioid dependence. Each item is scored on a scale from 0 to 3 to give an overall score by adding up the scores of the five items. A higher severity of dependence is reflected by a higher score. The original scale was developed in English and has very good reliability and validity. We used the Arabic version of the Severity of Dependence Scale (SDS) for our study [20].

STOP-Bang questionnaire [21]

The STOP-bang is a questionnaire used to screen patients for OSA. Its scoring system consists of eight questions starting with the acronym STOP-bang and is scored on the basis of yes/no answers (score: 1/0). Thus, the scores range from 0 to 8. At a score of less than or equal to 3, the scale is shown to have high sensitivity, 93 and 100% for moderate and severe OSA, respectively. As a result, it is considered very helpful in ruling out patients with moderate and severe OSA. However, the specificity at the same cutoff is low: 47 and 37% for moderate and severe OSA, respectively, resulting in fairly high false-positive rates. Therefore, patients are classified as being at high risk for OSA if they score 3 or greater and as being at low risk if they score below 3. For our study we used the Arabic version of the STOP-bang [22].

Epworth Sleepiness Scale [23]

This is a brief, self-administered, subjective measure of sleepiness which consists of an eight-point questionnaire. It is scored from 0 to 24 and assesses the probability that the respondent will fall asleep during different everyday situations. For our study, we used the Arabic version of Epworth Sleepiness Scale (ESS) [24].

Statistical analysis

Descriptive statistics were reported in the form of mean, range and SD, or (when appropriate) as frequencies (number of cases) and percentages. For comparative statistics of numerical data between study samples, we used the Student *t*-test for independent samples. For categorical data, we used the χ^2-test. When the expected frequency was less than 5, the Exact test was performed instead. Spearman's rank correlation equation was used to correlate between different variables. We considered a *P*-value of less than 0.05 as statistically significant. Statistical calculations were performed on the statistical package for the social science (Microsoft Windows, SPSS, version 15.0; SPSS Inc., Chicago, Illinois, USA).

Results

One hundred eligible individuals diagnosed with opioid dependence who were tramadol users participated in the study. A matched sample of 100 controls was also recruited. Table 1 shows no statistically significant difference between the two groups with regard to demographic characteristics except for marital status. Table 2 shows the clinical characteristics of the patient group. Sixty out of 100 (60%) participants in the patient group had a history of snoring compared with 42 out of 100 (42%) participants in the control group ($\chi^2 = 6.483$, $P < 0.011$). Forty-four out of 100 (44%) participants in the patient group had a history of fatigue compared with 56 out of 100 (56%) participants in the control group ($\chi^2 = 2.102$, $P = 0.147$).

When we compared patients and controls on STOP-bang and ESS scores, we found a statistically significant difference on both STOP-bang and ESS (Table 3), but both the patient and the control groups scored less than 3 on the STOP-bang, indicating that neither group reached the threshold for being high risk for OSA.

A statistically significant negative correlation ($P < 0.05$) was found for severity of dependence (using SDS) with OSA risk (using STOP-bang) and with daytime sleepiness (using ESS score) (Table 4). We did not correlate between STOP-bang or ESS with the dose, duration or pattern of tramadol use because the SDS score is related to behavioural patterns of drug taking, such as dose, frequency of use, duration of use, daily use and degree of contact with other drug users [19].

Correlation between STOP-bang scores and ESS scores showed a statistically significant positive correlation ($r = 0.476$, $P < 0.001$). This correlation was nonsignificant in the control group.

Table 1 Demographic characteristics of patients and controls

	Patient group ($N=100$)	Control group ($N=100$)	Test	*P*-value
Sex (male : female ratio)	88 : 12	92 : 8	$\chi^2=0.899$	0.346
Age [mean (SD)] (years)	34.10 (10.393)	33.60 (10.477)	$F=0.054$	0.735
Marital status			$\chi^2=57.694$	<0.001
Single	74	30		
Married	8	58		
Divorced	18	12		
Employment			$\chi^2=0.725$	0.725
Unemployed	6	6		
Employed	76	70		
Student	18	24		
Residence			$\chi^2=0.760$	0.439
Rural	68	70		
Urban	32	30		

Discussion

From our review of the literature, this is the first study to specifically investigate the risk for OSA in participants

Table 2 Clinical characteristics of the patient group

Age of onset of tramadol abuse [mean (SD)]	21.20 (7.160) years
Daily dose of tramadol [mean (SD)] (mg)	1233 (725.38)
Severity of Dependence Scale score [mean (SD)]	9.30 (1.778)
Route of intake ($N=100$)	
Oral	86
Intravenous	14
Using with whom ($N=100$)	
Alone	20
With others	80
Timing of usage ($N=100$)	
All day	12
Morning	36
Night	24
Before sleep	28
Purpose of intake ($N=100$)	
Medical	16
Novelty seeking	24
Escape from troubles	24
Peer pressure	36
Attempts to quit ($N=100$)	
Yes	74
No	26

Table 3 Comparison between the patient and control groups on STOP-bang and Epworth Sleepiness Scale

	Patient group ($N=100$)	Control group ($N=100$)	Test	*P*-value
STOP-bang score [mean (SD)]	2.90 (2.139)	1.90 (0.759)	$F=83.361$	<0.001
Mean Epworth Sleepiness Scale Score [mean (SD)]	8.32 (4.716)	4.46 (2.544)	$F=36.033$	<0.001

with opioid dependence using tramadol and which demonstrated that compared with healthy controls, there was a statistically significant difference for risk for OSA and daytime sleepiness compared with healthy controls. However, for both patients and controls, the risk for OSA did not reach the threshold for being high risk.

Other studies have investigated the risk for sleep apnoea with opioid use but not specifically for tramadol. Webster *et al.* [16] carried out a study on 140 patients who were using opioids for pain management for at least 6 months and found that 75% of the sample had sleep apnoea, of whom 39% had OSA, 24% had central sleep apnoea, 8% had both central and OSA (combined type) and 4% had sleep apnoea of indeterminate type. However, when the type of opioid medication was analysed it was found that only 3% used tramadol, whereas 4% were on methadone alone, 67% were on opioids other than methadone and 29% were on methadone plus other opioids. The nonmethadone opioids were oxycodone (69%), hydrocodone (32%), fentanyl (26%), morphine (21%) and hydromorphone (4%).

Wang *et al.* [17] found a statistically significant difference as regards sleep-disordered breathing when they compared 50 patients stabilized on methadone maintenance treatment who had previous heroin dependence with 20 healthy controls. None specifically reported tramadol use. Thirty per cent of the sample had central sleep apnoea, whereas 20% of them had the combined type. Mogri *et al.* [13] reported a prevalence of 36% for OSA, 24% for central sleep apnoea and 21% for the combined type in a sample of 98 participants on long-term opioid therapy for the management of chronic pain. They calculated the opioid medication as a morphine-equivalent dose but made no mention of the specific opioid medications that the study participants received (including tramadol). In a sample of 30 participants with substance misuse, Mahfoud *et al.* [25] reported a 53.3% prevalence of high risk for sleep apnoea (without specifying its type) using the Berlin screening questionnaire. Although 40% reported opioid dependence/abuse, the majority of the sample was polysubstance users, and hence it was not possible to conclude that this risk is specifically related to opioid or tramadol use.

Angarita *et al.* [26] reported that the acute use of small doses of opioids did not appear to significantly increase the risk for sleep apnoea, but that it was individuals who were receiving chronic opioid therapy (especially if in extended release form) who were at an increased risk for central and OSA with manifestations of central apnoea being dose-dependent in 30–90% of individuals, and with the frequency of sleep apnoea events correlating positively with both the duration of therapy and plasma levels [26].

Therefore, there are several possible explanations as to why tramadol users in our sample did not reach the threshold for 'high risk' for OSA. As tramadol has a shorter half-life compared with longer-acting opioids such as methadone, it may be that the effects of tramadol on REM sleep are less pronounced, especially with REM being associated with physiological loss of muscle tone and occurring more common in the latter half of the sleep cycle when sleep apnoea events are more likely to occur [27]. Given that only 28% of users in our sample reported using tramadol before bedtime, consequently the majority of participants did not use tramadol at a time when its effect on REM sleep would be most likely. In addition, the doses of tramadol taken may not have reached a threshold whereby it puts users at high risk for OSA. There is also the possibility that tramadol actually does not increase the risk for OSA.

Our study demonstrated a significant negative correlation between the severity of tramadol dependence (using SDS) and both the severity of OSA risk (using STOP-bang) and excessive daytime sleepiness (using ESS). Although it may seem unusual that the risk for OSA decreases with the increase in the severity of dependence, a possible explanation was reported by Bernards *et al.* [28], who administered remifentanil (a potent, short-acting opioid used in general anaesthesia) as an infusion in patients with moderate OSA (diagnosed using polysomnography); they demonstrated a decrease in the number of OSA events, but showed a marked increase in the number of central sleep apnoea events. They suggested that the reduction in OSA events was most likely due to the significant reduction in REM sleep caused by the remifentanil. However, they concluded that despite the fewer obstructive events, OSA was actually worse during infusion of remifentanil because of the significant increase in the number of central sleep apnoea events, suggesting that the main risk may not be obstructive but central apnoea [28]. It might be possible

Table 4 Correlation of Severity of Dependence Scale with STOP-bang and Epworth Sleepiness Scale scores

	STOP-bang		ESS	
	Correlation coefficient (*r*)	*P*-value	Correlation coefficient (*r*)	*P*-value
SDS	−0.590	<0.001	−0.445	<0.001

ESS, Epworth Sleepiness Scale; SDS, Severity of Dependence Scale.

that tramadol has a similar effect on OSA, and that any risk for apnoeic events during sleep is due to the proxy effect of central sleep apnoea effects rather than the effects of OSA per se.

Our study showed a statistically significant difference between patients and controls on ESS scores and also when we correlated OSA severity and SDS scores with the severity of excessive daytime sleepiness; our study demonstrated a significant positive correlation for OSA and ESS scores, and a significant negative correlation for SDS and ESS scores. Even though daytime sleepiness is not consistently found in every patient with OSA [29], it is still the most commonly reported daytime complaint found in OSA, resulting from the fragmented sleep and recurrent arousals seen in OSA [30]; therefore, perhaps the findings associated with ESS scores can be attributed to the confounding effects of OSA on daytime sleepiness.

Limitations

There were several limitations to our study. From our findings, we could not infer any causality between tramadol use and OSA; first, because our study only screened for risk for OSA as polysomnography was not conducted, and, second, because of the cross-sectional nature of our study, which only highlights association. Moreover, we relied on individual patient recall, which perhaps is not always accurate and may be prone to recall bias. Finally, in our sample we did not control for potential confounders such as diabetes, hypertension and BMI. Future research addressing these limitations should help answer these questions.

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Conflicts of interest

There are no conflicts of interest.

References

1 Johnson EO, Breslau N. Sleep problems and substance use in adolescence. Drug Alcohol Depend 2001; 64:1–7.

2 Dimsdale J, Norman D, DeJardin D, Wallace M. The effect of opioids on sleep architecture. J Clin Sleep Med 2007; 3:33–36.

3 Gillin JC. Are sleep disturbances risk factors for anxiety, depressive, and addictive disorders? Acta Psychiatr Scand 1998; 393:39–43.

4 Karam-Hage M. Treating insomnia in patients with substance use/abuse disorders. Psychiatr Times 2004; 21:1–7.

5 Gutstein H, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, editors. *Goodman and Gilman's the pharmacological basis of therapeutics*, 11th ed. New York: McGraw-Hill; 2005. pp. 547–591.

6 Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization guidelines for cancer relief: a 10 year prospective study. Pain 1995; 63:65–76.

7 Paulozzi L, Budnitz M, Yongli X. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006; 15:618–627.

8 Kay DC, Pickworth WB, Neider GL. Morphine-like insomnia from heroin in nondependent human addicts. Br J Clin Pharmacol 1981; 11:159–169.

9 Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. Pharmacol Rep 2009; 61:978–992.

10 Dayer P, Desmeules J, Collart L. Pharmacology of tramadol. Drugs 1997; 53:18–24.

11 Fawzi M. Some medicolegal aspects concerning tramadol abuse: The new Middle East youth plague 2010. An Egyptian overview. Egypt J Forensic Sci 2011; 1:99–102.

12 Webster LR. Methadone-related deaths. J Opioid Manag 2005; 1:211–217.

13 Mogri M, Desai H, Webster L, Grant BJ, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. Sleep Breath 2009; 13:49–57.

14 Shook JE, Watkins WD, Camporisi EM. Differential roles of opioid receptors in respiration, respiratory disease and opiate-induced respiratory depression. Am Rev Respir Dis 1990; 33:1–16.

15 Hurlé MA, Medavilla A, Florez J. Differential respiratory patterns induced by opioids applied to the ventral medullary and dorsal pontine surfaces of cats. Neuropharmacology 1985; 24:597–606.

16 Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. Pain Med 2008; 9:425–432.

17 Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunnington D, Kronborg I. Central sleep apnea in stable methadone maintenance treatment patients. Chest 2005; 128:1348–1356.

18 First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. *Structured clinical interview for DSM-IV axis I disorders (SCID-I) in handbook of psychiatric measures*. Washington, DC: American Psychiatric Press; 1995. pp. E2–E24.

19 Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, Strang J. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 1995; 90:607–614.

20 El-Hadidy MA, Al-Mogy A, Elsamanoudy AZ, El-Gilany A. Methylenetetrahydrofolate reductase C677T gene polymorphism in heroin dependence. J Addict Res Ther 2015; 6:2.

21 Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, *et al.* STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008; 108:812–821.

22 BaHammam AS, Al-Aqeel AM, Alhedyani AA, Al-Obaid GI, Al-Owais MM, Olaish AH. The validity and reliability of an Arabic version of the STOP-Bang Questionnaire for identifying obstructive sleep apnea. Open Respir Med J 2015; 9:22–29.

23 Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991; 14:540–545.

24 Ahmed AE, Fatani A, Al-Harbi A, Al-Shimemeri A, Ali YZ, Baharoon S, Al-Jahdali H. Validation of the Arabic version of the Epworth Sleepiness Scale. J Epidemiol Glob Health 2014; 4:297–302.

25 Mahfoud Y, Talih F, Streem D, Budur K. Sleep disorders in substance abusers: how common are they? Psychiatry (Edgmont) 2009; 6:38–42.

26 Angarita GA, Emadi N, Hodges S, Morgan PT. Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. Addict Sci Clin Pract 2016; 11:9.

27 Varga AW, Kishi A, Mantua J, Lim J, Koushyk V, Leibert DP, *et al.* Apnea-induced rapid eye movement sleep disruption impairs human spatial navigational memory. J Neurosci 2014; 34:14571–14577.

28 Bernards CM, Knowlton SL, Schmidt DF, DePaso WJ, Lee MK, McDonald SB, *et al.* Respiratory and sleep effects of remifentanil in volunteers with moderate obstructive sleep apnea. Anesthesiology 2009; 110:41–49.

29 Roure N, Gomez S, Mediano O, Duran J, de la Pena ML, Capote F, *et al.* Daytime sleepiness and polysomnography in obstructive sleep apnea patients. Sleep Med 2008; 9:727.

30 Schröder CM, O'Hara R. Depression and obstructive sleep apnea (OSA). Ann Gen Psychiatry 2005; 4:13–20.