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Sleep characteristics in patients with tramadol dependence

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***Abstract*---**Introduction: Despite the fact that tramadol is commonly assumed as a therapeutic medication, it has the potential to create addiction, especially when taken for extended durations and in high dosages. In Egypt, tramadol misuse has recently get to be a severe health issue. Tramadol and other opioids, have a clinically known influence on sleep. However, just a few studies have evaluated the influence of tramadol addiction on sleep. Objectives: 1). Tcomparing the sleep architecture of Tramadol-dependent patients to that of normal controls; 2).To find out what variables are connected with Tramadol misuse and alterations in sleep architecture. Methodology: The research was a case-control, comparison study that was conducted on a convenient sample of male Egyptian Tramadol addicts. The study includes 40 patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for tramadol addiction and were recruited from the inpatient addiction department at Cairo University's Psychiatry and Addiction Medicine Hospital, that were evaluated by comparing to a control group of 20 matched controls. The Addiction Severity Index (ASI), the Sleep Disorder Questionnaire (SDQ), and an overnight attended polysomnographic study (PSG) were administered to the participants. Results: When compared to the control group, patients had a higher sleep latency (P=0.000), a lower total sleep time (P=0.013) and sleep efficiency (P=0.000), a higher arousal index (P=0.000), and a lower percentage of both slow wave sleep (SWS) (P=0.004) and REM sleep (P=0.018). The patients' mean daily Tramadol use exhibited a very statistically significant negative relationship with total sleep time (r =-0.638, p =0.000) and sleep efficiency (r =-0.621, p =0.000), In addition, there was a very statistically substantial positive relationship with sleep latency (r=0.539, p=0.000). Conclusions: Patients with tramadol

addiction have a disrupted sleep pattern and quality, linked to less sleep efficiency and increased arousal from sleep, as well as lower SWS and REM sleep. These issues were linked to the usage of increased Tramadol dosages.

***Keywords*---**Tramadol, sleep disorders, Addiction and sleep

Introduction

Substance abuse disorders are frequently linked to sleep issues. Prior to their admission, 70 percent of patients treated for detoxification report sleeping issues, and 80 percent of them attribute these to their substance abuse disorders.. (Angarita et al., 2016)

Opioids have a significant impact on sleep. The ventrolateral preoptic nucleus includes opioid receptors, which is also a sleep enhancer and is involved in sleep regulation. Opioid peptides are believed to play a function in the initiation and maintenance of sleep. Excessive drowsiness and weariness are other potential side effects. (Garcia and Salloum , 2015).

Long-term opioid usage has been proven to alter the quality and amount of sleep, considering the fact that individuals on small dosage of opioid drugs report a subjective enhancement in sleep. (El Wasify M et al., 2018). Furthermore, those getting opioid medication for chronic pain were shown to have a significant association of both central and obstructive sleep apnea. (Webster et al., 2008).

Although, Tramadol is an opioid pain reliever which is being used to relieve pain ranging from mild to severe. Compared to morphine, tramadol has a decreased risk of dependency and respiratory depression. However, tramadol dependence can develop when taken at greater dosages and for long durations. (Adams et al., 2006) Tramadol is a serotonin and norepinephrine reuptake inhibitor, making it more stimulant and perhaps affecting sleep quality. (Walder et al., 2001).

A national survey done in 2015 by Ministry of health revealed that the most used substances among Egyptians were cannabinoids followed by alcohol and tramadol, where the use of cannabis and tramadol represented the most common combination in both rural and urban districts. Tramadol was the most common substance used among patients treated from addiction, reasons for the increase in use of Tramadol in Egypt include the belief that tramadol may enhance sexual performance and the ability to work for long hours and its availability in the form of easy ingestible tablets despite being a scheduled drug (Sabry et al., 2015, El Wasify M et al., 2018).

This research aimed to investigate the sleep architecture of Tramadol addicts to that of normal controls, as well as to figure out what factors connected to Tramadol addiction could be linked to differences in sleep architecture.

Subjects and Methods

The research was a case-control, comparison study that was conducted on a convenient sample of adult male Egyptian Tramadol addicts in the period from June 2017 to 2018. The study includes 40 patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for tramadol addiction and were selected from the inpatient addiction department at Cairo University's Psychiatry and Addiction Medicine Hospital, that were evaluated by comparing to a control group of 20 matched controls.

Patients with co-morbid psychiatric disorders (schizophrenia, mood disorder…etc.), patients with co-morbid chronic systemic disorders (Diabetes mellitus, hypertension …etc.), patients with tramadol withdrawal symptoms at the time of the assessment or using other medications known to affect sleep or substances other than tramadol were excluded.

All participants enrolled in this study were subjected to Kasr Al Ainy semi-structured clinical interview that include data on sociodemographic, family medical history, previous history, substance abuse, and smoking habits and the Structured Clinical Interview according to the DSM-IV (SCID-I) that was utilized to verify the tramadol dependency diagnosis. in patients and exclude other psychiatric disorders (First et al., 1996, Hatata et al., 2004).

On a scale of 0 to 5, the Clinical Opiate Withdrawal Scale (COWS) determines the severity of opiate symptoms of withdrawal. The sum of the scores denote the severity of withdrawal (5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; greater than 36 = severe withdrawal). Patients with score above 5 at the time of assessment were excluded (Wesson &Ling W, 2003). The Severity of Dependence Scale (SDS) 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 a high level of validity and dependability. We used the Arabic version of the scale to measure the severity of Tramadol dependence among our patients (Gossop et al., 1995, El-Hadidy et al., 2015). Urine screen for substances cannabis, benzodiazepine, cocaine, opiates including tramadol was applied to both patients and controls to confirm tramadol use and/or rule out use of other substances at the time of assessment. The participants for the control group were recruited through an advertisement placed at the Kasr Al Ainy hospital asking for volunteers to participate in this study.

Assessment of sleep

The Sleep Disorder Questionnaire (SDQ) is a helpful tool for determining the cause of different sleep problems. The shorter version of the questionnaire that has 45 items assessing four common groups of sleep related symptoms including sleep apnea, narcolepsy, psychiatric sleep disorders and periodic limb movement was used in this study. It is a self-rating questionnaire with a 5 point range, higher scores mean higher severity of symptoms (Douglas et al., 1994). The Arabic version of the SDQ was used in the current study (loza et al., 1999).

An overnight sleep technician attended polysomnography was done for all participants using Compumedics Profusion PSG 3.2 in the sleep lab of Psychiatry and Addiction Prevention Hospital, Faculty of Medicine, Cairo University. The electrodes were placed according to the American Academy of Sleep Medicine (AASM version 2.2) recommendations for electrode placement and filter settings. The electroencephalogram (EEG) included frontal, central, and occipital electrodes (referenced to M1 and M2), electrooculography (EOG) activity, submental electromyogram (EMG) activity, ECG activity, airflow, respiratory effort, and oximetry. Bio-calibration was done to check for the correct placements and corresponding recordings of parameters. The participants were taken to recording room 1 hour prior to their habitual sleep timings and were left to wake up spontaneously after at least 6 hours of recording. The recording times ranged from 11 PM. to 8 AM. Automatic scoring of sleep stages and other events was done and subsequently validated by manual scoring by an associate professor of Clinical Neurophysiology who was blinded to the diagnosis of the participants in a 30- second epoch (sleep staging) or a 5-minute epoch (respiratory events and limb movements) regarding to guidelines of AASM scoring manual version 2.2 (Berry et al., 2015). The PSG variables included total recording time (TRT), sleep onset latency (SOL), total sleep time (TST), sleep efficiency (TST/TRT X 100), wakefulness after sleep onset (WASO), total number of awakenings, REM latency, N1 percent (Stage 1 sleep), N2 percent (Stage 2 sleep) , N3 percent (Stage 3 sleep), REM percent (Rapid eye movement sleep), apnea hypopnea index (AHI), arousal index (AI), and periodic limb movement index (PLMI).

Ethical considerations

The Kasr Al Ainy Faculty of Medicine's ethics committee and Cairo University's ethical committee both accepted the research proposal. All investigators declare no conflict of interest according to the committee timelines. All participants were required to sign an informed written permission form. The lead investigator was in charge of evaluating the participant's records and information as well as reviewing signed consent forms. The patient's information was coded and saved on a personal computer with only the lead investigator having access.

Statistical analysis

Collected data were analyzed using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. For quantitative data, average and standard variation were used, while for categorical data, frequency (count) and relative frequency (percent) were used. The non-parametric Mann-Whitney test was used to make comparisons among quantitative variables. (Chan, 2003a). The Chi square ($\chi 2$) test was used to analyze categorized data. When the predicted frequency is less than 5, the exact test was utilized instead. (Chan, 2003b). The Spearman correlation coefficient was used to calculate correlations among quantitative variables. (Chan, 2003c). Using various characteristics, linear regression analysis was used to estimate dosage and severity. (Chan, 2004). Statistical relevance was considered as a P-value of less than 0.05.

Results

Participants were males with an average age of 31.21 ± 7.78 for patients and 35.40 ± 9.82 for controls. The two groups were matched as regards age, educational level, current occupation, marital status, family history of psychiatric disease, and Body Mass Index (BMI). In the patient group, the daily dose of tramadol used ranged from 300 mg to 2475 mg with a mean of 951.88 ± 508.1, and the duration of tramadol use between two and twenty years with average 6.28 ± 3.84. Main reasons for Tramadol use among patients were to increase work performance (47.5%), to enhance sexual performance (25%), peer pressure (20%) and novelty seeking (7.5%).

As outlined in table 1, the study reported that there was a statistically substantial variation among patients and controls as regards psychiatric sleep disorders (P=0.000) and periodic limb movement subscales (P=0.035) of the SDQ, while there was no substantial variation among both groups regarding apnea (P=0.169) and narcolepsy subscales (P=0.434). PSG findings revealed a statistically substantial variation among patients and controls in the TST, sleep onset latency, sleep efficiency, WASO, number of awakenings, AI, percentages of N1, N3, and REM sleep.

Correlation between the factors related to Tramadol use and the SDQ subscales showed that A positively significant association exists between the daily dosage and the psychiatric sleep disorders subscale (r =0.656, p=0.002).The average daily dose of tramadol showed a statistically significant negative correlation with TST (r= -0.638, p=0.000) and sleep efficiency (r=-0.621, p=0.000) and Sleep latency has a substantial positive association (r=0.539, p=0.000).

Discussion

Tramadol abuse has been an increasingly worrying epidemic in latest years. Despite the fact that drug misuse is not a new problem in Egyptian society, the vast variety of uses and illicit transactions linked with tramadol misuse make it the most easily available and inexpensive narcotic. (Salem et al., 2008). Tramadol has a tendency to impair sleep quality and quantity. It inhibits the reuptake of serotonin and norepinephrine, which enhances its stimulating characteristics and may impact sleep quality further. (El Wasify et al., 2018).

Despite the essential medical implications of understanding the effects of opioids on sleep, human investigations on changes in sleep architecture as a result of chronic opioid use are relatively uncommon. (Moore & Dimsdale, 2002). This lack of studies investigating sleep using polysomnography in Tramadol dependent patients in comparison to control subjects highlight the importance of the current study

The current study was a case-control study with the goal of comparing sleep architecture in tramadol addicts to matched control participants and determining the characteristics associated with tramadol addiction that may be linked to alterations in sleep architecture.

The median total sleep time (TST) differed significantly among the two groups in the present research. In contrary to our study, (Welder et al., 2001) showed that there was no substantial distinction between medication and placebo nights. The difference may be due to difference in the methodology as it was done on healthy volunteer with low doses of tramadol while our study was conducted to patients with tramadol dependence with much higher doses.

Regarding Sleep efficiency and sleep latency mean showed a high statistically substantial distinction between the two groups. This in in agreement with (Assad et al., 2011; Methyl et al., 2014). There was a significant variation among patients with opioid addiction and control participants in terms of sleep efficiency and latency. However, (Wang et al 2005) In terms of sleep efficiency and latency, there was no substantial variation among patients of opioid dependency on mehadone maintenance therapy (MMT) and control patients.

In addition, wake time after sleep (WASO) showed that The variance among the two groups was statistically relevant. This in agreement with (Mehtry et al., 2014; Assad et al., 2011) the variance between the patient and control groups was substantial. On the other hand (Wang et al., 2005) When compared the WASO and arousal index of MMT opioid addicted patients and controls, none found statistically significant differences.

The present study showed a statistically considerable variation in REM percentage of TST between the two groups. In agreement with (Wang et al., 2005) when compared to control participants, there was a considerable reduction in the REM percent of cases of opioid dependency on MMT. In addition (Mehtry et al., 2014; Assad et al., 2011)found no significant variation among the patients with opioid dependence compared to control group, this difference may be due to different type of patients as our study included only patients with tramadol dependence.

There was a statistically significant variation groups when it came to the percentage of slow wave sleep N3 (%) of TST. In the same context(Asaad et al., 2011) discovered a statistically significant decline in slow wave sleep (SWS). In contrary to (Mehtry et al., 2014) found no significant reduced SWS (%) of total sleep time between both patients and control groups .This difference may be due to the different methodology used and culture and the type of sample of our study.

The most common result in all of these research investigations is that NREM sleep is disrupted, as seen by a reduction in the percent of Slow Wave Sleep. This might be the cause of the subsequent rise in N2 percent. (Greco et al., 2008).

The mean of the Periodic Limb Movements Index shows a substantial statistical variance between the two groups. This is in line with (Methery et al., 2014) who discovered a substantial variance between the two groups. In contrary to (Assad et al., 2011) found no substantial variance between the patients and the control group.

Average daily dose patients' group had a statistically negative link with total sleep duration and sleep efficiency, whereas average daily dose patients group had a statistically high positive association with sleep latency. Other than that, there was no link between the average daily tramadol dosage and the results of the polysomnography. In contrary to our results (Asaad et al., 2011) and (Methry et al., 2014) found no link between the mean daily dosage of opioid misuse and the results of polysomnography. Some limitations were found included limitation of gender of participants males which limit the application of findings on females with Tramadol dependence, the presence of confounding factors that may include smoking and caffeine use by the participants which may affect sleep. Also, A single night of PSG was done with no accommodation night which might affect results due to first night effect. Future study that takes into account all of these constraints is advised, with a focus on the impact of different sleep management strategies on the overall result of substance misuse treatment.

Conclusion

Patients with tramadol addiction have a disrupted sleep pattern and quality, combined to less sleep efficiency and increased arousal from sleep, as well as lower SWS and REM sleep. These issues were linked to the usage of increased Tramadol dosages.

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Competing interests
There are no competing interests stated by the authors.

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Table (1)
Sleep Assessment and Polysomnographic Variables in Patients and Controls

Clinical Characteristics	**Patients** *N=40*	**Controls** *N=20*	***p***
Sleep Disorder Questionnaire Subscales (mean ±SD)			
Apnea	17.74± 9.01	14.95±4.38	0.169
Narcolepsy	20.84±7.38	19.45±3.94	0.434
Psychiatric Sleep Disorders	27.45±6.74	14.80±4.34	0.000**
Periodic Limb Movement Disorders	16.41±7.03	12.80±3.71	0.035*
PSG Variables (mean ±SD)			
TST[1] (minutes)	295.8 52.00	337.2 71.33	0.013*
Sleep onset latency (minutes)	33.41 13.00	14.40 6.54	0.000**
Sleep Efficiency[2]	69.40 10.97	84.35 6.67	0.000**
Awakenings number	10.15 3.84	7.15 2.70	0.002*
WASO[3] (minutes)	41.34 20.35	30.90 8.17	0.007*
Arousals index	21.14 7.12	19.8 3.39	0.000**
Stage N1 %	15.47 7.12	6.86 2.11	0.001*
Stage N2 %	50.69 7.09	50.16 6.41	0.211
Stage N3 %	17.61 5.28	22.96 4.67	0.004*
REM[4] %	15.37 6.21	20.06 5.25	0.018*
REM latency (minutes)	106.21 35.11	107.40 22.56	0.875
AHI[5]	2.10 1.53	1.82 1.18	0.475
PLMI[6]	8.82 4.87	2.65 1.41	0.000**

1- TST=Total Sleep Time, 2-Sleep Efficiency=TST/TRT x 100, 3-WASO = Wake After Sleep Onset, 4-REM=Rapid Eye Movement, 5-AHI=Apnea Hypopnea Index, and 6-PLMI=Periodic Limb Movement Index. P < 0.05 = * statistically substantial, P < 0.005 =**=highly statistically substantial.