Original Article

The Clinical, Polysomnographic And Biological Aspects Of Insomnia In Male Patients With Opioid Use Disorder

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Abstract

Background Substance use and misuse are serious issues that contribute to significant medical, psychological, and legal consequences later in life. Additionally, the relation between substance use disorder and sleep is reciprocal. Furthermore, sleep dysfunction in the context of substance use disorder may contribute to increased severity of substance use disorder and increased risk of relapse **Aim and objectives** to investigate patients with opioid use disorder comorbid with insomnia and assess their clinical and biological aspects of insomnia, cognitive function, and serum level of BDNF in comparison to those without substance use disorder. **Subjects and methods** This is a cross sectional comparative study. Cases were recruited from inpatient section and outpatient clinic in Psychiatry Department in Mansoura University Hospital. The research was done for one year from January 2021 to January 2022. **Result** shows that patients in heroin group show statistically significant (p=0.039) lower total sleep time (240.04±54.8) than control (275.2±48.9). They show also, statistically significant (p=0.027) longer sleep onset in comparison to the control group. Additionally, patients in heroin group show statistically significant (p=0.01) lower sleep efficiency (63.14±15.1 vs. 75.1±13.28) and higher number of awakenings in comparison to control group. Furthermore, they also show higher N1% (p=0.027) and lower N3% (p=0.036) of total sleep time in comparison to control group, duration of last abstinence period from heroin use disorder has a statistically significant (p=.007) strong negative correlation (r=-.586) with total sleep time. Additionally, duration of the time lasted since last abstinence from heroin has a statistically significant (p=.036) strong negative correlation (r=-.471) with N3% of total sleep time. **Conclusion** Heroin use disorder is associated with lower total sleep time, sleep efficiency, higher number of awakenings, higher N1% and lower N3% of total sleep time and longer sleep onset in comparison to the control group.

Keywords: The Clinical, Polysomnographic, Biological Aspects, Insomnia, Male Patients with Substance Use Disorder.

INTRODUCTION

Substance use and misuse are serious issues that contribute to significant medical, psychological, and legal consequences later in life (1).

Insomnia can be regarded as a risk factor, a consequence and a complication of opioid use disorder and it has been proposed that insomnia is one of the key withdrawal symptoms of opioid use disorder patients (2).

Opioid use outside of its appropriate clinical applications (that is, in the management of severe acute pain or anaesthesia) is an important public health issue given the potential addictiveness of these drugs, the extent of associated harms (such as overdose deaths) and the potential health sequelae of drug-use behaviours (for example, HIV and hepatitis C virus (HCV) infection and transmission, bacterial endocarditis, and neonatal abstinence syndrome) (3).

Many cases of substance use disorder suffer from sleep disturbances for a long period. This occurs in the phenomenon of ‘‘protracted abstinence,’’ which is defined as sign of drug abstinence after an acute withdrawal state (usually 1-week post-acute withdrawal). Sleep disturbances especially insomnia are

very common symptoms of opioid ‘‘protracted abstinence,’’ which may persist up to 6 months. These symptoms are considered one of the most common causes of craving and relapse (4).

Despite the fact that sleep disturbances are a major contributor to relapse, few objective assessment procedures to monitor sleep after the detoxification have been reported (5).

Furthermore, brain-derived neurotrophic factor (BDNF) has been found to play roles in many types of plasticity including drug addiction (6). Many abused drugs lead to changes in endogenous brain-derived neurotrophic factor (BDNF) expression in neural circuits responsible for addictive behaviors (7). Increases in serum levels of BDNF have been observed in drug addictions (8).

The BDNF is not just linked to insomnia; its levels may be considered a peripheral biomarker for the evaluation of cognitive function. It plays a critical role in activity-dependent neuroplasticity underlying learning and memory in the hippocampus (9).

Aim and objectives was to investigate patients with opioid use disorder comorbid with insomnia and assess their clinical and biological aspects of insomnia, cognitive function, and serum level of BDNF in comparison to those without substance use disorder.

Patients and Methods

This was a cross sectional comparative study, Cases were recruited from inpatient section and outpatient clinic in Psychiatry Department in Mansoura University Hospital. The research was done for one year from January 2021 to January 2022.

The participants were further subdivided into: **Group (I)** which included 20 patients with the diagnosis of opioid (heroin) use disorder comorbid with insomnia. **Group (II)** which included 20 controls.

Inclusion criteria of patients with substance use disorder comorbid with insomnia
All cases were males (as the vast majority of patients attending outpatient clinic of addiction unit in Psychiatry Department in Mansoura University Hospital are males) with age between 18-45 years. Patients met the diagnosis of substance use disorder comorbid with insomnia disorder according to DSM -5. Urine toxicology screen was positive for substance metabolites. Written informed consent was obtained.

Exclusion criteria of cases with substance use disorder
Presence of any other major psychiatric disorder (e.g., schizophrenia, delusional disorders, depressive or bipolar disorders …etc.), Presence of co-morbid major physical and neurological illness.

Criteria of the comparison group
A comparison group of volunteers matched with the patient group for age, sex, and education and with no apparent physical or psychiatric morbidity.

Ethical consideration
Approval of the Institutional Research Board in Mansoura University was obtained and procedures in concordance with the Declaration of Helsinki were followed. Furthermore, research participants were not subject to harm in any way and full informed consent was obtained from the participants. Finally, privacy of research participants was protected and they were free to withdraw from the research at any time without penalty.

Procedure
All procedures had been administered and achieved in the day before doing the full night polysomnogram

Clinical Assessment
Participants underwent a history taking and mental state examination to assess the presence of comorbid psychiatric disorders and establish the diagnosis of substance use disorder comorbid with insomnia disorder according to DSM 5 criteria.

The diagnosis for each patient was confirmed by at least two senior staffs.

Information was obtained regarding the substance that has been abused with stress on the followings: Age at which this substance use disorder started, number of hospital admissions, any medical or legal complications of this substance use disorder and sleep history was taken through the Structured Sleep Disorder Questionnaire.

Structured Sleep Disorder Questionnaire (5)
It consists of 72 questions regarding the following: Personal sleep rituals (e.g., time to go to bed, sleep hours, and sleep naps), or other habits affecting sleep, past or present history of sleep disturbance and medications used, sleep disorders which are insomnia, hypersomnia, parasomnias, or dyssomnias and effect of sleep disturbance on personal functioning.

Psychometric assessment
The participants in the research underwent the following psychometric assessment: **Insomnia Severity Index (ISI)**
Insomnia Severity Index (ISI) is composed of 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia.

Severity of Dependence Scale
The Severity of Dependence Scale (SDS) had been devised and validated to provide a short, easily administered scale which can be used to measure the degree of dependence experienced by users of different types of drugs.
The SDS contains five items, all of which are explicitly concerned with psychological components of dependence.

All night polysomnography
The participants underwent an overnight sleep study using polysomnography that will be continuously monitored by certified sleep technicians **(Model: Somte Polysomnography (PSG Amplifiers and recorders-Compumedics Australia)**.
The sleep laboratory in which the study was conducted had adjustable temperature controls. The ambient lighting remained continuous while subjects were awake, but was turned off during sleep periods.
No visitors or phone calls were allowed once the patient had gone to sleep.
Meals were provided on a regular basis. To control for the effect of irregular food intake on BDNF levels, all subjects who had reported that they were fasting or who were suffering from eating disorders were excluded from the study during the initial screening process.

Laboratory Assessment
Blood sample for assessment of serum level of BDNF
Blood sample was withdrawn from the participants by our nursing stuff in the Psychiatry Department in a dry tube. Fasting blood was collected between 7:30 to 8:00 A.M. then transferred to the Biochemical Lab immediately.
Urine sample
Those matching the selection criteria for the case group were investigated by urine drug screen.

Statistical Analysis
Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 26). The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test while Fisher exact and monte carlo test were used when expected cell count less than 5. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data and median (IQR) for non-normal data. The two groups were compared with independent t test (parametric) and Mann Whitney test (non-parametric). Pearson correlation was used to correlate continuous data.

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value). The results were considered significant when the $p \leq 0.05$. The smaller the p-value obtained, the more significant are the results.

Results
This study aims to investigate patients with opioid use disorder comorbid with insomnia and assess their clinical and biological aspects of insomnia, cognitive function, and serum level of BDNF in comparison to those without substance use disorder. **Group (1):** which included 20 patients with the diagnosis of opioid (heroin) use disorder comorbid with insomnia disorder. **Group (II):** This included 20 controls of

volunteers for comparison with the patient group. They are matched for age, sex, and education and with no apparent physical or psychiatric morbidity.

Table (1): Comparison of socio -demographic data among the studied groups

Socio -demographic data	Heroin group (n=20)	Control group (n=20)	Test of significance
			P1
Age in years Mean ± SD	28.80±5.63	30.90±10.35	t=0.79 P=0.43
Education Preparatory level Secondary level Diploma University	 5 (25.0%) 5 (25.0%) 5 (25.0%) 5 (25.0%)	 0 (0%) 10 (50.0%) 7 (35.0%) 3 (15.0%)	MC P=0.06

The mean age of heroin group was 28.80±5.63, and control group 30.90±10.35 and this is not statistically significant difference. Additionally, there is no statistically significant difference between the studied groups regarding education, occupation, residence and body mass index.

Table (2): Comparison between heroin group and control group on Hamilton anxiety rating scale

Hamilton anxiety rating scale	Heroin group (n=20)	Control group (n=20)	Test of significance
Hamilton anxiety rating scale	14.90±5.34	10.50±4.66	t=2.77 P=0.008*
Interpretation No anxiety Mild severity Mild to moderate Moderate to severe	 1 (5.0%) 14 (70.0%) 4 (20.0%) 1 (5.0%)	 6 (30.0%) 12 (60.0%) 2 (10.0%) 0 (0%)	MC P=0.11

P1: compare heroin & control groups, **t:** independent t test, **MC:** monte carlo test, **p value** ≤0.05 significant

Table (2) shows that patients in heroin group had a higher statistically significant (P=0.008) score on Hamilton anxiety rating scale than control group (14.90±5.34 and 10.50±4.66, respectively)

Table (3): Comparison between heroin group and control group on Hamilton depression rating scale

Hamilton depression rating	Heroin group (n=20)	Control group (n=20)	Test of significance
Total	10.65±4.72	7.25±2.69	t=2.79 P=0.008*
Interpretation Normal range Mild depression Moderate depression Severe depression	 5 (25%) 9 (45%) 5 (25%) 1 (5%)	 9 (45%) 10 (50%) 1 (5%) 0 (0%)	MC P=0.18

P1: compare heroin & control groups, **t:** independent t test, **MC:** monte carlo test, **p value** ≤0.05 significant

Table (3) shows that patients in heroin group had a higher statistically significant score (P=0.008 and P≤.001, respectively) on Hamilton depression rating scale than control group.

Table (4): Comparison between heroin group and control group on Montreal Cognitive Assessment test

MoCA	Heroin group (n=20)	Control group (n=20)	Test of significance
			P1
Visuospatial/executive	3.5±1.1	3.6±1.4	t= 0.25 P= 0.79
Naming	2.6±0.5	2.7±0.5	t= 0.65 P= 0.52
Forward & backward digit	1.7±0.47	1.4±0.82	t= 1.41 P= 0.16
Vigilance	0.55±0.5	0.65±0.4	t= 0.63 P= 0.53
Serial seven subtraction	2.05±0.6	1.7±0.6	t= 1.75 P= 0.08
Sentence repetition	1.2±0.4	1.3±0.47	t= 0.72 P= 0.47
Verbal fluency	0.2±0.4	0.4±0.5	t= 1.37 P= 0.17
Abstraction	1±0	1.35±0.4	t= 3.19 P=0.003*
Delayed recall	3.35±0.9	3.15±0.67	t= 0.77 P= 0.44
Orientation	5.85±0.36	6.0±0.0	t=1.83 P=0.07
Total MoCA	22.00±3.09	24.15±1.95	t=2.62 P=0.012*

P1: compare heroin & control groups, **t:** independent t test, **p value** ≤0.05 significant

Table (4) shows that there is a statistically significant difference (P=0.012) between heroin and control groups regarding the total MoCA score (22.00±3.09 and 24.15±1.95, respectively) and abstraction subcomponent (P=0.003) with higher values associated with control group.

Table (5): Comparison between heroin group and control group regarding the polysomnographic report

Ploysomnograph	Heroin group (n=20)	Control group (n=20)	Test of significance
			P1
Total sleep time in minutes	240.04±54.8	275.2±48.9	t=2.14 P=0.039*
Wake after sleep onset in minutes	31 (12.2-54.37)	34.50 (6.6-78.92)	Z=0.37 P=0.71
Sleep onset in minutes	70.5 (16-113)	35.25 (0.5-118)	Z=2.21 P=0.027*
Sleep efficiency in %	63.14±15.1	75.1±13.28	t=2.67 P=0.01*
Number of awakenings	5 (1-14)	2.50 (1-6)	Z=2.32 P=0.02*
Sleep latency to N1 in minutes	78.75 (39.5-99.75)	46.75 (18.7-104)	Z=1.42 P=0.15
Sleep latency to N2 in minutes	69 (35.8-104.5)	35.25 (24.1-61)	Z=2.64 P=.008*
Sleep latency to N3 (SWS) in minutes	89.50 (37.6-123.25)	46.85 (34-74.1)	Z=1.78 P=0.074
Stage R latency from sleep onset in minutes	0 (0-72.37)	81 (0-167)	Z=2.31 P=.021*
N1 duration in minutes	16.5 (9-37.7)	7 (2.25-26.37)	Z=2.21 P=.027*
N1 % OF TST	8.9 (2.5-69)	4.2 (0-100)	Z=2.22 P=0.027*

N2 duration in minutes	157 (92.5-210.1)	146.8 (117.25-178.72)	Z=0.29 P=0.76
N2 % OF TST	57.75 (42.1-83)	60.65 (47.65-64.62)	Z=0.41 P=0.67
N3 duration in minutes	32.75 (0-138.6)	77.00 (0-127.6)	Z=1.97 P=0.04*
N3 % OF TST	15.8 (0-54.2)	26.25 (0-53.7)	Z=2.1 P=0.036*
R duration in minutes	0 (0-0.37)	15.5 (0-47.37)	Z=2.45 P=.014*
R % OF TST	0 (0-0.15)	6.25 (0-14.55)	Z=2.42 P=.015*
Total arousals	5 (2.25-9.75)	3.0 (0.25-6)	Z=1.81 P=.071
Arousals index	1.25 (0.65-2.35)	0.8 (0.05-1.1)	Z=2.17 P=0.03*

P1: compare heroin & control groups, **t:** independent t test, Z**:** Mann Whitney test

Table (5) shows that patients in heroin group show statistically significant (p=0.039) lower total sleep time (240.04±54.8) than control (275.2±48.9). They show also, statistically significant (p=0.027) longer sleep onset in comparison to the control group. Additionally, patients in heroin group show statistically significant (p=0.01) lower sleep efficiency (63.14±15.1 vs. 75.1±13.28) and higher number of awakenings in comparison to control group. Furthermore, they also show higher N1% (p=0.027) and lower N3% (p=0.036) of total sleep time in comparison to control group.

Table (6): Serum BDNF level (ng/ml) among the studied groups

	Heroin group (n=20)	**Control group (n=20)**	**Test of significance P1**
Serum BDNF level (ng/ml)	1.16±0.39	1.19±0.78	t=0.12 P=0.91

P1: compare heroin & control groups, **t:** independent t test

There was no statistically significant difference between heroin group, group and control group regarding serum BDNF level.

Table (7): correlation between Polysomnographic results and clinical data of Heroin group

Polysomnographic data		**Duration of current substance**	**Last abstinence period**	**Time lasted since last abstinence**	**Lifetime duration of abuse**	**No. of previous hospitalizations**
Total sleep time in minutes	r	-.341	**-.586**	-.384	.010	-.160
	p	.142	**.007***	.095	.967	.500
Sleep onset in minutes	r	.085	.258	.085	.068	-.135
	p	.722	.271	.723	.776	.571
Sleep efficiency in %	r	**-.560**	-.330	-.342	-.329	-.143
	p	**.010***	.155	.140	.157	.546
Number of awakenings	r	**.459***	.077	.405	.387	.112
	p	**.042**	.747	.077	.092	.638
N1 duration in minutes	r	.069	.162	.364	-.167	.277
	p	.774	.494	.115	.480	.238
N1 % OF TST	r	-.002	.255	.262	-.329	.159
	p	.995	.279	.265	.157	.502
N3 duration in minutes	r	-.205	-.153	-.337	.070	-.246
	p	.386	.521	.146	.769	.295
N3 % OF TST	r	-.210	-.294	**-.471**	.132	-.257
	p	.375	.209	**.036***	.580	.274
R duration in minutes	r	-.352	-.005	-.126	-.131	-.421
	p	.128	.983	.596	.582	.064
R % OF TST	r	-.352	-.005	-.126	-.131	-.421
	p	.128	.983	.596	.582	.064
Arousals index	r	-.440	-.075	-.194	-.229	-.008

	p	.052	.754	.413	.332	.973

Patients in heroin group show that duration of heroin use disorder has a statistically significant (p=.01) strong negative correlation (r=-.560) with sleep efficiency and has a statistically significant (p=.042) strong positive correlation (r=.459) with number of awakenings.

Furthermore, duration of last abstinence period from heroin use disorder has a statistically significant (p=.007) strong negative correlation (r=-.586) with total sleep time. Additionally, duration of the time lasted since last abstinence from heroin has a statistically significant (p=.036) strong negative correlation (r=-.471) with N3% of total sleep time.

Discussion

In the current study, patients in heroin group had a higher statistically significant score on Hamilton anxiety rating scale than control group.

Similar results were obtained by Feingold et al. who conducted a study on suffered from chronic pain treated with prescription opioids (N=474), marijuana (N=329) or both (N=77).

Poor sleep quality has been observed in individuals with substance use disorders and is often a trigger for relapse (10).

In the current study, with the use of the subjective sleep questionnaire, patients in heroin complained from statistically significant higher subjective sleep onset latency than control group.

This was in accordance with Hartwell et al. who included 33 opioids dependent and 35 healthy controls. Subjective sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI). The results showed that there was significant group differences in subjective sleep quality were revealed in the PSQI ($p<0.01$) and ISI ($p<0.01$). Poor sleep quality (i.e., PSQI total score > 5) was identified in 80.6% of the PO group, as compared to 8.8% of the control group ($p<.001$). Significant group differences in sleep quality were identified in five of six actigraphy variables: total time asleep, sleep efficiency, latency of onset of sleep, total time awake and time mobile (11).

Also, Hsu et al. enrolled 121 heroin addicts. The mean of the PSQI was 9.1 ± 5.4, and 70.2% of patients had PSQI scores >5, indicating they were poor sleepers (12).

Substances like opioids are psychoactive drugs that may change brain function and structure after chronic use, and result in cognitive and behavioural deficits that remain even after detoxification. The prevalence of cognitive impairments in patients with SUD is still unclear and is estimated between 30% and 80% (13).

In the current study, there is a statistically significant difference between heroin and control groups regarding the total MoCA score (22.00±3.09 vs 24.15±1.95) and abstraction subcomponent with higher values associated with control group.

These results of negative cognitive consequences of heroin use disorder are in agreement with number of studies in literature examining the cognitive effects of opioid use disorder. This includes the study done by Schmidt and colleagues which demonstrated deficits in verbal capabilities, working memory and executive functions in abstinent opioid users (14) and the deficits in working memory in abstinent heroin users revealed by the work of (15).

This is also in harmony with the results obtained by (16) and (17) which emphasized the deficits in delayed recall in opioid use disorder patients.

Opioids induce cognitive impairment through their action on hippocampal and prefrontal cortex structures. It is shown that these drugs may enhance apoptosis and inhibited neurogenesis. An opioid-induced attenuation of neurogenesis in the hippocampus was earlier seen in male rats exposed to morphine (18).

In the current study, the heroin group had a statistically significant higher score on insomnia severity index when insomnia was put into categories; the incidence of severe insomnia was 30%

This agreed with a previous Egyptian study by Asaad et al. who included 33 opioid-dependent male patients who were admitted to the substance abuse treatment unit at the Institute of Psychiatry, Ain Shams University. The authors reported that there were significant differences in sleep complaints included reports of insomnia, hypersomnolence, increased sleep latency, and reduced sleep time in the group of patients. Regarding polysomnography, patients differed significantly from controls, in having prolonged sleep latency, decreased sleep efficiency, increased arousal index, increased stages I and II, and decreased slow wave sleep (SWS). Patients with moderate and severe depressive states had significantly lower SWS than those with mild depressive state (4).

Although opioids are perceived as sedating, chronic opioid use can be disruptive to sleep quality. In a sample of 62 patients on methadone maintenance therapy who reported disturbed sleep, total sleep time as measured by daily sleep diaries for one week was less than six hours, and polysomnography confirmed poor sleep efficiency and decreased total sleep time that correlated with scores on the Pittsburgh Sleep

Quality Index (PSQI) (19). In another study, patients on chronic methadone maintenance had increased nighttime wakefulness and reduced total sleep time, sleep efficiency, and REM sleep compared with normative values (20).

Despite the fact that sleep disturbances are a major contributor to relapse, few objective assessment procedures to monitor sleep after the detoxification have been reported (5). Hence, the importance of our polysomnographic findings in heroin use disorder patients:

Our study revealed a statistically significant increase (P=0.027) in sleep onset latency of heroin use disorder patients (70.5 (16-113)) in comparison with control group (35.25 (0.5-118)) when recorded by polysomnography. This finding is consistent with previous studies indicating increase of sleep onset latency in opioid use disorder patients (4, 19-21)

Some studies have found no difference in sleep onset latency between the heroin use group and control group (22, 23).

This difference could be attributed to methodological differences as these studies included the use of methadone substitution as a maintenance which is not the case in our study.

The sleep efficiency was statistically significant (P=0.01) lower in the heroin use disorder group (63.14±15.1) in comparison to control group (75.1±13.28). This finding is consistent with some other studies (19, 22, 24).

Concerning the analysis of NREM sleep, significant findings in our study included the statistically significant (P=0.027) increase in stage I and statistically significant (P=0.036) reduction in stage III (SWS) in heroin use disorder group in comparison to control group. This finding is consistent with other studies (4, 19, 21, 22) which reported similar findings.

Other researchers did not find any statistically significant difference between opioid use disorder group and control group in stage III (20, 25). This could be attributed to the use of Rechtshaffen and Kales (R&K) criteria (Rechtschaffen and Kales, 1968) in the study done by Howe and colleagues and to the early enrolment of patients for polysomnogram after one week of detoxification in the study done by Mehtry and colleagues.

A possible explanation for this disturbance in NREM sleep could be inferred from the study done by (26) which revealed that the influence of opiates on sleep may be mediated, at least in part, by the ventrolateral preoptic nucleus (VLPO), a key cell group for producing behavioural sleep.

The VLPO area has been a prominent element in the flip–flop model, essentially accounting for the multiple and diversified inhibition of wake-promoting groups during sleep (27).

Therefore, this could potentially explain the observed disturbance in the NREM sleep in detoxified heroin use disorder group.

Regarding REM sleep, this study showed that the percentage of REM sleep from the total sleep time was statistically significant (P=.015) lower in heroin use disorder group (0 (0-0.15)) in comparison to the control group (6.25 (0-14.55)).

This result is in agreement with the studies done by (19, 23, 25).

On the other hand, several other investigators (4, 5, 20, 22, 24) reported the absence of statistically significant difference between detoxified opioid use disorder patients and control group regarding the REM sleep.

This could be explained by the observation made by (28) that several studies have reported changes in patterns of sleep with progressive abstinence from opiates. At around five to seven days of acute abstinence from chronic heroin use, there is a decrease in REM sleep but After 6 weeks and up to 6 months of abstinence from methadone, there is a rebound increase in SWS and REM time to a higher level than baseline.

The current study is limited by the low small sample size included in each group. Also, the cross-sectional nature of the study decreases the power of the obtained results.

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