Sleep Profile in patients with chronic opiate abuse

Thesis

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Presented by

Mahmoud Mamdouh Elhabiby

Assistant lecturer of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Supervised by

Professor Mohamed Hamed Ghanem

Chairperson of Neuropsychiatry Department

Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Professor Tarek Asaad Abdo

Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Professor Mona Mansour Mohamed

Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Professor Alaa' Eldin Mohamed Soliman

Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Dr. Afaf Mohamed Abdel Samee'

Assistant professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

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Dedication

I want dedicate this work for my compassionate mother, loving father, wonderful wife, awesome mother in law and supportive brothers. They all supported me all over my life and still supporting me. I thank God for everything, but I thank Him most for my family.

LIST OF ABBREVIATION

5HT	:	5-Hydroxytryptamine Serotonin
A	:	Adenosine
AA	:	Alcoholics Anonymous
ACTH	:	Adrenocorticotropic hormone
ADP	:	Adenosine Diphosphate
APA	:	American Psychiatric Association
ARAS	:	Ascending Reticular Activating System
ARC	:	Arcuate nucleus
ASI	:	Addiction Severity Index
ATP	:	Adenosine Triphosphate
BDI	:	Beck Depression Inventory
BMI	:	Body Mass Index
BNST	:	Bed Nucleus of the Stria Terminalis
CB	:	Cannabinoid
CNS	:	central nervous system
CSF	:	Cerebro spinal fluid
DSM	:	Diagnostic and statistical manual of mental disorders
eCBs	:	Endocannabinoids

EEG	:	Electroencephalography
EMG	:	Electromyography
EOG	:	Electro-occulography
ESS	:	Epworth Sleepiness Scale
GABA	:	Gamma Amino Butyric acid
H	:	Histamine
ICD	:	International classification of diseases and causes of death
LDT	:	Laterodorsal Tegmental nucleus
LPH	:	Lipotropin hormone
MAP	:	Maudsley Addiction Profile
mCPP	:	meta-Chlorophenylpiperazine
MMT	:	Methadone Maintenance Therapy
MOS	:	Medical Outcome Study Sleep Questionnaire
MSH	:	Melanocyte Stimulating hormone
N/OFQ	:	nociceptin/orphanin FQ
NAc	:	Nucleus Accumbens
NMDA	:	N-methyl-D-aspartate
NREM	:	Non Rapid Eye Movement
NSAID	:	Non Steroidal Anti Inflammatory Drug
OFC	:	Orbitofrontal cortex

OSA	:	Obstructive Sleep Apnea
PAMs	:	GABA-A Positive Allosteric Modulators
PET	:	Positron Emission Tomography
PFC	:	Prefrontal cortex
PLH	:	perifornical lateral hypothalamus
PLMD	:	periodic limb movement disorder
POMC	:	Prepro-opiomelanocortin
PPT	:	Pedunculopontine Tegmental nucleus
PSG	:	Polysomnography
PSQI	:	The Pittsburgh Sleep Quality Index
RAS	:	Reticular Activating System
REM	:	Rapid Eye Movement
SCID	:	The structured clinical interview for DSM-IV-TR
SCN	:	Supra Chiasmatic Nucleus
SDB	:	Sleep Disordered Breathing
SOL	:	Sleep Onset Latency
SROM	:	Slow-Release Oral Morphine
SWS	:	Slow Wave Sleep
THC	:	Tetrahydrocannabinol
TMN	:	Tubero-mammillary nuclei
VLPO	:	Ventrolateral Preoptic nucleus

VMPO : Ventromedial Preoptic nuclei

VP : Ventral Pallidum

VTA : Ventral Tegmental Area

WHO : The World health organization

INTRODUCTION

Substance abuse is a worldwide common disorder. The United Nations Office for Drug Control and Prevention estimates that some 180 million people used illicit drugs in 1990s. Problems of substance abuse produce dramatic costs for all societies in the term of low productivity, transmission of infectious diseases, family and social troubles as well as crimes **(Mc Lellan et al., 2003)**.

Regarding physical complications, studies indicate that psychoactive substances have acute and chronic effects on sleep architecture. A single dose of alcohol causes decrease in rapid eye movement sleep, shortening of sleep-onset latency and increase late night disturbances **(Karam-Hage, 2004)**. Opiates cause increased wakefulness and decreased sleep time. On the other hand, benzodiazepines and barbiturates cause decrease sleep latency, decrease wakefulness and increased sleep time **(Buysse et al., 2001).**

On the other hand, in actively drinking alcoholics, specific sleep disturbances are reported, such as increased time required to fall asleep, frequent awakenings and a decrease in subjective sleep quality associated with daytime fatigue **(Aldrich et al., 1999).** Decreased SWS

during withdrawal may reduce the amount of restful sleep. Beyond withdrawal, sleep patterns may never return to normal in people with alcoholism **(Brower and Hall , 2001)**. After years of abstinence, alcoholics tend to sleep poorly, with decreased amounts of SWS and increased nighttime wakefulness contributing to daytime fatigue. When heavy drinking recurs, it leads to increased SWS (restful sleep) and decreased wakefulness. This apparent improvement in sleep continuity may promote continued drinking by associating the return to drinking with improved sleep **(Stein and Friedman 2005).** Unfortunately, as drinking continues, sleep patterns get disrupted, closing the cycle **(Aldrich et al., 1999).**

Although there is data on alcohol's long term effect on sleep, little is known about how the different substances of abuse affect sleep in humans especially after periods of abstinence **(Karam-Hage, 2004).** Yet, it is documented that these patients suffer from sleep disturbances ranging from difficulty initiating sleep to difficulty maintaining sleep and hypersomnia. Sleep disturbances in person taking psychoactive drugs have been found to persist long after withdrawing from these drugs **(Teplin et al., 2006).**

For some, sleep disturbance can be so severe as to reverse treatment success and precipitate a relapse to addiction or dependence **(Karam-Hage, 2004).** In fact,

Brower et al., 2001 found that the presence of insomnia was the most significant factor predicting relapse. Consequently, **Karam-Hage, 2004** suggests that vigilance is required when treating insomnia in patients with drug and alcohol problems.

It is worth mentioning that while this relationship is well documented, the underlying mechanism between sleep patterns and drug and alcohol abuse is not well understood **(Friedmann et al., 2003).** Therefore, the presence of insomnia should be viewed as a red flag to physicians and health care professionals, indicating that an assessment for drug and alcohol abuse is warranted **(Teplin et al., 2006).**

Rationale for the study:

The need for this study stems from many observations. The Egyptian population is huge (about 76 million) **(Central Agency for Public Moblisation and Statistics, 2008)**. It is worth mentioning that substance abuse is a common disorder. Recent studies showed that 9.8% of the Egyptian population abused illicit drugs. Another study showed that 11.9 of three samples of University student abused narcotics **(Okasha, 2007)**. This means that it affects a great part of the Egyptian population

causing severe health, social as well as economic burden **(Khalil et al, 2008)**.

Facing this problem necessitates treating these patients during intoxication, withdrawal as well as having a long term plan to prevent the relapse **(Giannini, 2000).** Although patients with opiate abuse disorder suffer from sleep complaints through all these phases, little systematic investigation is done in this field. Studying the sleep profile in those patients will help in diagnosing as well as treating sleep disturbances in these patients serving better therapeutic outcome **(Karam-Hage, 2004**).

Hypothesis:

The study hypothesis is that:

Patients with opiate abuse disorders have sleep disturbance with specific sleep profile that continue for a period of time even after discontinuation of abuse.

Subjects and Method

I- Subjects:

A- Site of the study:

Cases were selected from inpatients of the substance abuse treatment department in the Institute of Psychiatry, Ain Shams University Hospitals.

The Institute of Psychiatry, Ain Shams University Hospitals (ASUIP):

Is located in Western Cairo, serves both urban and rural areas, including Greater Cairo and other governates as well. ASUIP provides services to patients with psychiatric disorders providing 80 beds for inpatient management of various psychiatric disorders and 17 beds for inpatient substance abuse management.

B- Study design:

It is a Cross sectional, Case- Control observational study.

C- Selection of cases:

According to Med Calc computer program (a computer program for medical statistic), the minimum number of subjects is 30 subjects.

Sample selection:

1) The sample will be selected from the inpatients in the institute of psychiatry Ain Shams University, addiction treatment unit. All inpatients fulfilling the inclusion criteria will be offered to participate in the study until completion of the sample size.

2) Patients will be fulfilling the criteria for diagnosis of **Opioid Dependence** according to DSM IV criteria (as verified from SCID I patient version). As most of the patients abuse more than one substance, our study will include patients who have opiates as the main substance of abuse according to Addiction Severity Index.

3) The sample will include every admission fulfilling the inclusion criteria starting from the first of June 2006 till completion of cases.

b) Inclusion criteria:

1. Patients to be selected were using opiates regularly for at least 1 year.

2. Age ranges between 18-45 years to exclude mere effect of age.

3. All patients were males

4. Consenting patients using written informed consent.

c) Exclusion criteria:

1) History of any Axis I psychiatric disorders according to DSM IV verified by SCID I.

2) Patients with other Axis I Diagnosis as verified by SCID I.

3) Patients with co-morbid major physical illness (e.g. renal, hepatic or heart diseases) to exclude the effect of these illnesses or medications used on the sleep profile.

4) History of neurological diseases as cerebrovascular diseases to exclude its effect on the sleep profile.

5) Patients who refused to sign the consent.

Control group

A control group of 10 individuals of volunteers matched with the patient group for age and sex and with no apparent physical or psychiatric morbidity. They will be selected from the employees of the institute of psychiatry Ain Shams University.

Procedures:

- The study took place from 1st of June 2006 till 31st of May 2008.
- All the inpatients in the substance abuse department were examined to determine eligibility for participation in the study.

- Screening was conducted through clinical psychiatric interview according to inpatient psychiatric sheet of Ain Shams University Institute of Psychiatry, which examined demographic data, psychiatric history and examination as well as medical history information.
- Patients were examined 3 weeks following admission, after resolution of most of the symptoms of withdrawal.
- Based on response, individual subjects were approved to continue participation in this study. They were offered written informed consent before conducting any procedure.
- **Informed consent:**

  An informed written consent was offered for the potential participants of the study. It contained the name of the study and its aim. It also included detailed description of the procedure, the expected benefits as well as the side effects that may result from it which included sleep disturbances due to withdrawal of medication and inability to sleep at the night of performing polysomnogram due to changing place of sleeping.

  The participants were informed that they have the right to withdraw from the study at any time without justification. Moreover, they were informed that this study could be used for scientific

publication without the disclosure of the participants' personal identity.

- Patients who agreed on participation were subjected to full medical history and examination (general, cardiological, chest and neurological examination) to detect any neurological or chronic medical condition that would lead to exclusion from the study.
- Routine laboratory investigation including liver and kidney function, complete blood picture tests as well as ECG will be performed to confirm exclusion of major physical illness.
- All subjects of the study were assessed by using Structured Clinical Interview for DSM-IV (SCID I) diagnostic tool to diagnose opioid dependence and to exclude other Axis I diagnosis according to DSM VI classification.
- Then participants of the study were assessed by using Addiction Severity Index (ASI) Beck Depression Inventory (BDI), the Manifest Anxiety Scale as well as The Structured Clinical Interview for DSM Axis II Disorders (SCID II).
- Afterwards, patients performed Sleep assessment was done using all night polysomnography as well as Structured Sleep Disorder Questionnaire. Sleep assessment was performed when the participants were medication free for at least 7 days prior to study

to exclude the effect of any psychotropic medication on their polysomnography.

- Moreover, urine test for substances of abuse was performed to guarantee abstinence during the assessment period.

Tools:

1- Structured Clinical Interview for DSM-IV (SCID I) (First et al., 1995):

The study used the Arabic version of the structured clinical interview for DSM-IV axis I diagnosis (SCID-I) **(Elmesiry et al., 2004).**

- It is a semi-structured diagnostic interview which has been updated for DSM-IV.
- It begins with a section on demographic information and clinical background. Then there are 7 diagnostic modules, focused on different diagnostic groups: mood, psychotic, substance abuse, anxiety, somatoform, eating and adjustment disorders.
- Both required and optional probes are provided, and skip outs are subjected when no further questioning is warranted.
- It is considered the standard interview to verify diagnosis in clinical trials and is extensively used in other forms of psychiatric research.
- It is applied to the case group to

- - diagnose Opioid Dependence
- - exclude other Axis I diagnosis

2- Addiction severity Index (ASI 5th ed.):

It is a semi structured interview designed to provide a multidimensional assessment for the problems presented by patients with substance abuse disorder **(McLellan et al., 1992).**

It designed for use in inpatients and outpatients alcohol and drug abuse treatment settings.

It gathers information on seven functional areas often affected by substance abuse: medical status, employment and support, drug use, alcohol use, legal status, family or social status and psychiatric status. Each section includes questions about the frequency, duration and severity of the patient's problems over the patient's life and in the last 30 days.

The Arabic version of ASI (5th ed.) was used **(Qassem et al., 2003).** Questions include both objective assessment of these problems' severity as well as patient's subjective assessment of them **(Qassem et al., 2003; Khalil et al., 2008).**

The ASI was used in the study to:

- Ensure that the study will include patients who have opioids as the main substance of abuse.

- Study the pattern of opioids abuse over the life time of the patients and in the last 30 days before admission.

3- Beck Depression Inventory (BDI):

- It is performed to assess the severity of depression state.
- It is applied for the case group only.

The Beck Depression Inventory (BDI) is a series of questions developed to measure the intensity, severity, and depth of depression in patients with psychiatric diagnoses. Its long form is composed of 21 questions, each designed to assess a specific symptom common in depression. Subjects were asked to identify the statement that beat describe their feelings "right now" **(Beck et al., 1961).**

- Each of the 21 items has four responses of increasing severity. Numerical values from 0-3 are assigned each statement to indicate the degree of severity.
- **Scoring:** the total score is then interpreted that a score from 0 – 10 is considered normal, score from 11 – 18 is considered mild, score from 19 – 29 is considered moderate and 30 or above is considered severe depression.
- It is a widely used standardized, consistent instrument with proven validity and reliability and has been used in several studies. The Arabic version will be used for the study. **(Ghareeb, 2000)**.

- It is used after exclusion of depression by SCID I questionnaire to assess the depressive state of the patients just before the night of performing the polysomnogram. (BDI) can be used for such a purpose if used after exclusion of major depression by a diagnostic instrument and in presence of another psychiatric diagnosis **(Beck & Steer, 2000).**

4- The Taylor Manifest Anxiety Scale:

- It is performed to assess the anxiety state.
- It is administered to the case group.
- The Manifest Anxiety Scale **(Taylor, 1953)** is derived from the Minnesota Multiphasic Personality Inventory (MMPI) and is presented into a 50 item of yes / no questions for assessment of the anxiety state in those patients
- Questions are phrased in formal Arabic and can be understood by all those people who can read simple Arabic.
- Scoring: the total score indicates the severity of the anxiety state, score from 0 – 16 is considered normal,
  from 17-25 indicates mild anxiety,
  from 25-36 indicates moderate anxiety,
  while scores above 36 is indicates severe anxiety.
  It is used after exclusion of Anxiety disorders by SCID I questionnaire to assess the anxiety state of the patients

just before the night of performing the polysomnogram **(McDowell & Newell, 1996).**

5- The Structured Clinical Interview for DSM Axis II Disorders (SCID II):

SCID II is semi -structured clinical interview that is designed to categorically and dimensionally assess the personality disorders according to DSM IV **(First et al., 1997).**

- It is administered to evaluate an axis II diagnosis.
- It is applied to the case group.
- It is a semi-structured clinical interview that was developed to categorically and/or dimensionally assess the DSM-IV personality disorders. Items are organized by personality disorder. A 119 item yes/no screening questionnaire is available to reduce interview time by identifying personality disorders that are unlikely to be present. Paralleling the screen, the SCID-II interview contains 119 sets of questions (yes/no and open ended format) plus several additional questions to assess antisocial personality disorder. The interview also covers passive aggressive (negativistic) and depressive personality disorders from appendix B from DSM-IV (criteria sets and axes provided for further study).
- Each criterion is scored as 1 = absent or false, 2 = sub-threshold, 3 = threshold, or? = inadequate information.

Specific (but relatively brief) guidelines for a score of 3 are provided. Personality disorders may be scored categorically or dimensionally.

The study used the Arabic version of the structured clinical interview for DSM-IV axis II personality disorders (SCID-II) **(Hatata et al., 2004).**

6- All night Polysomnography (PSG)

All patients will do overnight polysomnography (PSG) in the institute of psychiatry Ain Shams University. The apparatus used is **Neurofax EEG2110, Digital Electroencephalograph, Nihon Kohden Corporation, Tokyo, Japan**. It can provide immediate staging, scoring and reporting of the PSG night.

All patients were consented to do overnight polysomnography (PSG) at no cost in the institute of psychiatry Ain Shams University.

Procedures for monitoring sleep:

Ten electrodes were used to determine sleep stages; two central scalp electrodes (03 and 04), and two fronto-parietal scalp electrodes (FP1, FP2), two at outer canthi of the eyes to record eye movements (Electrooculogram "EOG"), two chin electrodes to record mentalis electromyogram (EMG), two reference electrodes in the ear lobes (A1, A2).

Electroencephalogram (EEG):

Four channels EEG were used in standard assessment of sleep stages. After an accurate measurement of the skull according to the international 10 -20 system of electrode placement the hair is separated and the scalp is cleaned in preparation for electrodes application to ensure a good conducting medium. The EEG electrodes were attached to the scalp using ordinary paste.

Electrooculogram (EOG):

The main reasons to record eye movement activity during sleep is to record the cardinal sign of REM sleep i.e.; the phasic burst of rapid eye movements. Also detect the onset of sleep which is accompanied by slows rolling eye movements.

The standard EOG placement includes the right outer canthus (ROC) and the left outer canthus (LOC). The electrodes were placed offset from horizontal plane, one slightly above and one slightly below for detection of horizontal and vertical eye movements and a contra-lateral

auricular reference for each outer canthus was used (ROC/A1) and (LOC/A2).

Electromyogram (EMG):

The EMG from muscles beneath the chin is used as a criterion for staging REM sleep; the electrodes are placed beneath the chin overlying the mentalis/ submentalis muscles, two electrodes on each side.

In addition to EEG, EGG, EMG, three sensors for airflow, chest, and abdominal movements were also placed to score the incidence and length of apnea or hypopnea, and another two surface EMG electrodes over left tibialis anterior muscle for detection of periodic leg movements (PLMs).

Hypnographic all night PSG was performed which provides us with the following variables:

I- Sleep continuity

- Sleep continuity includes sleep latency, sleep efficiency, and arousal index.
- Sleep latency is the time from the beginning of the polysomnographic recording period to the onset of stage 2 sleep, for at least 10 uninterrupted minutes **(Chesson et al., 1997).**

- Sleep efficiency is the percentage of time in bed spent asleep. It is usually greater than 90% in the young and decreases somewhat with age **(Brower et al., 2001).**
- Arousal index is the total number of arousals per hour of sleep **(Chesson et al., 1997).**

II- Analysis of sleep architecture

which includes; percentages of NREM-sleep, stages (I, II, III, IV, and SWS) to total sleep time in addition to SWS latency, and PLM index (periodic limb movement index).

III- Apneas:

- Including total apnea/hour, different types of apnea (obstructive, central or mixed), desaturation/hour
- -Sleep apnea is defined as a cessation or near cessation of respiration for a minimum of 10 seconds **(American Sleep Disorders Association 1995).**
- -In obstructive sleep apnea an increase in respiratory effort occurs as patients attempt to breathe against the obstruction of the upper airway **(Chesson et al., 1997).**
- -In central sleep apnea, no respiratory effort and, therefore, no airflow occurs for a minimum of 10 seconds. Central apneas rarely occur in isolation, and patients typically have both central and obstructive apneas **(American Sleep Disorders Association 1995).**
- -Respiratory disturbance index is the total number of apneas and hypopneas per hour of sleep **(Chesson et al., 1997).**
- -The De-saturation Index is the number of oxygen de-saturations per hour of the polysomnographic recording period. Only de-saturations of 4% or more are counted as significant. This index has shown to be consistent with respiratory disturbances during sleep **(American Sleep Disorders Association 1995).**

IV- REM sleep analysis:

- REM-sleep analysis which includes REM percentage, and latency as well as duration and density of first REM period.
- -REM sleep latency refers to the time between sleep onset and the onset of the first episode of REM sleep **(Witzenhausen et al., 2001).**
- -REM% is the percentage of total sleep time spent in REM sleep **(Aldrich et al., 1999).**
- -REM density (REMD) is the ratio of rapid eye movements per time in REM sleep **(Althuis et al., 1998).**

7- Structured Sleep Disorder Questionnaire:

Sleep history was taken from all patients through the Structured Sleep Disorder Questionnaire **(Asaad and Kahla, 2001),** which 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.\
- Effect of sleep disturbance on personal functioning.

8- A urine screen for substances of abuse :

Urine screening for common substances of abuse (opiates, cannabis, benzodiazepines, barbiturates, cocaine and amphetamines) was performed on admission of patient to determine substance of abuse. Repeating this procedure prior to sleep study was considered to ensure abstinence during the assessment period.

The urine screening was performed at the laboratory of the institute of psychiatry, Ain Shams University using immunoassay technique. The apparatus used was **Viva-E Analyzer, immunoassay Analyzer, Dade Behring Corporation, Lieder Bach, Germany.**

9- Routine laboratory investigations:

Liver and kidney function tests as well as ECG were performed to exclude major physical illness (e.g. renal, hepatic or heart diseases).

Control Group:

Control group will be subjected to physical examination, SCID I (non-patient version), Sleep questionnaire as well as polysomnographic studying.

Statistical analysis:

All data were recorded and entered in a statistical package on a compatible computer and varied. Analysis was done using an SPSS- 15th version (2007). The results were tabulated, grouped and statistically analyzed using the following tests:

1. **Student's t Test (t):** for comparison between means of the different groups of patients.
2. **Spearman Correlation Test (r):** was used when studying the relationship (direction and power) of quantitative variables simultaneously.
3. **One Way ANOVA Test (F):** was used when comparing several means to see how several independent variables interact with each other and what effects these interactions have on a dependent variable.
4. **Pearson Chi Square Test (χ^2):** To detect whether there is a significant association between different categorical variables.
5. **P value:** Used to indicate the level of significance:
   P > 0.05: Non significant=NS
   P < 0.05: Significant=SIGN
   P < 0.01: Highly significant=HS
   P < 0.001: Very highly significant=VHS

Aim of the work

1. To study the profile of sleep in opioid abuse patients, following the period of detoxification
2. To highlight whether there is a remote effect of opioid abuse on sleep or not
3. To Study the nature of the sleep disturbance if present
4. To Explore factors that determine the sleep disturbance if present.

RESULTS

Recruitment of the sample:

Allover the study period, 54 patients were candidate for continuing the study.

8 refused to participate to the study or to sign the consent, 6 withdrew through the procedure.

Other 7 patients did not sleep during the polysomnography procedure although it was repeated twice.

Therefore, **33 patients** underwent the full procedure.

The present study provides a cross sectional examination of the profile of sleep in opioid dependence patients, following the period of detoxification and the different variables affecting them. So we recruited 33 patients with an established diagnosis of opioid dependence and 10 apparently healthy comparable controls.

The aim of the statistical analysis was to address the following:

1- The Demographic and Clinical profile of the sample.

2- The sleep profile of the sample.

3- The factors that may affect the sleep pattern of the sample.

SECTION (1)

The Demographic and Clinical profile of the sample

A. Demographic variables:

Table (1) clarifies that both the patients and the control group were matched as regards the age as no statistically significant difference between the 2 groups as shown by t test ($p>0.05$).

Table 4.1: Age of the subjects in case and control groups

	Cases	Control	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Age	27.061±5.868	30.800±7.208	-1.674	0.102

Both the patients and the control group were all males.

As regard the level of education 45.45% (n=15) of the sample graduated from university, 27.27% (n=9) from secondary 24.24% (n=8) from technical school, 9.09% (n=3) from preparatory school.

Table 4.2: Educational level of the cases

		N	%
Education	College graduate	15	45.45
	Technical School	8	24.24
	High School	9	27.27
	Preparatory	3	9.09

Regarding Marital Status, it is found that 87.8% (n=29) of sample were single, 9% (n=3) were married and 3% (n=1) divorced.

Table 4.3: Marital Status of the cases

		N	%
Marital Status	Single	29	87.88
	Married	3	9.09
	Divorced	1	3.03

As regard the level of occupation, 42.42% (n=14) of the sample were unemployed, 27.27% (n=9) were students, 18.18% were Working in professional jobs while 12.12% (n=4) were Skilled workers.

Table 4.4: Occupation of the cases

		N	%
Occupation	Professional	6	18.18
	Skilled worker	4	12.12
	Student	9	27.27
	Unemployed	14	42.42

B. Assessment of Substance Abuse in Cases:

As regarding the type of substance of abuse, 78.79% (n=26) were abusing heroine while 21.21% (n=7) of the sample were abusing Tramadol.

Regarding the route of abusing the opioids, 78.79% (n=26) were abusing via intra venous injection while 21.21% (n=7) of the sample were abusing orally.

In our study, 45.45 % (n=15) had family history of substance abuse where 54.55% (n=18) didn't have.

The duration of lifetime opioid abuse ranged from 3 years to 20 years with Mean (7.121 **±** 3.352). On the other hand, the duration of opioid abuse in the last 30 days before abstinence ranged from 22 days to 30 days with Mean (28.242 **±** 2.705).

Table 4.5: Duration of opioid abuse

	Range	Mean ± SD
Lifetime Duration of abuse in years	3.000-20.000	7.121 ± 3.352

Duration of abuse in the last 30 days in days	22.000-30.000	28.242 ± 2.705

The last abstinence period of the cases in our study ranged from Zero (Never abstinent before) to 19 months with Mean (5.333 ± 5.599). The time lapsed from last abstinence ranged from Zero (Never abstinent) to 20 months with Mean (7.242 ± 6.529).

Table 4.6: Last abstinence period and time lapsed since then in months

	Range	Mean ± SD
Last abstinence period in Months	0.000 - 19.000	5.333 ± 5.599
Time lasted since last abstinence in Months	0.000 - 20.000	7.242 ± 6.529

Regarding number of treatment trials, the range was from Zero to 12 with Mean (2.515 ± 2.938)

C. Medical and Psychiatric Assessment :

Medical Assessment:

In the study, the weight of the participant cases ranged from 55 kilograms to 95 kilograms with Mean

(74.848 **±** 10.047). Their height ranged from 162 centimeters to 192 centimeters with Mean (177.667 **± 8.003**). Moreover, their body mass index (BMI) ranged from 20.5 to 29.3 with Mean (23.694 ± 2.335).

Table 4.7: Weight, Height and Body Mass Index of the cases

	Range	Mean ± SD
Weight in kg	55.000 - 95.000	74.848 ± 10.047
Height	162.000 - 192.000	177.667 ± 8.003
Body Mass Index	20.500 - 29.300	23.694 ± 2.335

Examining the medical condition of the cases revealed that 60.61% (n=20) case was Hepatitis C Positive, 3.03% (n=1) was Hepatitis B positive and 36.36% (n=12) had no medical conditions.

Table 4.8: Medical condition of the cases

		N	%
Medical Disorders	No	12	36.36
	Hepatitis C	20	60.61
	Hepatitis B	1	3.03

ii. Psychiatric Assessment:

The study assessed the severity of depressive state in case group, but this questionnaire was not performed to the control group as we excluded any current psychiatric morbidity. This performed questionnaire revealed that the

48.48% of cases (n=16) had moderate state, 42.42% (n=14) had mild state, 6.06% (n=2) Severe and 3.03 (n=1) was normal.

Table 4.9: Depressive state of the cases according to BDI

		N	%
Beck Depression Inventory	Normal	1	3.03
	Mild	14	42.42
	Moderate	16	48.48
	Severe	2	6.06

As for the severity of anxiety state, both mild and moderate anxiety states counted for 48.48% of cases (n=16) where as only 3.03% of the cases (n=1) had severe anxiety state.

Table 4.10: Anxiety state of cases according to Manifest Taylor Anxiety scale

		N	%
Manifest Taylor Anxiety scale	Mild	16	48.48
	Moderate	16	48.48
	Severe	1	3.03

Examining the cases of the study for personality disorder using SCTDII showed that 45.45% of the cases had no personality disorder. According to DSM IV the most

frequent personality cluster among cases group was cluster C (24.24%) followed by cluster B (18.18%), while the mixed personality disorders represented (9.09%) and multiple personality disorders 3.03%.

Table 4.11: Personality Disorders in Cases

	N	%		N	%
No personality	15	45.45	No personality	15	45.45
Cluster B	6	18.18	Antisocial	3	9.09
			Narcisstic	2	6.06
			Borderline	1	3.03
Cluster C	8	24.24	Avoidant	6	18.18
			Dependant	2	6.06
Mixed	3	9.09	Mixed	3	9.09
Multiple	1	3.03	Multiple	1	3.03
Total	33	100.00	Total	33	100.00

SECTION (2)

The Sleep profile of the sample

A. Clinical Complaints regarding Sleep:

Sleep history was taken from all cases as well as control subjects through the structured sleep disorders questionnaire **(Asaad and Kahla, 2001)** and revealed the following:

Regarding the initial insomnia (Difficulty in falling asleep), Data presented in table (17) showed that the opiate

dependant patients suffered more from initial insomnia, around 81% of the studied group in comparison to (10%) of the control group. ***There was very high significant difference between cases and control subjects regarding initial insomnia.***

Table 4.12: Case-control comparison regarding Initial Insomnia

Difficulty in falling asleep		Cases	Control	Total
Yes	N	27	1	28
	%	81.82	10.00	65.12
No	N	6	9	15
	%	18.18	90.00	34.88
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	17.426		
	P-value	0.000***		

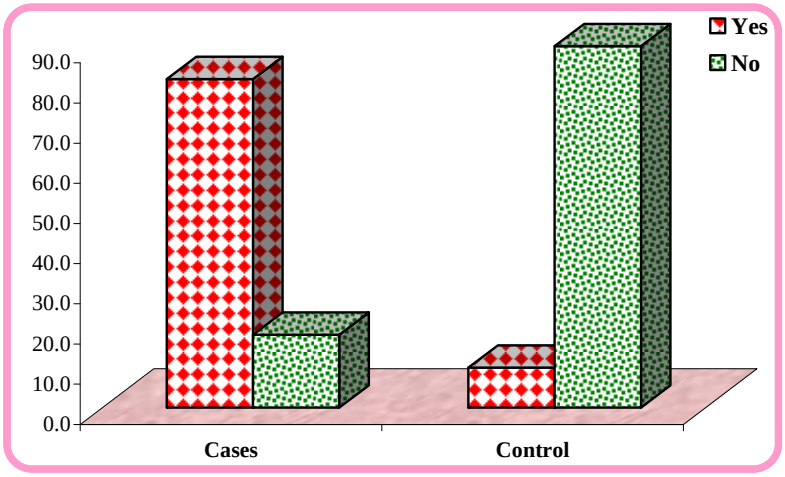

Figure 4.1: Case-control comparison regarding Initial Insomnia

Regarding night sleeping hours of subjects, the Mean regarding the cases was 6.65 hours ± 1.45.

Table 4.13: Night sleeping hours of Cases

Gr.	Night Sleeping Hours	
	Range	Mean ± SD
Cases	3.00 - 12.00	6.65 ± 1.45

In the current study, there was both subjective and objective assessment of Sleep Latency. The subjective sleep onset latency (SOL) was assessed by the subjects during performing sleep questionnaire to assess time between settling down on the night and falling asleep. Regarding subjective sleep onset latency (SOL) of the subjects, the Mean regarding the cases was 47.5 minutes ± 13.97; while in control subjects the Mean was 17.8 ± 5.64. ***There was very highly significant difference between cases and control subjects regarding time taken to sleep (SOL).***

Table 4.14: Case-control comparison regarding subjective sleep onset latency (SOL)

Gr.	Subjective Sleep Onset Latency (SOL)		T-test	
	Range	Mean ± SD	t	P-value
Cases	15.000 - 60.000	47.500 ± 13.970	6.819	0.000***
Control	12.000 - 30.000	17.818 ± 5.564		

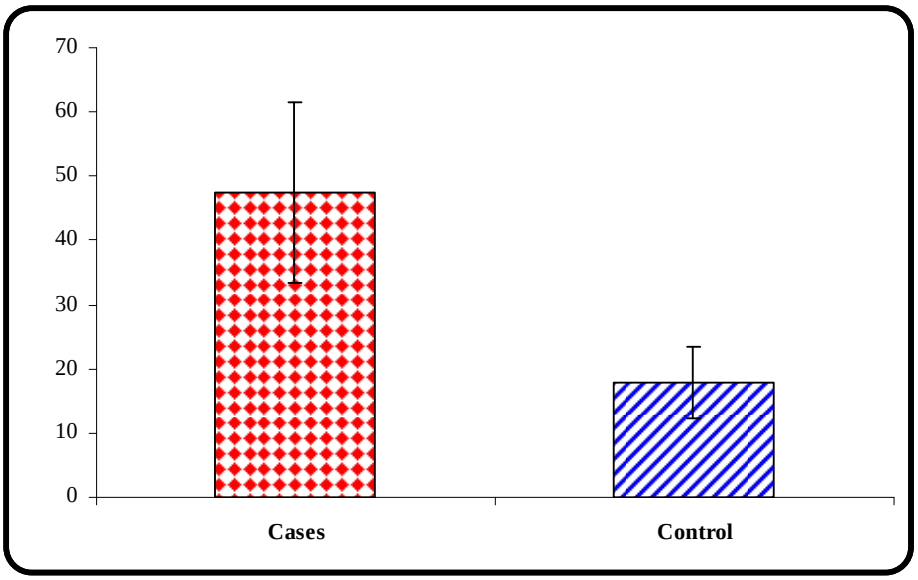

Figure 4.2 : Case-control comparison regarding subjective sleep onset latency (SOL)

Regarding the Intermediate Insomnia (Interrupted sleep -Awakening during sleep), the study showed that the opiate dependant patients suffered more from interrupted sleep, around 57% of the studied group in comparison to (10%) of the control group. ***There was highly significant***

difference between cases and control subjects regarding Intermediate Insomnia.

Table 4.15: Case-control comparison regarding Intermediate Insomnia

Interrupted sleep		Cases	Control	Total
Yes	N	19	1	20
	%	57.58	10.00	46.51
No	N	14	9	23
	%	42.42	90.00	53.49
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	6.982		
	P-value	0.008**		

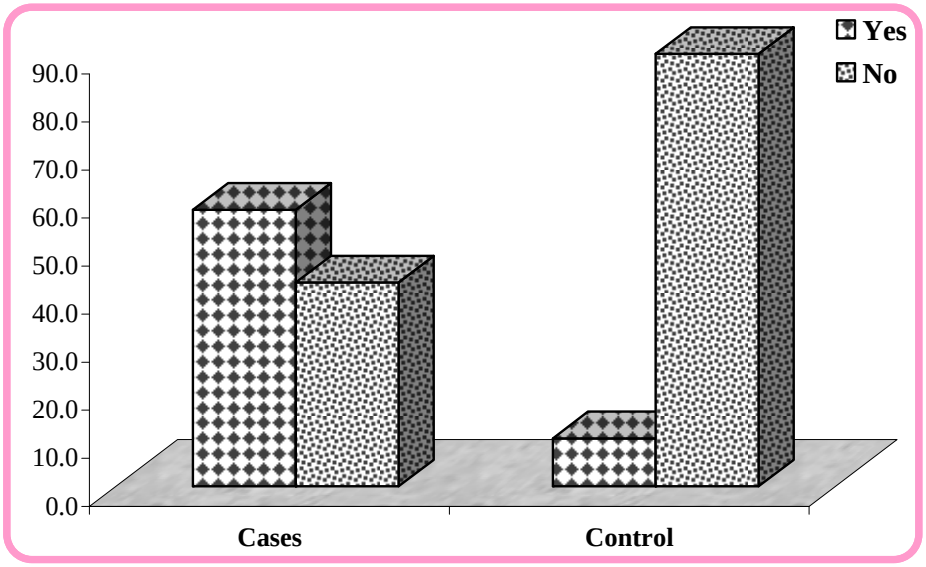

Figure 4.3: Case-control comparison regarding Intermediate Insomnia

The Number of awakenings during sleep of the cases ranged from 0 to 4 times with Mean 1.4 times ± 1.366.

Table 4.16: Number of awakenings during sleep

	Range	Mean ± SD
Number of awakenings during sleep	0.000 - 4.000	1.438 ± 1.366

The current study showed that the opiate dependant patients suffered more from Late Insomnia (Early morning awakening), around 48% of the studied group in comparison to (0%) of the control group. ***There was highly significant difference between cases and control subjects regarding early morning awakening.***

Table 4.17: Case-control comparison regarding Late Insomnia

Early morning awakening		Cases	Control	Total
Yes	N	16	0	16
	%	48.48	0.00	37.21
No	N	17	10	27
	%	51.52	100.00	62.79
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	7.722		
	P-value	0.005**		

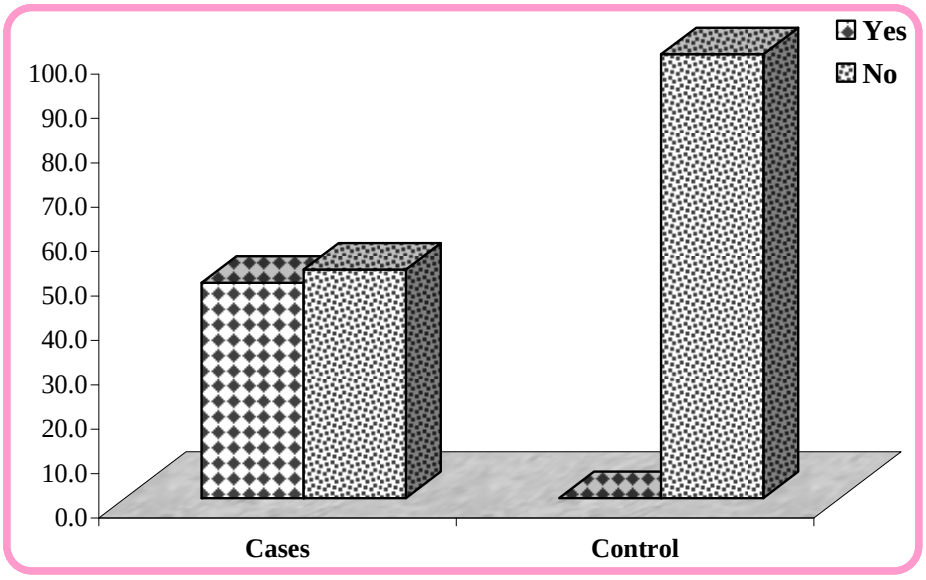

Figure 4.4: Case-control comparison regarding Late Insomnia

Regarding the Daytime Hyper somnolence Data presented in table (4.18) showed that the opiate dependant patients suffered more from that complaint with percentage (67%) of the studied group in comparison to (0%) of the control group. ***There was very high significant difference between cases and control subjects regarding hyper somnolence.***

Table 4.18: Case-control comparison regarding Daytime Hypersomnolence

Daytime Hypersomnolence		Cases	Control	Total
Yes	N	22	0	22
	%	66.67	0.00	51.16
No	N	11	10	21
	%	33.33	100.00	48.84
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	13.651		
	P-value	0.000***		

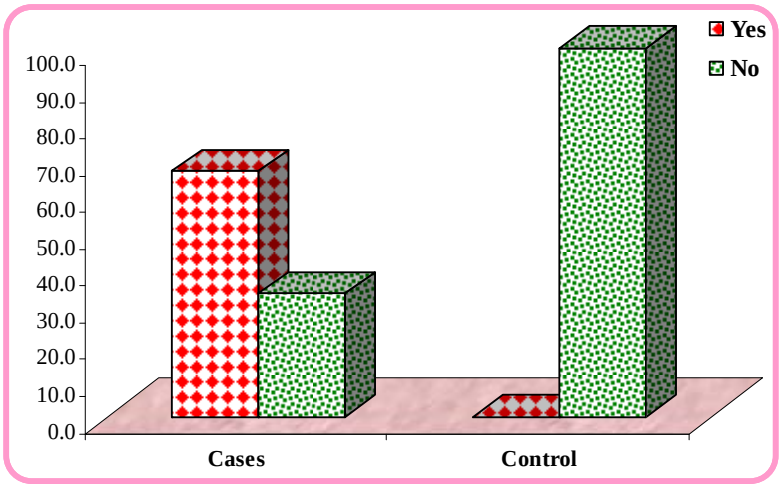

Figure 4.5: Case-control comparison regarding Daytime Hyper somnolence

Daytime sleeping hours ranged from 0 to 2 with Mean 1.03 hour ± 0.86.

Table 4.19: Daytime sleeping hours in cases

	Range	Mean ± SD
Day sleeping hours	0.000 - 2.000	1.031 ± 0.861

Regarding Snoring during sleep, the current study showed that opiate dependant patients suffered from that complaint with percentage (30%) of the studied group in comparison to (10%) of the control group. ***There was no statistically significant difference between cases and control subjects regarding snoring***.

Table 4.20: Case-control comparison regarding Snoring

Snoring		Cases	Control	Total
Yes	N	10	1	11
	%	30.30	10.00	25.58
No	N	23	9	32
	%	69.70	90.00	74.42
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	1.662		
	P-value	0.197		

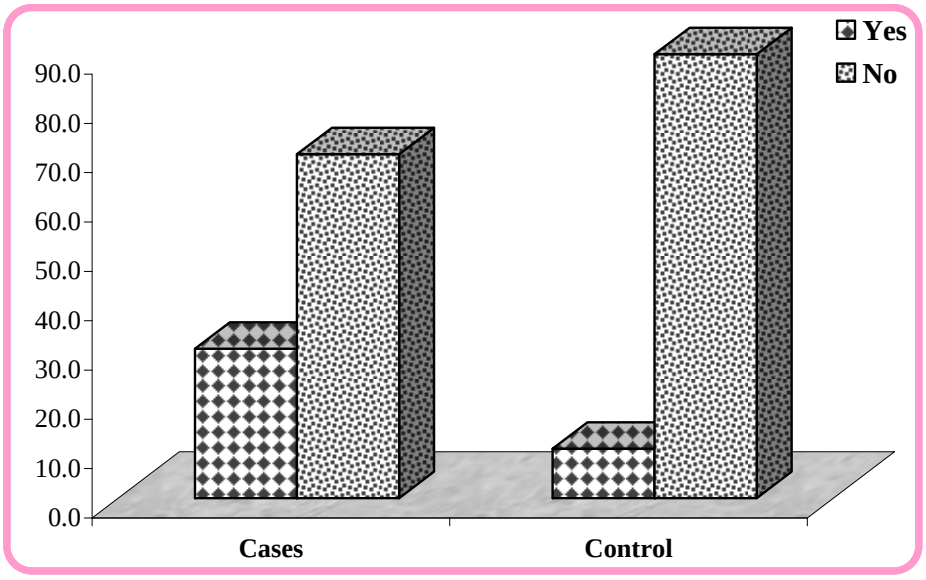

Figure 4.6: Case-control comparison regarding Snoring

Regarding experiencing nightmares, the current study showed that opiate dependant patients suffered from that complaint with percentage (36%) of the studied group in comparison to (30%) of the control group. ***There was no statistically significant difference between cases and control subjects regarding nightmares***.

Table 4.21: Case-control comparison regarding Nightmares

Nightmares		Cases	Control	Total
Yes	N	12	3	15
	%	36.36	30.00	34.88

No	N	21	7	28
	%	63.64	70.00	65.12
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	0.137		
	P-value	0.711		

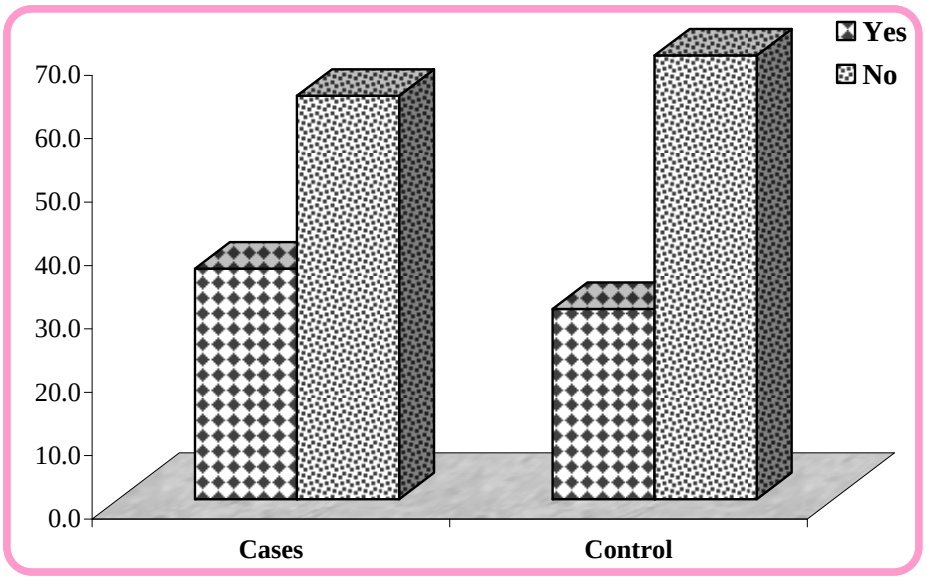

Figure 4.7: Case-control comparison regarding Nightmares

Regarding Sleep talking, the current study showed that opiate dependant patients suffered from that complaint with percentage (42%) of the studied group in comparison to (0%) of the control group. ***There was highly significant difference between cases and control subjects regarding sleep talking***.

Table 4.22: Case-control comparison regarding Sleep talking

Sleep talking		Cases	Control	Total
Yes	N	14	0	14
	%	42.42	0.00	32.56
No	N	19	10	29
	%	57.58	100.00	67.44
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	6.290		
	P-value	0.012**		

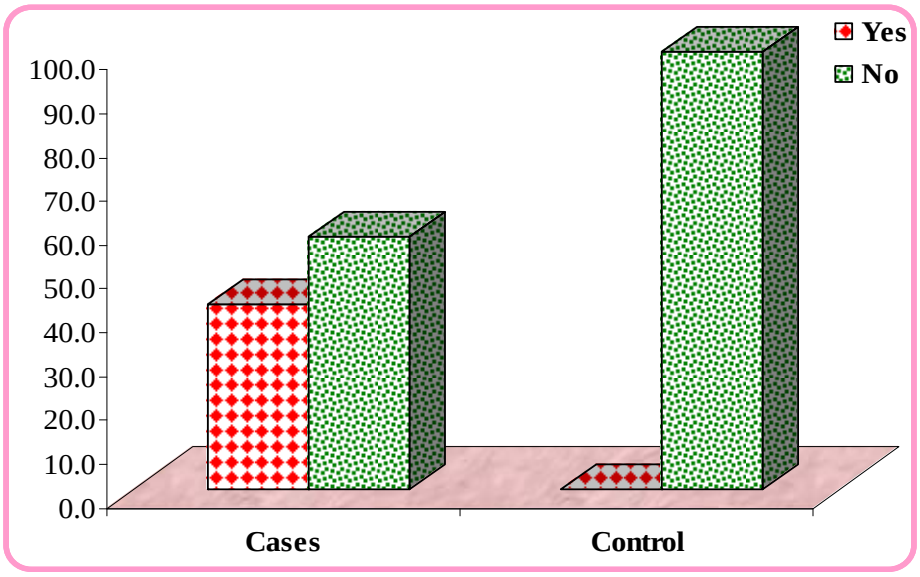

Figure 4.8: Case-control comparison regarding Sleep talking

Regarding Sleep Acid Reflux, the current study that the case subjects suffered from that complaint with percentage (33%) of the studied group in comparison to (0%) of the control group. ***There was significant difference between cases and control subjects regarding Sleep Acid Reflux.***

Table 4.23: Case-control comparison regarding Sleep Acid Reflux

Sleep acid reflux		Cases	Control	Total
Yes	N	11	0	11
	%	33.33	0.00	25.58
No	N	22	10	32
	%	66.67	100.00	74.42
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	4.479		
	P-value	0.034*		

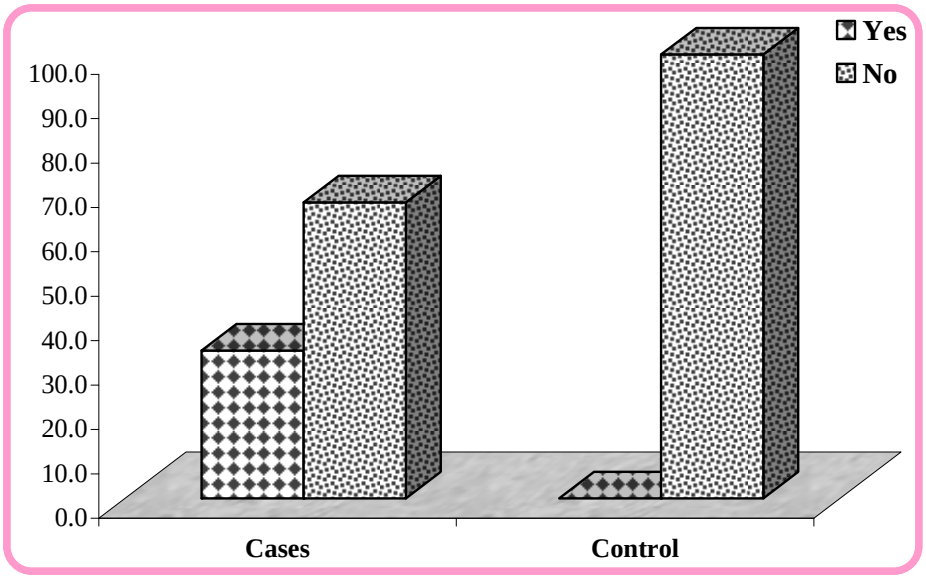

Figure 4.9: Case-control comparison regarding Sleep Acid Reflux

Regarding Nocturnal Enuresis , the current study that opiate dependant patients suffered from that complaint with percentage (6%) of the studied group in comparison to (0%) of the control group. *There was no statistically significant difference between cases and control subjects regarding nocturnal enuresis***.**

Table 4.24: Case-control comparison regarding Nocturnal enuresis

Nocturnal enuresis		Cases	Control	Total
Yes	N	2	0	2
	%	6.06	0.00	4.65
No	N	31	10	41
	%	93.94	100.00	95.35
Total	N	33	10	43
	%	100.00	100.00	100.00
Chi-square	X^2	0.636		
	P-value	0.425		

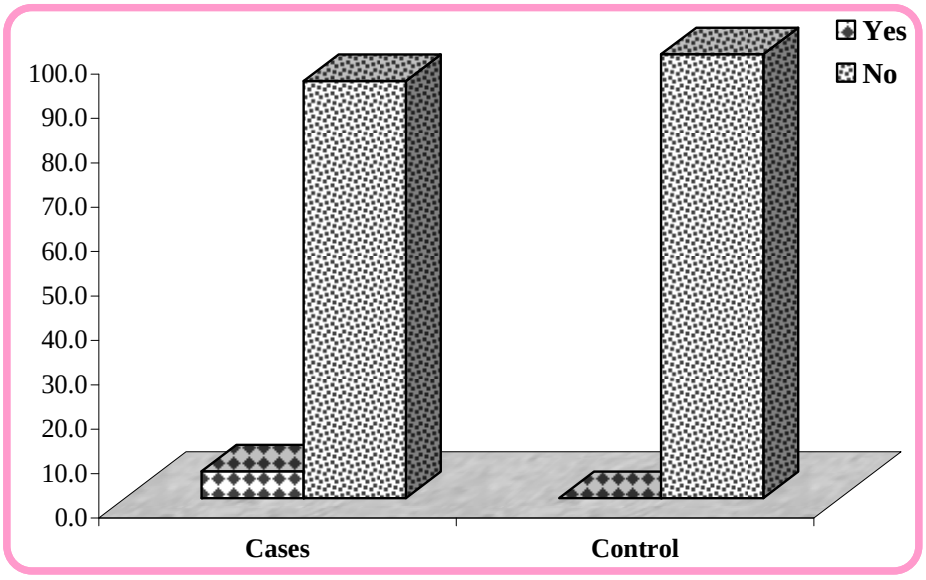

Figure 10: Case-control comparison regarding Nocturnal enuresis

B. Polysomnography Findings:

This section of results discusses the sleep laboratory findings comparing opioids abusing patients to healthy controls.

Comparison of Sleep latency, sleep efficiency and arousal index

Regarding sleep latency, sleep efficiency and arousal index, there were marked affection in cases. That is to say that there was significant lengthening of sleep latency, significant diminish of sleep efficiency, and significant rise of arousal index in opioid dependant patients as compared to healthy controls.

Sleep latency was of mean 46.6 minutes ± 13.1 in cases compared with mean 18.8 minutes ± 2.6 in control. ***There was very high significant difference between cases and control subjects regarding sleep latency***.

Sleep Efficiency was of mean 42.7% ± 10.7 in cases compared with mean 91.5% ± 2.5 in control. ***There was very high significant difference between cases and control subjects regarding sleep efficiency***.

As for Arousal Index, the cases of opioid dependence have mean 19.3 ±2.1 while control subjects have mean 5.4±2.0. ***There was very high significant difference between cases and control subjects regarding arousal index***.

Table 4.25: Case-control Comparison regarding Sleep latency, sleep efficiency and arousal index

	Gr.			
	Cases	Control	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Sleep Latency	46.606 ± 13.140	18.800 ± 2.573	6.600	0.000***
Sleep Efficiency	42.672 ± 10.717	91.500 ± 2.451	-14.182	0.000***
Arousal Index	19.300 ± 2.142	5.360 ± 2.019	18.250	0.000***

Comparison of NREM Sleep Parameters:

The study shows that there is a significant increase in both stage 1 and stage 2 of NREM sleep in opioid dependence patients as compared to healthy controls, while stages 3 and 4 as well as SWS% are significantly reduced .

The percentage of stage 1 of sleep of cases was of mean 16.9 ± 3.9 while in control was 4.0 ± 0.6. ***There was very high significant difference between cases and control subjects regarding Stage I % of sleep.***

The percentage of stage 2of sleep of cases was of mean 54 ± 3.4while in control was 50.9 ± 0.9. ***There was very high significant difference between cases and control subjects regarding Stage II % of sleep.***

The percentage of stage 3 of sleep of cases was of mean 3.1 ± 1.7 while in control was 10.1 ± 0.6. ***There was***

very high significant difference between cases and control subjects regarding Stage III % of sleep.

The percentage of stage 4 of sleep of cases was of mean 2.5 ± 1.4 while in control was 10.1 ± 0.5. ***There was very high significant difference between cases and control subjects regarding Stage IV % of sleep.***

The percentage of Slow Wave Sleep of cases was of mean 5.6 ± 2.7 while in control was 20.2 ± 0.6. ***There was very high significant difference between cases and control subjects regarding SWS.***

Table 4.26: Case-Control comparison regarding NREM Sleep Parameters.

	Gr.			
	Cases	Control	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Stage I %	16.884 ± 3.937	4.050 ± 0.662	10.182	0.000***
Stage II %	54.869 ± 3.357	50.890 ± 0.874	3.682	0.001***
Stage III %	3.109 ± 1.655	10.130 ± 0.604	-13.059	0.000***
Stage IV %	2.514 ± 1.438	10.090 ± 0.491	-16.259	0.000***
SWS %	5.637 ± 2.726	20.220 ±0.594	-16.666	0.000***

Comparison between REM sleep measurements

This study shows that there is no statistically significant difference of REM sleep parameters between opioid dependence patients and healthy controls**.**

Table 4.27: Case-Control comparison regarding REM Sleep Parameters.

	Gr.			
	Cases	Control	T-test	
	Mean ± SD	Mean ± SD	t	P-value
REM %	21.981 ± 4.870	24.840 ± 1.153	-1.827	0.075
REM Density	20.694 ± 0.942	20.640 ± 0.878	0.161	0.873
REM Latency	62.291 ± 3.479	64.800 ± 4.662	-1.843	0.073

Comparison of Respiratory Variables of Sleep between cases and control.

Table (4.28) shows that there is no significant difference regarding respiratory variables in opioid dependence patients as compared with healthy controls.

Table 4.28: Case-Control comparison regarding Respiratory Variables of Sleep.

		Range	Median	Mean rank	Mann-Whitney Test	
					Z	P-value
Total apnea\hour	Cases	0.000 - 4.300	0.000	22.652	-0.911	0.363
	Control	0.000 - 0.600	0.000	19.850		
Obstructive apnea\hour	Cases	0.000 - 2.300	0.000	22.667	-0.932	0.351
	Control	0.000 - 0.400	0.000	19.800		
Central apnea \hour	Cases	0.000 - 0.500	0.000	21.833	-0.358	0.720
	Control	0.000 - 0.100	0.000	22.550		
Mixed apnea\hour	Cases	0.000 - 1.800	0.000	22.167	-0.284	0.776
	Control	0.000 - 0.100	0.000	21.450		
Desaturation events\hour	Cases	0.000 - 1.800	0.000	21.935	-1.168	0.243
	Control	0.000 - 0.500	0.000	18.100		
Total hypopnea\h	Cases	0.000 - 1.400	0.000	23.106	-1.369	0.171
	Control	0.000 - 0.300	0.000	18.350		
Obstructive hypopnea\hour	Cases	0.000 - 1.400	0.000	23.106	-1.369	0.171
	Control	0.000 - 0.300	0.000	18.350		
Central hypopnea\hour	Cases	0.000 - 0.000	0.000	22.000	0.000	1.000
	Control	0.000 - 0.000	0.000	22.000		
Mixed hypopnea\hour	Cases	0.000 - 0.000	0.000	22.000	0.000	1.000
	Control	0.000 - 0.000	0.000	22.000		
Respiratory Disturbance Index (RDI)	Cases	0.000 - 5.400	0.000	23.485	-1.692	0.091
	Control	0.000 - 0.900	0.000	17.100		

Comparison of Periodic Leg movements between cases and control

This study shows that there is no statistically significant difference of

Periodic leg movements in opioid dependence patients as compared with healthy controls.

Table 4.29: Case-Control comparison regarding Periodic Leg movements.

	Gr.			
	Cases	Control	T-test	
	Mean ± SD	Mean ± SD	t	P-value
PLMI	2.255 ± 0.416	2.130 ± 0.337	0.862	0.393

SECTION (3)

The factors that may affect the sleep pattern of the sample

A. Factors affecting sleep complaints:

i- Substance Abuse Pattern:

Relation between Type of Opioids abused and different sleep complaints:

In the patient group, there was no correlation between type of opioids and different sleep complaints ($p>0.05$).

Table 4.30: Relation between Types of Opioids abused and sleep complaints

Substance		Heroine		Tramadol		Chi-square	
		N	%	N	%	X^2	P-value
Difficulty in falling asleep	Yes	20	76.92	7	100.00	1.974	0.160
	No	6	23.08	0	0.00		
Interrupted sleep	Yes	14	53.85	5	71.43	0.698	0.403
	No	12	46.15	2	28.57		
Early morning awakening	Yes	13	50.00	3	42.86	0.113	0.737
	No	13	50.00	4	57.14		
Daytime Hypersomnolence	Yes	17	65.38	5	71.43	0.091	0.763
	No	9	34.62	2	28.57		
Snoring	Yes	8	30.77	2	28.57	0.013	0.911
	No	18	69.23	5	71.43		
Nightmares	Yes	10	38.46	2	28.57	0.233	0.629
	No	16	61.54	5	71.43		
Sleep talking	Yes	12	46.15	2	28.57	0.698	0.403
	No	14	53.85	5	71.43		
Sleep acid reflux	Yes	10	38.46	1	14.29	1.451	0.228
	No	16	61.54	6	85.71		

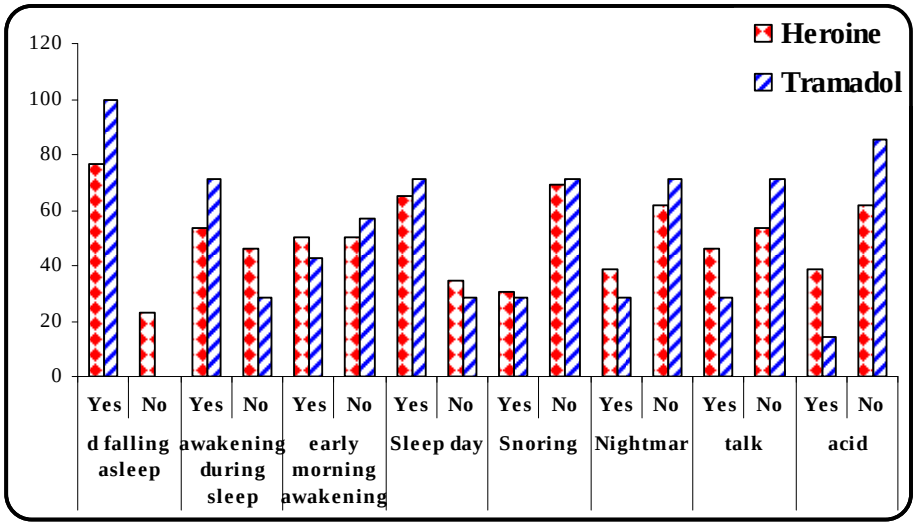

Figure 4.11: Relation between Types of Opioids abused and sleep complaints

Relation between Method of abuse of Opioids and different sleep complaints:

In our study, there was no correlation between Method of abuse and different sleep complaints ($p>0.05$).

Table 4.31: Relation between Method of abuse of Opioids and different sleep complaints

Substance		Intra venous injection		Oral		Chi-square	
		N	%	N	%	X^2	P-value
Difficulty in falling asleep	Yes	20	76.92	7	100.00	1.974	0.160
	No	6	23.08	0	0.00		
Interrupted sleep	Yes	14	53.85	5	71.43	0.698	0.403
	No	12	46.15	2	28.57		
Early morning awakening	Yes	13	50.00	3	42.86	0.113	0.737
	No	13	50.00	4	57.14		
Daytime Hypersomnolence	Yes	17	65.38	5	71.43	0.091	0.763
	No	9	34.62	2	28.57		
Snoring	Yes	8	30.77	2	28.57	0.013	0.911
	No	18	69.23	5	71.43		
Nightmares	Yes	10	38.46	2	28.57	0.233	0.629
	No	16	61.54	5	71.43		
Sleep talking	Yes	12	46.15	2	28.57	0.698	0.403
	No	14	53.85	5	71.43		
Sleep acid reflux	Yes	10	38.46	1	14.29	1.451	0.228
	No	16	61.54	6	85.71		

Relation between Life time duration of abuse of Opioids and different sleep complaints:

Moreover, there was no correlation between Life time duration of opioid abuse and different sleep complaints. ($p>0.05$)

Table 4.32: Relation between Life time duration of abuse of Opioids and sleep complaints

	Lifetime Duration of abuse in years			
	No	Yes	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Difficulty in falling asleep	7.308 ± 3.674	6.667 ± 1.751	0.413	0.683
Interrupted sleep	8.278 ± 3.893	5.786 ± 1.929	2.190	0.036
Early morning awakening	8.200 ± 4.313	6.294 ± 2.024	1.632	0.113
Daytime Hypersomnolence	6.429 ± 2.501	8.636 ± 4.411	-1.817	0.079
Sleep talking	6.923 ± 2.431	7.368 ± 3.961	-0.361	0.721
Sleep acid reflux	8.545 ± 4.344	6.476 ± 2.600	1.692	0.101

Relation between duration of abuse of Opioids in the last 30 days and different sleep complaints:

There was statistically significant correlation between duration of abuse of opioids in the last 30 days and sleep talking (p=0.025). Otherwise, there was no correlation with duration of abuse in the last 30 days and other sleep complaints.

Table 4.33: Relation between duration of abuse of Opioids in last 30 days and sleep complaints

	Duration of abuse in the last 30 days			
	No	Yes	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Difficulty in falling asleep	28.231 ±2.643	29.333 ± 1.633	-0.973	0.339
Interrupted sleep	28.778 ± 2.211	28.000 ± 2.855	0.869	0.392
Early morning awakening	28.400 ± 2.444	28.471 ± 2.625	-0.078	0.938
Daytime Hypersomnolence	28.429 ± 2.638	28.455 ± 2.339	-0.027	0.978
Sleep talking	29.615 ± 0.961	27.632 ± 2.910	2.361	0.025*
Sleep acid reflux	29.273 ± 1.679	28.000 ± 2.775	1.388	0.175

Relation between Last abstinence period and different sleep complaints:

In our study, there was no correlation between last abstinence period in months and different sleep complaints. ($p>0.05$)

Table 4.34: Relation between Last abstinence period and different sleep complaints

	Last abstinence period in Months			
	No	Yes	T-test	
	Mean± SD	Mean ± SD	t	P-value
Difficulty in falling asleep	5.500 ± 5.798	5.500 ± 5.167	0.000	1.000
Interrupted sleep	5.889 ± 5.820	5.000 ± 5.491	0.439	0.664
Early morning awakening	6.267 ± 5.663	4.824 ± 5.637	0.721	0.476
Daytime Hypersomnolence	5.286 ± 5.746	5.909 ± 5.576	-0.294	0.771
Sleep talking	5.538 ± 5.238	5.474 ± 5.985	0.032	0.975
Sleep acid reflux	7.545 ± 6.609	4.429 ± 4.833	1.526	0.138

Relation between Time Lapsed since last abstinence and different sleep complaints:

In our study, there was no correlation between Time Lapsed since last abstinence period in months and different sleep complaints. ($p>0.05$)

Table 4.35: Relation between Time Lapsed since last abstinence and different sleep complaints

	Time lasted since last abstinence in Months			
	No	Yes	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Difficulty in falling asleep	7.654 ± 6.776	6.667 ± 5.610	0.330	0.743
Interrupted sleep	8.722 ± 7.160	5.857 ± 5.362	1.248	0.222
Early morning awakening	9.000 ± 5.720	6.118 ± 7.008	1.264	0.216
Daytime Hypersomnolence	7.190 ± 6.728	8.000 ± 6.325	-0.330	0.744
Sleep talking	9.231 ± 6.821	6.263 ± 6.163	1.281	0.210
Sleep acid reflux	9.455 ± 6.639	6.429 ± 6.337	1.263	0.216

Relation between Times of abstinence and different sleep complaints:

There was statistically significant correlation between times of treatment of opioids and early morning awakening (p= 0.013). There was also statistically significant correlation between times of treatment of opioids and sleep ***acid reflux (p=0.011).*** Otherwise, there was no correlation between times of abstinence and other sleep complaints.

Table 4.36: Relation between Times of treatment and different sleep complaint.

	Times of treatment			
	No	Yes	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Difficulty in falling asleep	2.769 ± 3.089	1.833 ± 2.317	0.695	0.493
Interrupted sleep	3.333 ± 3.481	1.643 ± 1.781	1.653	0.109
Early morning awakening	3.933 ± 3.615	1.412 ± 1.502	2.634	0.013*
Daytime Hypersomnolence	1.952 ± 2.061	3.818 ± 3.995	-1.756	0.089
Sleep talking	3.615 ± 3.380	1.895 ± 2.470	1.666	0.106
Sleep acid reflux	4.364 ± 3.957	1.667 ± 1.742	2.693	0.011*

ii- Clinical and psychological status:

Relation between the severity of the Depressive State and Sleep Complaints:

In our study, there was no correlation between the severity of the Depressive State and different sleep complaints ($p>0.05$).

Table 4.37: Relation between the severity of the Depressive State and Sleep Complaints:

Beck Depression Inventory		Normal		Mild		Moderate		Severe		Chi-square	
		N	%	N	%	N	%	N	%	X^2	P-value
Difficulty in falling asleep	Yes	0	0.00	10	71.43	15	93.75	2	100.00	7.492	0.058
	No	1	100.00	4	28.57	1	6.25	0	0.00		
Interrupted sleep	Yes	1	100.00	7	50.00	11	68.75	0	0.00	4.598	0.204
	No	0	0.00	7	50.00	5	31.25	2	100.00		
Early morning awakening	Yes	0	0.00	7	50.00	9	56.25	0	0.00	3.223	0.359
	No	1	100.00	7	50.00	7	43.75	2	100.00		
Daytime Hypersomnolence	Yes	0	0.00	10	71.43	11	68.75	1	50.00	2.424	0.489
	No	1	100.00	4	28.57	5	31.25	1	50.00		
Snoring	Yes	1	100.00	4	28.57	4	25.00	1	50.00	2.900	0.407
	No	0	0.00	10	71.43	12	75.00	1	50.00		
Nightmares	Yes	1	100.00	4	28.57	6	37.50	1	50.00	2.287	0.515
	No	0	0.00	10	71.43	10	62.50	1	50.00		
Sleep talking	Yes	1	100.00	4	28.57	8	50.00	1	50.00	2.880	0.411
	No	0	0.00	10	71.43	8	50.00	1	50.00		
Sleep acid reflux	Yes	1	100.00	5	35.71	5	31.25	0	0.00	3.067	0.381
	No	0	0.00	9	64.29	11	68.75	2	100.00		

Relation between the severity of the Anxiety State and Sleep Complaints:

In our study, there was no correlation between the severity of the Anxiety State and different sleep complaints. ($p>0.05$)

Table 4.38: Relation between the severity of the Anxiety State and Sleep Complaints

Manifest Anxiety Scale		Mild		Moderate		Severe		Chi-square	
		N	%	N	%	N	%	X^2	P-value
Difficulty in falling asleep	Yes	11	68.75	15	93.75	1	100.00	3.590	0.166
	No	5	31.25	1	6.25	0	0.00		
Interrupted sleep	Yes	9	56.25	9	56.25	1	100.00	0.760	0.684
	No	7	43.75	7	43.75	0	0.00		
Early morning awakening	Yes	5	31.25	10	62.50	1	100.00	4.224	0.121
	No	11	68.75	6	37.50	0	0.00		
Daytime Hypersomnolence	Yes	10	62.50	11	68.75	1	100.00	0.656	0.720
	No	6	37.50	5	31.25	0	0.00		
Snoring	Yes	6	37.50	3	18.75	1	100.00	3.704	0.157
	No	10	62.50	13	81.25	0	0.00		
Nightmares	Yes	5	31.25	6	37.50	1	100.00	1.940	0.379
	No	11	68.75	10	62.50	0	0.00		
Sleep talking	Yes	7	43.75	6	37.50	1	100.00	1.527	0.466
	No	9	56.25	10	62.50	0	0.00		
Sleep acid reflux	Yes	7	43.75	3	18.75	1	100.00	4.313	0.116
	No	9	56.25	13	81.25	0	0.00		

Relation between the Presence of Personality disorder and Sleep Complaints:

Table (4.39) shows that the presence of personality disorder [Diagnosed by using SCID II] has no direct correlation with different sleep complaints (p.0.05).

Table 4.39: Relation between the Presence of Personality disorder and Sleep Complaints

		Personality Disorders							
		No		Yes		Total		Chi-square	
		N	%	N	%	N	%	X^2	P-value
Difficulty in falling asleep	Yes	12	36.36	15	45.45	27	81.82	0.061	0.805
	No	3	9.09	3	9.09	6	18.18		
Interrupted sleep	Yes	8	24.24	11	33.33	19	57.58	0.203	0.653
	No	7	21.21	7	21.21	14	42.42		
Early morning awakening	Yes	9	27.27	7	21.21	16	48.48	1.460	0.227
	No	6	18.18	11	33.33	17	51.52		
Daytime Hypersomnolence	Yes	8	24.24	14	42.42	22	66.67	2.200	0.138
	No	7	21.21	4	12.12	11	33.33		
Sleep talking	Yes	4	12.12	10	30.30	14	42.42	2.795	0.095
	No	11	33.33	8	24.24	19	57.58		
Sleep acid reflux	Yes	5	15.15	6	18.18	11	33.33	0.000	1.000
	No	10	30.30	12	36.36	22	66.67		

B. Factors affecting Polysomnography:

i- Substance abuse pattern:

Relation between Type of Opioids abused and Polysomnography findings:

In the patient group, there was no correlation between type of opioids and polysomnography findings ($p>0.05$).

Table 4.40: Relation between Type of Opioids abused and Polysomnography findings.

	Substance			
	Heroine	Tramadol	T-test	
	Mean ± SD	Mean ± SD	t	P-value
SL	47.519 ± 14.203	43.214 ± 7.952	0.764	0.450
SE	43.025 ± 11.095	41.361 ± 9.856	0.359	0.722
Stage I	16.784 ± 3.392	17.254 ± 5.874	-0.276	0.784
Stage II	54.973 ± 3.157	54.483 ± 4.285	0.338	0.737
Stage III	3.301 ± 1.525	2.396 ± 2.041	1.298	0.204
Stage IV	2.496 ± 1.306	2.580 ± 1.976	-0.135	0.894
SWS %	5.797 ± 2.394	5.041 ± 3.900	0.645	0.524
REM %	21.687 ± 4.963	23.073 ± 4.701	-0.663	0.512
REMD	20.608 ± 0.942	21.014 ± 0.937	-1.014	0.318
REM L	62.273 ± 3.143	62.357 ± 4.837	-0.056	0.956
Index	19.246 ± 2.325	19.500 ± 1.381	-0.274	0.786
PLMI	2.312 ± 0.437	2.043 ± 0.251	1.549	0.132

Relation between Method of abuse of Opioids and Polysomnography findings:

In the patient group, there was no correlation between Method of abuse and polysomnography findings ($p>0.05$).

Table 4.41: Relation between Method of abuse of Opioids and Polysomnography findings

	Route of Abuse			
	Intra venous injection	Oral	T-test	
	Mean ± SD	Mean ± SD	t	P-value
SL	47.519 ± 14.203	43.214 ± 7.952	0.764	0.450
SE	43.025 ± 11.095	41.361 ± 9.856	0.359	0.722
Stage I	16.784 ± 3.392	17.254 ± 5.874	-0.276	0.784
Stage II	54.973 ± 3.157	54.483 ± 4.285	0.338	0.737
Stage III	3.301 ± 1.525	2.396 ± 2.041	1.298	0.204
Stage IV	2.496 ± 1.306	2.580 ± 1.976	-0.135	0.894
SWS %	5.797 ± 2.394	5.041 ± 3.900	0.645	0.524
REM %	21.687 ± 4.963	23.073 ± 4.701	-0.663	0.512
REMD	20.608 ± 0.942	21.014 ± 0.937	-1.014	0.318
REM L	62.273 ± 3.143	62.357 ± 4.837	-0.056	0.956
Index	19.246 ± 2.325	19.500 ± 1.381	-0.274	0.786
PLMI	2.312 ± 0.437	2.043 ± 0.251	1.549	0.132

Relation between Life time duration of abuse of Opioids and Polysomnography findings:

Moreover, there was no correlation between Life time duration of opioid abuse and Polysomnography findings. ($p>0.05$)

Table 4.42: Relation Between lifetime duration of abuse and polysomnography findings

	Duration of abuse in years	
	r	P-value
SL	0.108	0.549
SE	-0.191	0.288
Stage I	-0.201	0.262
Stage II	0.189	0.293
Stage III	0.066	0.715
Stage IV	-0.050	0.784
SWS %	0.012	0.945
REM %	0.080	0.657
REMD	-0.310	0.080
REM L	0.129	0.473
Index	-0.024	0.893
PLMI	0.219	0.220

Relation between duration of abuse of Opioids in the last 30 days and Polysomnography findings:

There was statistically significant correlation between duration of abuse of opioids in the last 30 days and

periodic limb movements (p=0.016). Otherwise, there was no correlation with duration of abuse in the last 30 days and other polysomnography findings.

Table 4.43: Relation between duration of abuse in 30 days and polysomnography

	Duration of abuse in the last 30 days	
	r	P-value
SL	0.155	0.388
SE	-0.021	0.909
Stage I	0.024	0.896
Stage II	0.182	0.311
Stage III	0.035	0.847
Stage IV	-0.161	0.370
SWS %	-0.079	0.664
REM %	-0.177	0.324
REMD	-0.074	0.681
REM L	-0.087	0.630
Index	0.117	0.517
PLMI	0.415	0.016*

Relation between Last abstinence period and Polysomnography findings:

There was statistically significant correlation between duration of last abstinence period and REM latency (p=0.033). Otherwise, there was no correlation between last abstinence period and other polysomnography findings.

Table 44.4: Relation between last abstinence period and polysomnography

	Last abstinence period in Months	
	r	P-value
SL	0.188	0.294
SE	-0.310	0.079
Stage I	-0.064	0.722
Stage II	0.247	0.166
Stage III	0.179	0.319
Stage IV	0.066	0.714
SWS %	0.138	0.442
REM %	-0.064	0.725
REM Density	-0.012	0.947
REM Latency	-0.372	0.033*
Index	0.155	0.389
PLMI	0.316	0.073

Relation between Time Lapsed since last abstinence and Polysomnography findings:

In our study, there was no correlation between Time Lapsed since last abstinence period in months and Polysomnography findings. ($p>0.05$)

Table 4.45: Relation between Time Lapsed since last abstinence and Polysomnography findings.

	Time lasted since last abstinence in Months

	r	P-value
SL	0.015	0.934
SE	-0.044	0.806
Stage I	0.172	0.339
Stage II	0.149	0.408
Stage III	0.026	0.884
Stage IV	-0.027	0.881
SWS %	-0.004	0.982
REM %	-0.089	0.623
REMD	-0.163	0.365
REM L	-0.182	0.310
Index	-0.089	0.622
PLMI	0.105	0.559

Relation between Times of Treatment and Polysomnography findings:

In our study, there was no correlation between times of treatment and Polysomnography findings (p>0.05).

Table 4.46: Relation between Times of Treatment and Polysomnography findings

	Times of treatment	
	r	P-value
SL	0.205	0.254
SE	-0.272	0.126
Stage I	-0.174	0.332

Stage II	0.306	0.083
Stage III	-0.011	0.949
Stage IV	0.002	0.993
SWS %	-0.011	0.952
REM %	0.053	0.771
REMD	-0.119	0.511
REM L	-0.098	0.588
Index	-0.075	0.678
PLMI	0.109	0.545

ii- Clinical and psychological status:

Relation between the severity of the Depressive State and Polysomnography findings:

There was high statistically significant correlation between severity of depressive state as measured by Beck Depression Inventory in cases and Stage 3of sleep (p=0.001).

There was high statistically significant correlation between severity of depressive state as measured by Beck Depression Inventory in cases and slow wave sleep percentage (p=0.014).

Other than that, there was no correlation between the severity of the Depressive State and other polysomnography findings ($p>0.05$).

Table 4.47: Relation between the severity of the Depressive State and Polysomnography findings.

	Beck			
	Mild	Moderate	T-test	
	Mean ± SD	Mean ± SD	t	P-value
SL	48.750 ± 16.337	44.938 ± 9.490	0.794	0.434
SE	42.585 ± 12.342	43.623 ± 9.404	-0.261	0.796
Stage I	15.876 ± 3.804	17.596 ± 4.325	-1.149	0.260
Stage II	53.796 ± 3.023	56.101 ± 3.572	-1.893	0.069
Stage III	4.144 ± 1.657	2.175 ± 1.166	3.801	0.001*
Stage IV	2.636 ± 1.387	2.238 ± 1.506	0.750	0.460
SWS %	6.851 ± 2.665	4.383 ± 2.464	2.635	0.014*
REM %	22.272 ± 7.283	21.677 ± 2.044	0.314	0.756
REMD	20.436 ± 1.072	20.794 ± 0.827	-1.031	0.311
REM L	62.493 ± 4.275	62.294 ± 3.074	0.148	0.884
Index	19.750 ± 2.596	18.763 ± 1.673	1.254	0.220
PLMI	2.364 ± 0.465	2.106 ± 0.319	1.791	0.084

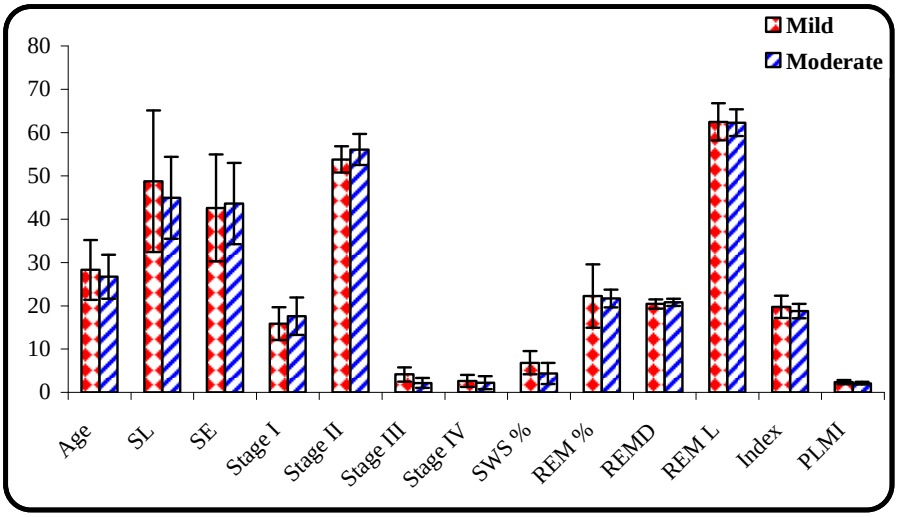

Figure 4.12: Relation between the severity of the Depressive State and Polysomnography findings.

Relation between the severity of the Anxiety State and Polysomnography findings:

In our study, there was no correlation between the severity of the Anxiety State and polysomnography findings ($p>0.05$).

Table 4.48: Relation between the severity of the Anxiety State and Polysomnography findings

	Manifest Anxiety Scale			
	Mild	Moderate	T-test	
	Mean ± SD	Mean ± SD	t	P-value
SL	49.844 ± 15.909	42.594 ± 8.754	1.597	0.121
SE	43.269 ± 11.828	42.336 ± 10.173	0.239	0.813
Stage I	18.081 ± 4.406	15.792 ± 3.264	1.670	0.105
Stage II	54.469 ± 3.027	55.193 ± 3.808	-0.595	0.557
Stage III	3.076 ± 1.895	3.129 ± 1.499	-0.088	0.931
Stage IV	2.013 ± 1.387	2.991 ± 1.402	-1.985	0.056
SWS %	5.089 ± 2.874	6.149 ± 2.640	-1.087	0.286
REM %	21.116 ± 6.041	22.813 ± 3.543	-0.969	0.340
REMD	20.850 ± 0.992	20.544 ± 0.926	0.903	0.374
REM L	61.431 ± 2.681	62.919 ± 4.063	-1.222	0.231
Index	19.613 ± 2.573	19.081 ± 1.692	0.690	0.496
PLMI	2.350 ± 0.475	2.150 ± 0.348	1.359	0.184

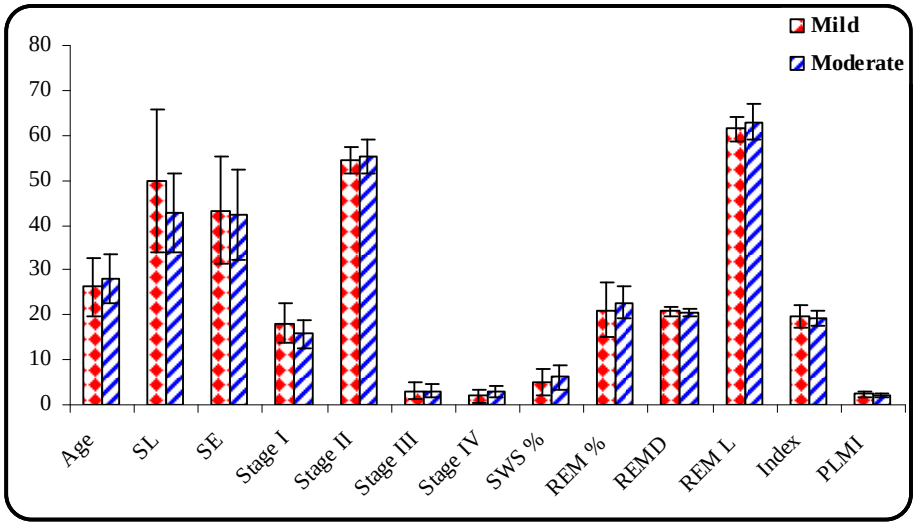

Figure 4.13: Relation between the severity of the Anxiety State and Polysomnography findings.

DISCUSSION

According to **WHO/UNODC** report published in **2004**, the Middle East is one of the areas where opioid use and related problems are predominant. This can be verified revising statistics published by Egyptian ministry of health denoting that 9.8 % of the Egyptian population abused psychoactive substance at some point of their life **(Elghoz et al., 2006)**. Inspite of this percentage, substance abuse patients form only 3% of the outpatient percentage as well as 4% of the inpatient percentage of the patients seeking psychiatric advice in mental health facilities **(Ghanem et al., 2004)**. Opioid abuse and dependence is the highest prevalent disorder among patients seeking help in substance abuse clinics in Egypt **(Khalil et al., 2008).**

The complexity of opioid abuse problem rises from many factors. There is a diversity of forms of the substance itself starting from opium itself and including medications such as Codeine and Morphine reaching totally illegal substance such as heroine. Moreover, there are different methods of abusing opioids including the highly dangerous and infectious intra venous injection. Although opioid is not the most commonly used substance of abuse yet it may be on the top of the list regarding hazardous consequences of dependence **(Winstock & Strang, 2000).**

The complexity of opioid dependence led to diversity of pharmacological treatment. Opioid is the only class of substance of abuse that has available agonist therapy (Methadone), partial agonist therapy (Bupernorphine) and antagonist therapy (Naltrexone). In addition to these agents, there are some medications that help in treating various stages of opioid dependence treatment yet not pharmacologically related to opioids (e.g. Lefoxidine) **(Stahl, 2008).**

All these factors made studying any phenomenon related to opioid dependence a complicated task. This is obvious while revising researches related to sleep profile in opioid dependent patients. There is scarcity of researches in this field although some are dated since early seventies **(Martin et al., 1973).** Moreover, these researches show differences in subjects' selection especially regarding the phase of opioid dependence (acute intoxication, early withdrawal, late withdrawal or long term maintenance). Another factor that is markedly changeable all through these studies is the type of therapy of the patients. The spectrum of therapy included placebo, methadone, Naltrexone or even no therapy at all. All these factors resulted in the paucity of human data available regarding

the effects of short and long-term opioid use on sleep architecture (**Wang & Teichtahl, 2007)**.

Clinical Sleep Complaints of the sample:

Results of the present study show that 81% of the studied group showed initial insomnia, 57% of the studied group had interrupted sleep and 48% of them had late insomnia. Also in the patients group, 67% suffered from day time somnolence, 42% suffered from sleep talking and 33% of them suffered from sleep acid reflux. All these complaints showed statistically significant difference from the control group.

On the other hand, comparing case group to control subjects showed no statistical significance regarding snoring, experiencing nightmares as well as nocturnal enuresis.

The mean night sleeping hours of cases was 6.6 hours SD ± 1.45 and the subjective sleep onset latency was 47.5 minutes SD ± 13.97. Both values were of statistical significant difference when compared to those of control.

Studying sleep profile of the patients started with assessment of the patient sleep complaints. Large percentage of patients suffered from clinical symptoms regarding their sleep. The most common complaint was Initial Insomnia (Difficulty in falling asleep). The current study showed that 81% of the opiate dependant patients in the studied group suffered from initial insomnia.

The current results confirm those of ***Oyefesso et al 1997*** who found that initial insomnia was prevalent in a rate of 83% of examined opiates dependant patients undertaking methadone detoxification.

On the other hand, his data indicated that initial insomnia was prevalent in control group with percentage 48% which was higher than the current study control group prevalence rate (10%). This difference in rates of initial insomnia in control group may be related to the group size (10 in the current study in comparison to 25) as well as using different tools of assessment of subjective sleep complaints as he used St Mary's Hospital (SMH) Sleep Questionnaire. It is worth mentioning that both studies revealed statistically significant difference between cases and control subjects regarding initial insomnia.

The percentage of Initial Insomnia in the current case group differs from that of the study conducted by ***Mekky et al 2009*** as the percentage of regular opiate users suffering from this complaint was 64%. Rates of this complaint were lower in his results putting in consideration his larger sample size (50 cases of opioid use) as well as including all forms of regular opioid use (not specifying dependence) as well as not specifying certain time of interview in relation to opioid use (intoxication or withdrawal).

In the current study, the mean subjective Sleep Onset Latency (SOL) of cases was 47.5 minutes while control was 17.8 minutes. The current results are close to those of ***Oyefesso et al 1997*** who found that the median sleep onset latency of opiate addicts was 45 minutes and that of control was 15 minutes. Both studies found high statistical significance between case and control group regarding Sleep Onset Latency.

Yet, the current study results differ from that of ***Besweck et al., 2003.*** This group of scientists compared some subjective sleep parameters following Methadone and Lefoxidine detoxification. 2 weeks after the detoxification, Subjective mean sleep latency was assessed and results were about 100 minutes. Many differences

between the current study design and that of ***Besweck et al*** can explain this difference. First, the sample size of ***Besweck et al*** study was much larger (118 subject). Moreover, although their study was designed for comparing methods of detoxification of opioid dependence, the majority of his sample used other substances of abuse 30 days before undergoing detoxification (e.g. 59% of the sample used cocaine for 14 days within the last 30 days before detoxification). Nevertheless, assessment of the sleep complaints was done using a self-report sleep questionnaire which was not tested for validity or reliability. Finally, using diazepam in treating withdrawal symptoms and not excluding patients suffering from anxiety and depression were other reasons for explaining such difference.

Regarding mean night sleep time, the current study showed 6.65 hours. Close results were found in the study conducted by ***Burke et al., 2008.*** They conducted their study on patients entering treatment and still using opioids together with other substances and found the mean hours slept every night in the studied sample (113 patients) equals 6.3 hours. But more interesting data was found in this study as they found that 71 of these patients used substances to increase and decrease sleepiness with mean sleeping hours 6.3 while 28 used substance to increase their

sleepiness with mean sleeping hours 6.2. Only 10 patients did not use substance to increase or decrease their sleepiness and had mean hours slept at night 6.7 hours.

Another close result was that of ***Mitchell et al*** study in ***2004.*** They found the mean sleeping hours of opioid dependent patients on maintenance Methadone therapy was 7.3 hours while when the patients were shifted to maintenance Slow-Release Oral Morphine (SROM) therapy the mean sleeping hours was 6.2 hours putting in consideration their smaller sample size (18 cases) as well as the presence of two types of opioid agonist therapy which could explain this difference.

There was a more obvious difference and other studies regarding duration of sleep. ***Oyefesso et al 1997*** found the median sleeping hours to be 5.3 hours while ***Besweck et al 2003*** found the mean total sleep to be 5.6 after 2 weeks of Lefoxidine Detoxification and 4.8 following Methadone Detoxification. The most prominent difference between the current study and these two studies is the type of detoxification and the timing of the study.

Another sleep complaint was proved by the current study was interrupted night sleep as there was statistically significant difference regarding this complaint between

case and control subjects. The prevalence of this complaint in cases was 57.5 percent while in control was 10 %. The mean regarding their number of awakening was 1.4 times.

Oyefesso et al 1997 also found statistically significance between cases and controls regarding this complaint yet with different percentages (88% in cases while 30.8% in control) with median of times of nocturnal awakenings equals 2.

Besweck et al 2003 also reported the presence of nocturnal awakening in patients undergoing detoxification using Lefoxidine and Methadone. According to their self report questionnaire, they calculated time of nocturnal awakening after 2 weeks of detoxification to be about 30 minutes for patients using Methadone and 90 minutes for those who underwent Lefoxidine detoxification.

While examining various aspects of sleep in opioid dependant patients, the current study found statistically significant difference between them and control subjects regarding Late Insomnia (Undesired Early Morning Awakening) with percentage of 48.4%. No recent studies were found specifically analyzing this complaint in opioid dependent patients. It is worth mentioning that ***Oyefesso et al 1997*** found that 80% of their sample representing cases of opioid dependent patients suffered from

Inadequate Sleep Quantity in comparison to 30.8% of control subjects. This difference was of statistical significance.

The current study found statistically significant difference between case and control subjects regarding daytime somnolence with higher incidence in case group. The current findings are consistent with previous studies indicating increased day time sleepiness of opioid dependant patients in comparison to control. However, in most of these studies, the researchers used Epworth Sleepiness Scale (ESS) designed by ***Johns, 1991***. The ESS is an 8-item questionnaire that measures self-reported daytime sleepiness across common situations. Scores range from 0 (low sleepiness) to 24 (high sleepiness), with scores of higher than 10 indicative of excessive daytime sleepiness.

Although the studies join their opinion in the higher incidence of day time sleepiness in opioid dependant patients than control, they differ in the severity of this complaint. In the current study, this complaint was assessed by the sleep questionnaire through questions describing the subjective feelings of somnolence of subjects and measuring the hours slept in daytime by them. 67% of the current studied group suffered from this complaint with mean sleeping hours in daytime 1.4 hthe current.

Peles et al 2009 found high day time sleepiness in methadone maintained opioid dependant patients as concluded by their mean ESS scores (12 ± 4.9 for high dose methadone maintenance and 13.1 ± 4.9 for low dose).

Whereas ***Wang et al 2008*** found patients on methadone maintenance had statistically significant increased daytime sleepiness (as measured by ESS), compared to the control group, although the average ESS was within the clinical normal range (7.1 ± 5). The same result was found in the research done by ***Burke et al 2008*** where the mean ESS score for patients was 7.8 ± 5.2 while that of control was 5.9 ± 2.2 which was also a statistically significant difference.

As for studying various phenomenon that occur during sleep, Sleep Talking was the highest occurring phenomenon in opioid dependent cases with prevalence rate 42.4 % and with statistically significant difference when compared to control subjects.

Sleep talking is associated with brief arousals from stages I and II NREM sleep ***(Shneerson, 2005).*** Applying this scientific fact can explain these as the findings of the polysomnography regarding the subjects of the current

study show prolonged stage I and II of NREM sleep with increased arousal.

This percentage differs from that of ***Mekky et al 2009*** as the percentage of Sleep Talking in their study was 10% and the study contained no control group.

Another phenomenon that showed statistically significant difference between case and control groups in the current study is Sleep-related gastroesophageal reflux. During sleep, the lower oesophageal sphincter tone is reduced during sleep, and gastric fluid can reflux into the oesophagus, particularly in the supine position. The tone of the upper oesophageal sphincter (cricopharyngeus) may also fall during sleep, allowing oesophagopharyngeal reflux ***(Shneerson, 2005)***. Moreover, the case subjects of the current study had risk factors of gastroesophageal reflux including cigarette smoking, excessive drinking of tea and coffee **(Haber, 2003).**

Snoring prevalence rate in the current case subjects was 30 %. This is confirmed with the results of ***Mekky et al 2009*** who mentioned that the prevalence of snoring in his sample was 32%.

There was no statistical difference between cases and control groups in the current study regarding the

phenomenon of snoring. This data joined those published by ***Burke et al 2008*** comparing opioid dependant cases with normative sample and finding no significant difference regarding snoring.

Although the assessment of sleep complaints in the current study did not include a specific item of the patients' satisfaction regarding their sleep, yet it is obvious from the multiple complaints of the case subjects that they have various kinds of sleep disturbance. This indicates that most of the opioid dependent patients subjectively suffer from abnormal pattern of sleep as manifested by their complaints.

This is consistent with the results of most of the studies assessing opioid dependent patients' satisfaction regarding sleep. ***Oyefesso et al 1997*** found that 88% of their sample representing cases of opioid dependent patients suffered from Inadequate Sleep Quantity in comparison to 46.2% of control subjects. This difference was of statistical significance. Recently, Burke ***et al 2008*** found statistically significant difference comparing opioid dependant cases with normative sample regarding sleep disturbances in general using *Medical Outcomes Study Sleep Questionnaire,* a self-report assessment of sleep functioning over the past month.

Sleep architecture in opioid dependant patients:

Studying the sleep profile of opioid dependent patients needs more than analyzing the subjective complaints of the patients. An objective tool of studying sleep should be used side by side with analyzing various complaints and using various questionnaires. This tool is best represented in the Polysomnogram. It gives a deeper look to the nature of sleep of these patients. Moreover, it explores the nature of difference between the sleep pattern of opioid dependant patients in comparison to normal control. Unfortunately, and inspite of the important medical implications of studying effect of opioid on sleep, human studies dealing with changes in sleep architecture related to chronic opioid use are extremely rare **(Moore & Dimsdale, 2002).**

In ***2007, Wang and Teichtahl*** published an important review of publications analyzing the studies available on PUBMED published between 1966 and 2005 investigating sleep and respiration during sleep in adult humans chronically using opioids. They found important data in the form of the following:

- The total number of studies is 18 study with only 5 studies since 1996
- Only four (22%) of the studies had sample size >10.

- Only 6 studies (33%) had normal subjects as control group for comparison. However, the normal subjects and patients were matched for age and BMI in only two studies.
- Only 5 studies (28%) investigated respiration during sleep.

All these data shows the importance of the current study and the difficulty regarding comparing the current work with others'.

As for the present study results concerning sleep architecture of opioid dependant cases and their comparison to healthy control subjects, there were many important obser5vations. Regarding sleep latency, sleep efficiency and arousal index, there were marked affection in cases. That is to say that there was significant lengthening of sleep latency, significant diminish of sleep efficiency, and significant rise of arousal index in opioid dependant patients as compared to healthy controls.

Comparing NREM parameters of cases and control subjects showed that there is a significant increase in both stage 1 and stage 2 of NREM sleep in opioid dependence patients as compared to healthy controls, while stages 3 and 4 as well as SWS% are significantly reduced . On the other hand, comparing REM sleep components of opioid dependent patients to control subjects showed no

statistically significant difference regarding REM % of total sleep time, REM density as well as REM latency. The same finding was related to respiratory variables after studying these variables respiratory variables in opioid dependence patients as compared with healthy controls. There was no statistically significant difference regarding sleep apnea parameters whether central, obstructive or mixed.

Comparison of Sleep latency, sleep efficiency and arousal index

The current data revealed that there is a statistically significant increase regarding the sleep latency of case subjects in comparison to control subjects when recorded by polysomnography. The mean sleep latency of opioid dependant cases was 46.6 ± 13.1 minutes compared with 18.8 ± 2.6 minutes in control subjects.

The current findings are consistent with previous studies indicating increase of sleep latency in opioid dependant patients. ***Lukas et al 1996*** showed a statistically significant increase in sleep latency comparing dually dependent patients on opioid and cocaine to normal subjects. The study was conducted 5-7 days after detoxification as the patients were totally free from drugs as. The mean of sleep latency was 50.5± 30.4 for cases and 13.7± 12.7 for control. Although this study was conducted on patients dependant on two substances (opiates and cocaine) yet it gives the closet results to the current study regarding the sleep latency. The reason for this similarity is assumed to be performing the polysomnogram study after a period of detoxification in a drug free case sample and receiving no medication.

Another study by ***Staedt et al 1996*** found increased sleep latency in opioid dependant patients whether on Methadone Maintenance therapy or Naltrexone therapy in comparison to normal control. The mean of sleep latencies were 19.5±12.1 for the Methadone group, 15.04±6.5 minutes to the Naltrexone group and 13.3±9.5 minutes for the control. Unfortunately, the researchers did not analyze the difference between the 3 groups to determine if this increase in sleep latency was statistically significant or not.

The study design of ***Staedt et al 1996*** shows some similarities to the current study as subjects were not allowed to use alcohol during the study and the control sample was formed of 10 subjects. However, many differences in the methodology also exist. The long duration of maintenance therapy with means of 33 months for Methadone and 10 months for Naltrexone, the presence of cases abusing cocaine, cannabinoids as well as benzodiazepines during the study as well as absence of randomization of the sample are the main points of differences.

On the other hand, some studies did not find a statistical significant difference between Sleep Latency in opioid dependent cases and control subjects. For example, ***Teichtahl et al., 2001*** performed polysomnographic studies

on 10 methadone maintenance opioid dependant patients, compared them to 9 normal control subjects and found no statistical difference regarding sleep latency (sleep onset latency was 7.7 ± 11.9 for cases and 6.8 ± 6.3 for controls). It is worth mentioning that the difference in sample size and studying opioid dependant patients with at least 2 months methadone maintenance treatment could be the explanation of the difference between this study and the current study.

Another recent study that does not confirm with the current results regarding sleep latency is that study published by ***Wang et al., 2005.*** They found no statistical difference regarding sleep latency between MMT opioid dependant patients and control subjects (mean sleep latency for cases is 9.7 ± 9.1 and for 13.9 ± 17.4. Although this study was performed on a relatively large sample (50 patients and 20 controls) yet there are some limitations concerning the results. Large percentage of the cases had another substance or medication that affects the sleep architecture while performing the study (38% Benzodiazepines, 38% Cannabinoids and 14% Antidepressants). Having the patients on MMT for at least 2 months is another reason that explains the difference in results than the current study.

In the current study, there was marked decrease in Sleep Efficiency regarding opioid dependant patients (mean sleep efficiency of cases was 42.7% ± 10.7) and there was a statistically significant difference when compared to control (mean sleep efficiency of control was 91.5% ± 2.5).

This finding is close to the result of ***Lukas et al 1996*** as they also found statistical difference between cases of cocaine and opiates dependence when compared to control subjects regarding sleep efficiency. Although the average sleep efficiency indexes were 70-72% yet they stated that many patients had indices around 50% and one patient had sleep efficiency index of 13%.

Teichtahl et al 2001 also found statistical significance when comparing the sleep efficiency percentage of MMT opioid dependant patients and controls. However, the mean percentage of sleep efficiency in cases was higher than the current study (83% ± 9).

Two recent studies show decrease sleep efficiency percentage in opioid dependent patients yet in absence of comparison to control subjects. The first was performed by ***Peles et al*** in ***2009*** on 44 MMT opioid dependant patients and concluded that their average sleep efficiency percentage was 73%. The second study refer to ***Sharkey et***

al 2009 who performed polysomnographic studies for 2 groups of opioid dependant MMT patients (group 1 for 1 night and group 2 for 2 nights) and had the results of sleep efficiency of means 82.9% ± 9.5 and 85.0% ± 9.6 for group 1 and 2 respectively. Although ***Sharkey et al 2009*** considered these values as decreased sleep efficiency compared to normal figures, they explained the relative increase of their results higher than previous studies to their use of home polysomnography where patients performed the polysomnogram at their homes using portable devices and thus minimizing the effect of change of environment on sleep that was present in the previous studies.

In the contrary to these studies, ***Wang et al 2005*** found no statistical difference between cases of opioid dependence on MMT when compared to control subjects regarding sleep efficiency. Limitations of this study have been mentioned before.

The difference of value of sleep efficiency percentage between the current study and most of the other studies can be explained by the fact that the current case subjects were toxicologically free and received no medication at the time of the study while cases in other studies were either on Methadone Maintenance Treatment, or abusing substance. Another difference is that in the current study

included single night polysomnography while most of other studies performed more than one night polysomnography which causes more adaptation to the environment and increases the sleep efficiency.

The current study also showed statistically significant difference between the cases of opioid dependence and control subjects regarding Arousal Index. The mean arousal index for cases was 19.3±2.1 while control subjects have mean 5.4±2.0.

The current study confirms with that of ***Staedt et al., 1996*** who found statistically significant difference regarding arousal index between opioid addicts on Naltrexone therapy and those on MMT. The mean arousal indexes were 1.93 and 8.6 in patients on Naltrexone and Methadone therapy respectively.

Other 2 studies that differ in their results from the current study are that of ***Wang et al., 2005*** and ***Teichtahl et al., 2001***. Both did not find statistical significant difference when comparing the Arousal Index of MMT opioid dependant patients and controls.

Studying NREM Sleep:

Polysomnogram was used in the current study to examine the components of NREM sleep as a part of

studying sleep profile of opioid dependant patients. Comparing these findings to control subjects' data gives an idea of the effect of chronic opioid use on sleep pattern even after abstinence for weeks.

In the current study , it was concluded that there is a significant increase in both stage 1% and stage 2 % of NREM sleep in opioid dependence patients as compared to healthy controls, while stages 3 % and 4 % as well as SWS% are significantly reduced. These differences were of statistical significance.

In comparing the current data to other studies investigating NREM sleep in opioid dependent cases versus control subjects, we detected that nearly all studies concluded discrepancy concerning the sleep profile of cases from controls. However, there was a diversity of data regarding the exact nature of this difference.

Shaw et al 2005, found very close results to the current study when examining sleep profile of 7 volunteers once under baseline conditions and another time after injection of Morphine. Results showed statistically significant increase in stage 2% of sleep as well as statistically significant decrease in SWS % when comparing sleep study findings before and after Morphine injections.

The only different result from NREM characteristics in the current study was regarding Stage 1% where they found no statistical difference in this stage between pre and post opioid injection sleep records while it was significantly higher in cases group of the current study.

Similar results were concluded by ***Teichtahl et al 2001*** as he found statistical significant increase in stage 2% in opioid dependant patients on MMT when compared to control subjects. They also found statistically significant decrease in SWS % and found an increase in stage 1% yet it was not statistically significant.

In the same context, ***Lukas et al 1996*** found statistically significant decrease in stage 3 and stage 4 percentages in dually dependant opiates and cocaine participants in comparison to control group. They also found increase in stage 1 and stage 2 percentages yet with no statistical significance.

Another study conducted by ***Staedt et al., 1996*** revealed marked decrease in SWS time in opioid dependant patients whether on MMT or Naltrexone therapy in comparison to normal control (methadone 35.51 ± 34.48 min, Naltrexone 44.39 ± 22.04 min, controls 86.51 ± 22.04 min) ,but no statistical analysis was performed for this result.

In the current study, the percentage of stage 1 of sleep of cases was of mean 16.9 ± 3.9; stage 2% mean was 54 ± 3 stage 3% was 3.1 ± 1.7 stage 4% 2.5 ± 1.4 while SWS percentage of cases was of mean 5.6 ± 2.7.

These results that shows increase in both stage 1 and 2% as well as decrease of SWS (stage 3 and 4) comes with the results of some studies of sleep profile in opioid dependant patients inspite of lacking the presence of comparable control.

One of these studies is that of ***Alattar & Scharf, 2009*** who performed polysomnogram study for 6 patients receiving sustained release opioids for their chronic pain condition and found that stage 2% mean was 66 ± 18 while SWS percentage of cases was of mean 3.1 ± 4.7.

Peles et al 2009 reached the same conclusion examining the sleep profile of patients on MMT whether

having chronic or non chronic pain. They found prolongation of stage 2% (57.4 ± 19 for patient with chronic pain and 66.6 ± 14.2 for patients with non chronic pain). They also found decrease in SWS % (6.6±8 and 7.5±7.9 for chronic pain group and non chronic pain group respectively).

The hallmark finding in all these studies is disruption in NREM sleep in the form of decrease of Slow Wave Sleep percentage (Stage 3% and Stage 4%). This may be the reason for the consequent increase in Stage 2%. Reviewing the literature carries the possible explanation of this phenomenon. Many studies tried to explain the mechanism and site of action of opioids in the process of sleep. Recent studies attribute the opioids role in sleep–wake regulation by the direct central opioid inputs to the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus. The VLPO was discovered to have μ and κ receptors which are likely involved in mediating the hypnotic response to high levels of opioid analgesics **(Greco et al., 2008).**

It is worth mentioning that VLPO plays a crucial role in initiating and maintaining NREM sleep (to the extent that it is considered the main switch of NREM sleep) **(Kryger et al., 2005)**. Furthermore, opioid dependence cause severe disturbance in the endogenous opioid system **(Martin et al., 2007)**. Therefore, it is expected that opioid dependent patients will have disruption in the NREM sleep that is mediated by many neurotransmitters including endogenous opioid system which is disrupted in these patients.

This was not identical to what ***Walker et al 2007*** concluded. Although they found statistically significant increase in stage 2% in patients chronically using opioid compared to another group of patients not using opioids, they found no statistically significant difference between the 2 groups concerning stage 3 and stage 4 percentages. And to the contrary to the current results, they found statistically significant decrease regarding stage 1% in patients chronically using opioids in comparison to those not using opioids. But the difference in the methodology of the research can explain such a difference. ***Walker et al., 2007*** cases (chronically using opioids) and control groups (not using opioids) consisted of patients suffering from chronic painful conditions and medical disorders (including hypertension, arrhythmias, gastroesophageal

reflux disorder, hypothyroidism as well as depression). Moreover, both groups were using various medications including Ibuprofen, Statins, Benzodiazepines as well as Gabapentin. Finally, the study was conducted while the case group was still using opioids.

Wang et al., 2008 showed the same pattern of results like ***Walker et al., 2007*** while examining the NREM sleep of opioid dependent patients compared to control subjects. They statistically significant decrease of stage 1% as well as statistically significant increase in stage 2% in opioid dependant patients on MMT compared to control group. It is worth mentioning that this group of scientists did not find statistically significant difference between the 2 groups concerning stage 3 and stage 4 percentages. The difference in the results between this study and the current study may be related to the selection of the case group in ***Wang et al 2008*** study as the patients group were on opioid agonist therapy (Methadone) and their toxicological test showed that they were abusing other substances such as benzodiazepines and cannabinoids. Moreover, 14% of the members of the cases group were taking antidepressants.

Studying REM Sleep:

Data collected from the current study suggested that there is no statistically significant difference of REM sleep parameters between opioid dependence patients and healthy controls. This finding was applied to REM percentage of total sleep time, REM latency as well as REM density.

Comparable data in other studies revealed similar data regarding REM percentage of total sleep time. ***Teichtahl et al 2001*** found no statistically significant difference between patients on MMT and control regarding REM %. ***Lukas et al., 1996*** share the same finding with the current study as they also found no statistically significant difference between dually dependant opiates and cocaine participants in comparison to control group regarding REM percentage of total sleep time. Similar result was concluded by ***Staedt et al 1996*** after examining REM% in opioid dependent patients on Naltrexone therapy or Methadone therapy and comparing them to control group and finding no statistically significant difference between the 3 groups. Recently, ***Walker et al 2007*** confirmed such result by comparing REM % in patients chronically using opioids to those not using opioids.

This was different to what ***Wang et al 2005*** recorded. They found statistically significant decrease in the REM %

of cases of opioid dependence on MMT when compared to control subjects.

On the other hand, fewer studies examined REM latency and Density in opioid dependant patients. ***Wang et al 2008*** assessment for REM latency showed no statistical significant difference between opioid dependant patients on MMT and control subjects which confirms with the current results.

Another study that examined sleep latency was that of ***Sharkey et al. 2009.*** Although they did not have control subjects in their study, yet they found the mean REM latency in the opioid dependent group underwent 1 night polysomnography 63± 47 minutes. This finding was close to the value of the REM latency in the case group of the current study 62.2 ± 3.4

This differs from the result of ***Lukas et al., 1996*** where they found statistically significant decrease in REM latency in dually dependant opiates and cocaine participants in comparison to control group 5 days after the detoxification period. This difference can be attributed to the sample selection of their study as they worked with polysubstance abusers mainly abusing cocaine and opiates in the same time.

The current study also found no statistically significant difference between cases and control groups regarding REM Density. Very few studies analyzed this complaint in patients using opioids. ***Shaw et al., 2005*** found statistically significant difference in REM density comparing acute intravenous administration of Morphine in health volunteers in comparison to recorded REM density after administration of placebo and baseline sleep conditions.

Studying Respiratory Variables of Sleep:

The current study shows that there is no significant difference regarding respiratory variables of sleep in opioid dependence patients as compared with healthy controls. This included the absence of central, obstructive or mixed apnea as well as hypopnea.

In comparing the current data to those found in literature, presence of a different conclusion was detected. Most of the studies report the presence of Sleep Disordered Breathing (SDB) in patients using opioids in a chronic manner. ***Teichtahl et al 2001*** assume that they performed the first study that detected SDB in opioid dependent patients on MMT comparing them to control subjects as 6 out of his 10 case subjects suffered from central sleep apnea. ***Wang et al 2005*** reached the same conclusion when

he found statistically significant difference regarding Sleep Disordered Breathing when he compared 50 opioid dependent patients on MMT to 20 normal control subjects. 30% of his sample had central sleep apnea while 20% of them had mixed central and obstructive sleep apnea. These findings were supported by the study of ***Walker et al 2007*** as they found statistically significant difference regarding central apnea index of patients chronically using opioids to those non using opioids. A larger study was done by ***Webster et al 2008*** who performed their study on a sample consisting of 140 patients who were chronically using opioids and found that 75% of patients showed abnormal apnea–hypopnea index, while 25% had no sleep apnea. Of those with abnormalities, 39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea.

Therefore, by reviewing the literature, it was concluded by several authors that chronic usage of opioids predisposes to sleep disordered breathing in its various forms. However, there is a core difference between all these studies and the current one. Patients in all these studies were using opioids at the time of study whether in the form of Methadone or in the form of other opioid analgesics. In the current study, patients were opioid free

for at least one month. We therefore suggest the Sleep disordered breathing is related to the direct effect of the opioids especially after chronic use. The current suggestion is supported by the case report of ***Ramar, 2009***. He reported the complete resolution of sleep disordered breathing of one of his patients who stopped Methadone after chronic use. This patient suffered from chronic pain condition, was on Methadone therapy for 4 years during which she suffered from sleep disordered breathing as confirmed by polysomnography. She was weaned off Methadone and after 2 weeks of stoppage of Methadone, recent polysomnography showed resolution of the sleep disordered breathing condition.

It is clear that after reviewing the literature documenting sleep profile in chronic opioid abusers, there is diversity of information that are sometimes contradictory. There are several reasons for this diversity. ***Wang and Teichtahl, 2007,*** stated in their clinical review studying the current knowledge regarding the effects of opioids on sleep and respiration during sleep that there are four basic phases of opioid dependence and withdrawal. These phases are drug induction phase, drug maintenance phase, acute abstinence phase and protracted abstinence phase. Sleep architecture changes are different for each of the 4 phases.

As the current study was performed one month after abstinence, (7-10 days after detoxification), it study sleep architecture in the beginning of the protracted abstinence phase. The diversity of information resulted from comparing the current study with studies performed in other stages as well. This was mandatory as we can hardly find studies in this phase.

The second reason for conflicting results is that case subjects in most of the studies reviewed and compared to the current study were on MMT (Methadone Maintenance Therapy) while were case subjects were drug free. This gives strength to the current study as Methadone has its own effect on the sleep profile.

Finally, there are some methodological differences in the studies discussed above compared to the present study. These differences include the presence of some confounding factors in the case subjects (abuse of other substances than opioids during the study, presence of Axis I diagnosis other than opioid dependence and the presence of medical conditions in the case subjects). Another important difference was the limited number of case and control subjects in most of the studies.

The factors that may affect the sleep pattern of the sample:

Few studies were done to assess the sleep profile in chronic opioid abusers. However, studies analyzing the factors that within the opioid abusers and their relationship with sleep subjective and objective sleep parameters are considered to be extremely rare. Many reasons contribute to the rarity of these studies. First, there are limited number of researches studying opioids and their relation with sleep in general. Second, the number of case in these studies is usually small rendering its division to subgroups for further analysis so difficult with doubts about the reliability of the results arising from such subgrouping. Finally, there are many factors that can affect both sleep and opioid dependence making it difficult to choose the appropriate tools for such an analysis.

We tried to avoid these difficulties in the current study by ignoring subgroups consisting of very a little number of cases, using the appropriate statistics for small numbers and using reliable assessment tools in assessing variables. Inspite of these precautions, there are still limitations regarding the results in this part of the study.

Regarding factors affecting assessment of sleep pattern of the patients, of the case group, the current study failed to find statistically significant correlation between sleep complaints and life time duration of opioid abuse.

The current data was consistent with what ***Peles et al 2008*** highlighted in their study. They divided their case subjects into two groups according to the dose of Methadone they receive. Mean duration of opioid abuse before starting MMT in the high dose Methadone group was 21.9 ± 8.8 years while that of the low Methadone dose group was 14.2 ± 9.2 years. Inspite of that difference in the lifetime duration of opioid abuse, there was no statistically significant difference regarding sleep quality of the patients as assessed by PSQI *(The Pittsburgh Sleep Quality Index)* or their feeling of daytime hypersomnolence as assessed by ESS *(The Epworth Sleepiness Scale)* .

This was not in the same line to what ***Peles et al 2006*** concluded. They found statistically significant correlation

between sleep quality as measured by PSQI and number of years of opioid abuse in opioid dependent patients. Yet further analysis of this result revealed that the statistically significant correlation was mainly related to subjective sleep quality. There was no correlation between years of opioid abuse and subjective sleep latency, sleep duration or subjective sleep efficiency.

The difference between these results and the current study arises from the difference in their methodology. ***Peles et al 2006*** study was conducted on larger number of subjects (101 case), on MMT, their drug screen showed other substances of abuse and sleep assessment questionnaire was different.

It is worth mentioning that the current study failed to find statistically significant correlation between sleep complaints and most of the other factors regarding opioid abuse including type of opioid, method of abuse, last abstinence period as well as time lapsed since last abstinence period. This is similar to what ***Burke et al 2008*** exhibited as he found no correlation between the opioid abuse pattern as recorded by *Addiction Severity Index* (ASI) and various sleep complaints including day time somnolence recorded by ESS as well as other sleep parameters (sleep disturbance, adequacy and problems

and sleep shortness of breath) as recorded by MOS *(Medical Outcome Study Sleep Questionnaire).*

Regarding the frequency of opioid abuse in the last 30 days before starting detoxification, the only sleep complaint found statistically correlated to this variable was Sleep Talking. Other than that, all other sleep complaints were not correlated to the frequency of opioid abuse in the last 30 days.

This finding is close to what ***Stein et al 2004*** recorded in their study. They found no statistically significant correlation between sleep related problems as measured with PSQI and heroine use in the last 30 days before performing their study with opioid dependent subjects on MMT.

Another related result is that of ***Peles et al 2006*** who found no correlation between sleep quality (as recorded by PSQI) and recent opiate intake assessed by detecting opiates in the urine of the opioid dependant patients participating in the study. None of these studies assessed Sleep Talking relation to pattern of opioid dependence.

The correlation between sleep talking and frequency of opioid abuse in the last 30 days can be explained in the

prospective of the neurobiology of sleep talking. This phenomenon increases in the sleep pattern characterized by more transference and transitions between various sleep phases. We suggest that increase frequency and amount of opioid intake has such an effect on the sleep architecture.

Another variable in opioid abuse that was significantly correlated to some sleep complaints was the Times of Treatment. It was statistically correlated to Early Morning Awakening and Sleep Acid Reflux. We consider that this finding is based on the fact that frequency of treatment is equivalent to enduring multiple times of withdrawal and relapse. This endurance may lead to changes in the brain functions resulting in disturbance in the sleep circuits manifested in decrease sleeping hours and early morning awakening. Another explanation lies in considering recurrent failure in treatment a precipitating factor for a depressive equivalent manifested by early morning awakening.

As for the correlation with Sleep Acid Reflux, it may be related to the current use of symptomatic treatment in detoxification that contains large doses of NSAID used as analgesics and causing hyperacidity and acid reflux manifested mainly during sleep. Another suggested explanation lies in the fact of considering withdrawal state

as a biological stress which leads to the release of endogenous steroids resulting in hyperacidity.

The next step of the current study was detecting correlation between the sleep complaints and the psychological status of patients. The current study failed to detect any statistically significant correlation between sleep complaints and the psychological status of the patients assessed for the presence of depressive or anxiety state.

Studies that have investigated the relation between psychological status of the patients and sleep parameters provide conflicting data. Some of them give close results to the current study. ***Wang et al, 2008*** assessed the day time sleepiness (recorded by ESS) in opioid dependent patients that fall in the categories of mild, moderate or severe depressive state range (as recorded by *BDI-Beck Depression Inventory*) and found no statistically significant difference. In the same context, ***Beswick et al 2003*** did not find statistically significant correlation between subjective sleep latency as well as awakening time when after relating them to anxiety and depressive status of the patients recorded by *Maudsley Addiction Profile (MAP)*. On the other hand, ***Stein et al 2004*** concluded that poorer global sleep quality (as measured by PSQI) is associated with depressive and anxiety symptoms in opioid dependent patients on MMT.

This result does not confirm to the current study as they used the DSMVI diagnostic criteria for assessing the depressive and anxiety symptoms and this finding was related to subjects suffering from Major Depressive Disorder or Generalized Anxiety Disorder while in the current study, subjects with Axis on diagnoses other than Opioid Dependence were excluded from the study. Furthermore, depressive and anxiety symptoms were assessed by tools to diagnose the psychological state at the time of the study and not longitudinally.

As for DSM Axis II diagnoses and their relation to the sleep complaints, the current study shows that the presence of personality disorder [Diagnosed by using SCID II] in patients with opioid dependence has no direct correlation with different sleep complaints. No comparable data was found in other studies.

Regarding factors affecting polysomnography findings of the patients in the case group, the current study failed to find any statistically significant correlation between polysomnography and various variables of opioid dependence history of the case group.

Regarding the correlation between the polysomnography findings and the psychological status of

patients, the current study detected a statistically significant correlation between depressive state of the cases and SWS especially stage III of NREM sleep. This stage was found to be significantly lower in opioid dependant patients with moderate depressive state compared to those with mild depressive state. This may verify the fact the depressive status of these patients is secondary to their dependence condition and thus giving a non specific finding more related to the dependence condition rather than having genuine Major Depressive disorder with its specific sleep changes.

CONCLUSION

The results of the study suggest that patients with opioid abuse disorders suffer from sleep disturbance that continues for a period of time even after discontinuation of abuse. Sleep laboratory studies shows that the nature of this disturbance is related to NREM sleep parameters and with no marked correlation to abuse variables. .

LIMITATIONS

- Although cases were matched with control subjects regarding age and sex yet there was no matching of body mass index.
- All cases and control subjects who participated in the study were males. Gender difference limits applying the findings on female opioid abusers.
- The cross-sectional sample from one inpatient addiction unit as well as the number of participants may not be enough to generalize the current results to the population based cases.
- Nicotine and Caffeine may act as confounding factors affecting the sleep profile of cases although all patients abused one cigarette packet per day and were asked to stop caffeine intake 12 hours prior to performing polysomnogram.
- Although all case subjects did not receive psychotropic medications for 10 days before polysomnogram performance, some of the previously taken drugs have long term psychotropic effect including effect on sleep (e.g. Fluoxetine).

- Polysomnogram studies were done for the participants over single night only. Therefore, difficulty adapting to a novel sleep environment in only one day may play a role in sleep disturbance in opioid-dependent patients.

SUMMARY

Substance use disorder is one of the most complicated problems that face not only medical professionals but the whole community. Problems of substance abuse produce dramatic costs for all societies in the term of low productivity, medical complications, family and social troubles as well as crimes.

Regarding physical complications, studies indicate that psychoactive substances have acute and chronic effects on sleep architecture. Sleep disturbances occurs in various forms and stages of substance use and related nearly all the psychoactive substances. Sleep pattern of patients differ with time and most of the patients are not aware of these changes. Moreover, the co-occurrence of other psychiatric disorders with psychoactive substance use increases the difficulty of identifying and treating the sleep disturbances.

Scientific data as well as clinical experience highlight opioids as one of the main psychoactive substances of abuse affecting sleep. Such an effect occurs in various stages of opioid abuse: drug induction phase, drug maintenance phase, acute abstinence phase and protracted abstinence phase. For some, sleep disturbance can be so severe as to reverse treatment success and precipitate a

relapse to addiction or dependence. Inspite of these important facts and their significant clinical implications, a very little number of studies were done exploring this phenomenon.

Based on that, this study was conducted aiming to study the profile of sleep in opioid abuse patients following the period of detoxification , determining the nature of the sleep disturbance in them if present and highlighting the factors related to this disturbance.

Accordingly, all opioid dependant male patients admitted in the substance abuse department at the Institute of Psychiatry, Ain Shams University and approving to participate in this study were included as the case group. Their age ranges between 18-45 years and they had history of regular opioid abuse for at least one year. Patients with Axis I psychiatric disorders according to DSM IV, co-morbid major physical illness or history of neurological diseases were excluded from the study. A control group of 10 individuals of volunteers was formed for the case control comparison. They were matched with the patient group for age and sex and with no apparent physical or psychiatric morbidity.

The study took place from the 1st of June 2006 till 31st of May 2008.

All the inpatients in the substance abuse department were examined to determine eligibility for participation in the study.

Screening was conducted through clinical psychiatric interview according to inpatient psychiatric sheet of Ain Shams University Institute of Psychiatry, which examined demographic data, psychiatric history and examination as well as medical history information.

Patients were examined 3 weeks following admission, after resolution of most of the symptoms of withdrawal.

Patients who agreed on participation were subjected to full medical history and examination (general, cardiological, chest and neurological examination) to detect any neurological or chronic medical condition that would lead to exclusion from the study.

Routine laboratory investigation including liver and kidney function, complete blood picture tests as well as ECG will be performed to confirm exclusion of major physical illness.

All subjects of the study were assessed by using

Tools to diagnose case group:

- Structured Clinical Interview for DSM-IV (SCID I) diagnostic tool to diagnose opioid dependence and to exclude other Axis I diagnosis according to DSM VI classification.
- Addiction Severity Index (ASI) to ensure that the study will include patients who have opioids as the main substance of abuse and study the pattern of opioids abuse over the life time of the patients and in the last 30 days before admission.

Tools to assess the psychological status of the cases:

- Beck Depression Inventory (BDI): to assess the severity of depression state.
- Taylor Manifest Anxiety Scale: to assess the anxiety state.
- The Structured Clinical Interview for DSM Axis II Disorders (SCID II): to evaluate an axis II diagnosis.

Tools to study Sleep Profile (applied for cases and control subjects):

- Comprehensive Sleep Disorder Questionnaire: To assess Personal sleep rituals as well as Sleep disorders which are insomnia, hypersomnia, parasomnias, or dyssomnias.
- All Night Polysomnography (PSG): to analyze the sleep architecture of the subjects including General sleep aspects NREM and REM sleep characteristics as well as assessment of respiratory variables during sleep.

Sleep assessment was performed when the participants were medication free for at least 7 days prior to study to exclude the effect of any psychotropic medication on their polysomnography.

Moreover, urine test for substances of abuse was performed to guarantee abstinence during the assessment period.

The results of the study were obtained using the statistical package of the SPSS- 15th version. The statistical processes performed were Student's t test, Spearman Correlation test, ANOVA test as well as Chi Square test.

The Main Findings in the Study were:

As regard the demographic and clinical profile of the sample:

The current study showed that the socio-demographic characteristics of the sample pointed that all patients were males with mean age group 27 years. The majority of the subjects were single (n=29, 87%) while 9% (n=3) were married and 3% (n=1) divorced. 45.5% sample were college graduate (n=15), whereas 27% (n=9) graduated from secondary and 24% (n=8) from technical school while the rest 9% (n=3) from preparatory school.

As regard the level of occupation, 42% (n=14) of the sample were unemployed, 27% (n=9) were students, 18% were working in professional jobs while 12% (n=4) were skilled workers.

Assessment of the substance abuse pattern showed that 79% (n=26) of the patients sample abused Heroine by intra venous injection while 21% (n=7) of them abused Tramadol orally.

The duration of lifetime opioid abuse ranged from 3 years to 20 years with mean 7 years. On the other hand, the duration of opioid abuse in the last 30 days before abstinence ranged from 22 days to 30 days with mean 28

days. Regarding abstinence, the mean last abstinence period of the cases in our study was 5.3 months and the time lapsed from last abstinence was of mean 7.2 months. The patients mean trials of treatment was 2.5 times.

Examining the medical condition of the cases revealed that 61% (n=20) case was Hepatitis C Positive, 3% (n= 1) was Hepatitis B positive and 36% (n=12) had no medical conditions.

Regarding the depressive state of the patients according to Beck Depression Inventory, 48% of cases (n=16) had moderate state, 42% (n=14) had mild state, 6% Severe state and 3 (n=1) was normal.

As for the severity of anxiety state, both mild and moderate anxiety states counted for 48% of cases (n=16) where as only 3% of the cases (n=1) had severe anxiety state. Examining the cases of the study for personality disorder using SCTDII showed that 45% of the cases had no personality disorder. According to DSM-IV classification the most frequent personality cluster among cases group was cluster C (24.24%) followed by cluster B (18.18%), while the mixed personality disorders represented (9%) and multiple personality disorders 3%.

As regard the Clinical Sleep Complaints of the sample:

81% of the studied group showed initial insomnia, 57% of the studied group had interrupted sleep and 48% of them had late insomnia. Also in the patients group, 67% suffered from day time somnolence, 42% suffered from sleep talking and 33% of them suffered from sleep acid reflux. All these complaints showed statistically significant difference from the control group.

On the other hand, comparing case group to control subjects showed no statistical significance regarding snoring, experiencing nightmares as well as nocturnal enuresis.

The mean night sleeping hours of cases was 6.6 hours SD ± 1.45 and the subjective sleep onset latency was 47.5 minutes SD ± 13.97. Both values were of statistical significant difference when compared to those of control.

As regard the sleep laboratory findings of the sample according to polysomnography:

Regarding sleep latency, sleep efficiency and arousal index, there were marked affection in cases. That is to say that there was significant lengthening of sleep latency, significant diminish of sleep efficiency, and significant rise of arousal index in opioid dependant patients as compared to healthy controls.

Comparing NREM parameters of cases and control subjects showed that there is a significant increase in both stage 1 and stage 2 of NREM sleep in opioid dependence patients as compared to healthy controls, while stages 3 and 4 as well as SWS% are significantly reduced . On the other hand, comparing REM sleep components of opioid dependent patients to control subjects showed no statistically significant difference regarding REM % of total sleep time, REM density as well as REM latency. The same finding was related to respiratory variables after studying these variables respiratory variables in opioid dependence patients as compared with healthy controls. There was no statistically significant difference regarding sleep apnea parameters whether central, obstructive or mixed.

Periodic leg movements during sleep in opioid dependence patients also showed no statistically significant difference when compared with healthy controls.

Analysis of factors affecting Clinical Sleep Complaints of the sample:

In the current study, various factors related to substance abuse were analyzed in relation to sleep complaints of the sample group. This analysis showed that sleep talking was significantly correlated to the frequency of abuse in the last 30 days before abstinence. Moreover, late insomnia in the form of early morning awakening and sleep acid reflux showed statistically significant correlation with the number of treatment trials. Other than that, factors related to opioid abuse including type of opioid , route of abuse, lifetime abuse duration and duration of last abstinence period were not correlated to sleep complaints of case group in the current study.

Similarly, no statistically significant correlation was detected between the sleep complaints of the cases and the tested psychological parameters in the study including depressive and anxiety status as well as the presence of personality disorder.

Analysis of factors affecting sleep laboratory findings of the sample:

Regarding factors affecting polysomnography findings of the patients in the case group, the current study failed to find any statistically significant correlation between sleep laboratory findings detected by polysomnography and various variables of opioid dependence of the case group. These variables included type of opioid, route of abuse, lifetime abuse duration, frequency of abuse in last 30 days, treatment trials and duration of last abstinence period.

This was different to the study findings regarding correlation between the sleep laboratory findings and psychological status of the cases. There was statistically significant correlation between depressive state of the cases and SWS especially stage III of NREM sleep. This stage was found to be significantly lower in opioid dependant patients with moderate depressive state compared to those with mild depressive state. On the other hand, polysomnography findings of the case group in the study could not be correlated to the anxiety state of the cases.

The study carried some limitations including being conducted on males only, not matching body mass index between case and control groups and the presence of some confounding factors such as the use of caffeine and nicotine by the patients as well as environmental change as a factor affecting sleep.

The study concludes that patients with opioid abuse disorders suffer from sleep disturbance that continues for a period of time even after discontinuation of abuse. Sleep laboratory studies shows that the nature of this disturbance is related to NREM sleep parameters and with no marked correlation to abuse variables such as duration of abuse and type of opioids.

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الملخص العربي

يعتبر اضطراب سوء استخدام المواد المؤثرة نفسياً واحداً من أكثر الظواهر انتشاراً على مستوى العالم. فقد قدر مكتب الأمم المتحدة لمكافحة المخدرات والجريمة عدد مستخدمي العقاقير غير القانونية بحوالي ١٨٠ مليون شخصاً حول العالم وذلك خلال عقد التسعينات من القرن العشرين.

وتنبع خطورة سوء استخدام المواد المؤثرة نفسياً من المشكلات والخسائر الذي يسببها على كافة الأصعدة والي تتمثل في القلة الإنتاجية للمتعاطين، انتشار المشاكل الصحية والأمراض المعدية بينهم، الاضطرابات العائلية والاجتماعية بالإضافة إلى ارتفاع معدلات الجريمة.

وجدير بالذكر أن الدراسات أثبتت ارتفاع معدل الاضطرابات النفسية الأخرى بين مرضى سوء استخدام المواد المؤثرة نفسياً.ويظهر هذا بوضوح في شكل تعدد الشكاوى والأعراض النفسية التي يعاني منها هؤلاء المرضى والتي تترك أثراً حتى بعد التوقف عن التعاطي.

وتعد اضطرابات النوم أحد أهم هذه الأعراض فقد أوضحت الدراسات العملية والملاحظات الإكلينيكية أن سوء استخدام المواد المؤثرة نفسياً لها أثر على منظومة النوم عند هؤلاء المرضى سواء كان هذا الأثر قصير الأجل أو مزمناً. وبالرغم من تعدد المواد التي يتعاطاها مرضى سوء استخدام المواد المؤثرة نفسياً إلا أن ظاهرة اضطرابات النوم عند هؤلاء المرضى تعد ظاهرة واسعة الانتشار بينهم مع اختلاف أنواع المواد أو نمط التعاطي منتظماً كان أو عشوائياً.

وتشير الدلائل العلمية أن الأفيونات واحد من المواد ذات التأثير النفسي والتي تؤثر كغيرها من هذه المواد تأثيراً بالغاً على النوم. وقد سجل العلماء وجود خلل في نوم مستخدمي الأفيونات سواء مع تعاطي الجرعات الأولى أو التعاطي

المنتظم. كما أثبتت الدراسات ظهور اضطرابات شديدة في النوم عند هؤلاء المرضى سواء في بداية الامتناع عن التعاطي مروراً بمرحلة أعراض الانسحاب، وقد تستمر هذه الاضطرابات حتى بعد مرور شهور من التوقف عن استخدام الأفيونات.

قد تصل شدة اضطرابات النوم عند بعض المتعاطين إلى حد عرقلة تعافيهم من التعاطي مما يجعل اضطرابات النوم سبباً رئيسياً يؤدي إلى انتكاسة مرة أخرى والعودة إلى مرحلة التعاطي النشط في مرض الإدمان.

وبالرغم من هذه الملاحظات العلمية، فإن هناك ندرة شديدة في الأبحاث التي تناولت خصائص النوم في أثناء تعاطي الأفيونات أو في أثناء المراحل الأولى أو المتقدمة من أعراض الانسحاب و ذلك على مستوى العالم.

وبناء على ذلك ظهرت أهمية إجراء هذه الدراسة:

فرضية الدراسة:

تفترض هذه الدراسة أن المرضى الذين يتعاطون الأفيونات يعانون من اضطرابات في النوم ذات أنماط محددة التي تستمر لفترة من الزمن حتى بعد التوقف عن التعاطي.

الهدف من العمل:

الهدف من العمل هو البحث في الفرضية السابقة ودراسة ما يلي:

١- دراسة نمط النوم في مرضى تعاطي الأفيونات بعد انتهاء أعراض الانسحاب.
٢- توضيح وجود أثر تعاطي أفيونات على النوم أم لا .
٣- دراسة طبيعة اضطراب النوم إذا كان موجوداً.
٤- استكشاف العوامل التي تؤدي إلى حدوث هذا الاضطراب عند مرضى سوء استخدام الأفيونات.

منهج البحث

عينة البحث

تتكون عينة البحث من ٣٣ مريض ، من المرضى الذين يترددون على وحدة علاج الإدمان، بمركز الطب النفسي، بجامعة عينت شمس، والذين يستوفون شروط الانضمام لعينة البحث.

مكان الدراسة:

وحدة علاج الإدمان ، مركز الطب النفسي – كلية الطب بجامعة عين شمس.

اختيار العينة:

١- تم اختيار عينة الحالات من المرضى المحجوزين للعلاج بوحدة لإدمان، في مركز الطب النفسي، بجامعة عين شمس.
٢- المرضى المختارين توافرت فيهم شروط سوء استخدام الأفيونات، وذلك طبقاً للمعايير التشخيصية لنظام التشخيص الإحصائي الأمريكي DSM IV (وذلك من خلال استيفاء المقابلة الإكلينيكية المنشئة للتشخيص SCID I). وبما أن معظم المرضى يتعاطون أكثر من مادة، فإن الدراسة تتضمنت الذين يعتمدون على الأفيون كمادة تعاطي أساسية وفقاً لمقياس شدة الإدمان Addiction Severity Index.
٣- تتضمنت العينة كل مريض تم حجزه بوحدة علاج الإدمان، بدأ من الأول من شهر يونيو لعام ٢٠٠٦م، على أن يكون مستوفياً لشروط الانضمام لعينة البحث، وذلك حتى استكمال عدد العينة.

شروط الانضمام لعينة البحث:

١- تم اختيار المرضى الذين استخدموا الأفيونات بشكل منتظم لمدة عاماً على الأقل.
٢- تتراوح أعمار المرضى ما بين ١٨ إلى ٤٥ عاماً.

٣- جميع المرضى من الذكور.
٤- الحصول على موافقة كتابية من المريض قبل إجراء البحث، وذلك بعد الشرح الوافي لمبررات البحث وأهدافه.

شروط الاستبعاد من عينة البحث:

١- يتم استبعاد المرضى الذين يعانون من اضطرابات نفسية أخرى، وفقاً لنظام التشخيص الإحصائي الأمريكي DSM IV.
٢- يتم استبعاد المرضى الذين يعانون من أمراض عضوية خطيرة.
٣- يتم استبعاد المرضى الغير راغبين في المشاركة في البحث.

أدوات البحث:

١- استخبار اضطرابات النوم الشامل.
٢- مقياس "بيك" للاكتئاب.
٣- مقياس "تايلور" للقلق.
٤- معمل نوم طوال الليل.
٥- المقابلة الإكلينيكية المنشئة للتشخيص الإحصائي الأمريكي١ SCID I
٦- المقابلة الإكلينيكية المنشئة للتشخيص الإحصائي الأمريكي٢ SCID II
٧- مقياس شدة الإدمان Addiction Severity Index.
٨- تحليل بول لكشف المخدرات.
٩- تحاليل معملية روتينية.

العينة الضابطة:

تتكون العينة الضابطة من ١٠ (عشرة) متطوعين لهم نفس العمل والجنس والحالة الاجتماعية لعينة المرضى ولكن لا يعانون من أي أمراض عضوية أو اضطرابات نفسية.

الإجراءات البحثية:

مدة الدراسة:

استمرت هذه الدراسة بدءًا من الأول من يونيو ٢٠٠٦ م حتى ٣١ مايو ٢٠٠٨م.

الإجراءات البحثية:

- تم إجراء فحصاً مبدئياً بواسطة استمارة الفحص الخاصة بمركز الطب النفسي كلية الطب جامعة عين شمس والتي تشمل معلومات التاريخ الشخصي المرضي والنفسي للنريض بالإضافة إلى الفحص الطبي والنفسي وذلك عند دخول المريض إلى القسم الداخلي بالمركز.

- تم إعادة فحص المرضى بعد مرور ٣ أسابيع من دخولهم للمركز وذلك بعد انقضاء فترة أعراض الانسحاب.
- تم عرض فكرة البحث على المرضى المحجوزين في القسم الداخلي لعلاج الإدمان بمركز الطب النفسي بجامعة عين شمس وعرض المشاركة فيه ذلك بعد الحصول على موافقة كتابية من المريض تم فيها شرح أهمية البحث وخطواته والمزايا التي ستعود على المشاركين والآثار الجانبية التي قد يتعرضون إليها بالإضافة إلى توضيح إمكانية رفض المشاركة في البحث أو الانسحاب في أي وقت دون حدوث أي أثر لذلك على العملية العلاجية.

وبعد التوقيع على الموافقة الكتابية بدأ تطبيق خطوات البحث وهي:

- التأكد من عدم وجود أي أمراض عصبية أو باطنية عند المرضى قد تؤثر على قياسات النوم عندهم وذلك بتطبيق الكشف الطبي الشامل وإجراء

المعامل الروتينية لهم والتي تتضمن وظائف الكبد ووظائف الكلى بالإضافة إلى صورة دم كاملة كما تم عمل رسم قلب كهربائي لنفس الهدف.

- تم تطبيق المقابلة الإكلينيكية المنشئة للتشخيص الإحصائي الأمريكي (١) SCIDI وذلك لتشخيص الاعتمادية على الأفيونات واستبعاد أي اضطرابات نفسية أخرى وفقاً لنظام التشخيص الإحصائي الأمريكي.

- تم تطبيق مقياس شدة الإدمان للتأكد من أن تشخيص المرضى ولتسجيل نمط تعاطي الأفيونات طوال التاريخ المرضي للمشاركين في الدراسة.

- بالنسبة للقياسات النفسية الأخرى، تم تطبيق مقياس "بيك" لقياس مستوى الحالة الاكتئابية للمرضى كما تم تطبيق مستوى "تايلور" لقياس مستوى القلق بالإضافة إلى المقابلة الإكلينيكية المنشئة للتشخيص الإحصائي الأمريكي "٢" SCID II لتشخيص اضطرابات الشخصية.

- أما بالنسبة لقياسات النوم فقد تم تطبيق استخبار اضطرابات النوم الشامل والذي يقيس كافة أعراض اضطرابات النوم كما أنه يساعد على وصف طبيعة النوم وصورته بالنسبة للمرضى أما أداة الدراسة الأخرى فكانت معمل النوم طوال الليل والذي يدرس مراحل النوم وقياسات الحيوية (خاصة قياس التنفس) أثناء النوم.

- كما تم عمل تحليل للتأكد من خلو جسم المرضى من المخدرات أثناء فترة التقييم.

نتائج البحث:

بالنسبة للنتائج الوصفية لعينة البحث أظهرت ما يلي:

- شملت هذه الدراسة المرضى الذكور وكان متوسط أعمارهم ٢٧ عاماً.
- كان أغلب المشاركين عزاباً (٨٧%) ولا يعملون (٤٢%).

بالنسبة للخصائص الإكلينيكية للعينة:

- ٧٩% من عينة المرضى كانوا يتعاطون الهيروين عن طريق الحقن الوريدي بينما كان ٢١% يتعاطون ترامادول عن طريق البلع.
- تراوحت مدة تعاطي الأفيونات ما بين ٣ إلى ٢٠ سنة بمتوسط ٧ سنوات.
- على صعيد آخر فإن مدة تعاطي الأفيونات في الثلاثين يوماً الأخيرة تراوحت ما بين ٢٢ إلى ٣٠ يوماً بمتوسط ٢٨ يوماً.
- بالنسبة لفترات العلاجية فقد بلغ متوسط مرات العلاج للمرضى ٢.٥مرة وبلغ متوسط فترة التوقف عن التعاطي ٣.٥ شهور
- وأسفر الفحص الطبي للمرضى عن وجود ٦١% من المرضى مصابين بالالتهاب الكبدي الفيروسي سي بينما خلا ٣٦% من العينة من أي أمراض.

- أما بالنسبة للمقاييس النفسية فقد أظهر مقياس بيك لقياس الحالة الاكتئابية أن ٤٨% من عينة المرضى يعانون من حالة اكتئابية متوسطة بينما ٤٢% من حالة اكتئابية طفيفة.
- أما بالنسبة لمستوى القلق فقد عاني ٤٨% من الحالات من مستوى قلق خفيف وعانت نفس النسبة من حالة قلق متوسط بينما مثلت حالات القلق الشديد ٣% فقط.
- أظهر الدراسة أن ٥٥% من عينة مرضى سوء استخدام الأفيونات يعانون من اضطراب في الشخصية مقابل ٤٥% لا يعانون من هذا الاضطراب النفسي.

مقاييس اضطرابات النوم:

الأعراض المختلفة لاضطرابات النوم ووصف نمط النوم:

- اشتكى ٨١% من عينة الدراسة من الأرق في بداية النوم بينما كانت الشكوى فمن أرق مواصلة النوم (كثرة الاستيقاظ ليلاً – النوم المتقطع) حوالي ٥٧% أما أخر أنواع الأرق (أرق نهاية اليوم – الاستيقاظ المبكر) فقد عاني منه ٤٨% ممن شملهم البحث.
- من ناحية أخرى ، عاني ٦٧% من الحالات من رغبة شديدة في النوم أثناء ساعات النهار (النعاس النهاري) و٤٢% من عينة الدراسة من ظاهرة التكلم أثناء النوم وأخيراً لاحظ ٣٣% من مستخدمي الأفيونات وجود ظاهرة الارتجاع الحمضي في المريء أثناء النوم.
- وعند تحليل هذه الشكاوى ومقارنتها مع الشكاوى الصادرة من العينة الضابطة، أظهرت نتائج البحث وجود فروق ذات قيمة إحصائية هامة بين المجموعتين.

- من ناحية أخرى، أظهرت نتائج البحث عدم وجود اختلاف ذو قيمة إحصائية عن مقارنة مجموعة الحالات المرضية مع المجموعة الضابطة وذلك بخصوص اضطرابات الشخير، والكوابيس الليلية بالإضافة إلى اضطراب عدم التحكم في البول أثناء النوم (السلس البولي الليلي).

- بلغ متوسط ساعات النوم عند الخالات ٦.٦ ساعة كما أن متوسط الوقت المستغرق حتى بداية النوم كان ٤٧.٥ دقيقة مما أعطى اختلافاً ذا قيمة إحصائية هامة عند مقارنته بمجموعة الضبط.

نتائج معمل النوم:

بمقارنة حالات سوء استخدام الأفيونات بالمجموعة الضابطة أظهر معمل النوم أن هذه الحالات تعاني من زيادة شديدة في الوقت المستغرق حتى بداية النوم، كما كان هناك انخفاضاً واضحاً في كفاءة النوم بالإضافة إلى ارتفاع معدل اليقظة والأرق أثناء النوم. كل هذه الفروق كانت ذات قيمة إحصائية هامة.

بالنسبة لمراحل النوم المختلفة فقط ظهرت الاختلافات ذات القيمة الإحصائية عند مقارنة مرحلة النوم التي لا تحدث فيه حركة للعينين بين عينة المرضى والعينة الضابطة. فقد تبين وجود ارتفاع في نسبة المرحلة الأولى والثانية من النوم كما كان هناك انخفاض ظاهر في نسبة المرحلة الثالثة والرابعة ونسبة النوم ذي الموجات المخية البطيئة (النوم العميق) كانت كل هذه الفروق ذات قيمة إحصائية هامة.

اختلف الأمر عند دراسة مرحلة النوم ذي الحركة السريعة للعين حيث لم تظهر الدراسة أي اختلافات ذات قيمة إحصائية عند مقارنة مكونات هذه المرحلة في عينة المرضى والعينة الضابطة.

وأظهرت الدراسة نفس النتيجة عند مقارنة قياسات التنفس عند النوم حيث لم توجد اختلافات ذات قيمة إحصائية عند مقارنة مرضى سوء استخدام الأفيونات بالعينة الضابطة تبين عدم وجود فروق في نسبة انقطاع التنفس أثناء النوم سواء كان انسدادياً، رئيسياً أو مختلطاً.

العوامل المؤثرة في بالشكاوى المرتبطة بالنوم:

بالنسبة لتحليل العوامل الخاصة بالشكاوى المرتبطة بالنوم، تم تحليل عدة عوامل خاصة بسوء استخدام الأفيونات وعلاقتها بالشكاوى المرتبطة بالنوم لدى مجموعة البحث

وقد أوضح هذا التحليل بوجود علاقة ذات دلالة إحصائية هامة بين مدة تعاطي الأفيونات في الثلاثين يوماً السابقة للبحث وبين شكوى التحدث أثناء النوم.
كما تبين وجود علاقة ذات قيمة إحصائية بين عدد مرات العلاج من الإدمان وأرق نهاية اليوم (الأرق المتأخر) بالإضافة إلى الارتجاع الحمضي أثناء النوم.

أما بخلاف ذلك، لم يظهر البحث وجود أي علاقة ذات قيمة بين عوامل سوء استخدام الأفيونات وشكاوى النوم.
على نفس المنوال، لم يثبت وجود علاقة إحصائية بين مظاهر اضطرابات النوم والمقاييس النفسية الخاصة بالحالة الاكتئابية ومستوى القلق بالإضافة إلى وجود اضطرابات في الشخصية.

العوامل المؤثرة في نتائج معمل النوم:
أظهرت الدراسة عدم وجود علاقة ذات قيمة إحصائية بين نتائج معمل النوم ونمط سوء استخدام الأفيونات بما في ذلك نوع الأفيونات، أسلوب التعاطي، تاريخ التعاطي أو مرات العلاج.

تختلف هذه النتيجة عند دراسة علاقة نتائج معمل النوم بنتائج المقاييس النفسية للمرضى فقد أظهرت الدراسة وجود علاقة ذات قيمة إحصائية هامة بين الحالة الاكتئابية للمرضى وبين النوم العميق حيث وجد انخفاض ملحوظ في نسبة النوم العميق (المرحلة الثالثة والمرحلة الرابعة من النوم) عند المرضى ذوي الحالة الاكتئابية المتوسطة مقارنة بأولئك ذوي الحالة الاكتئابية الطفيفة.

الجدير بالذكر أن الدراسة لم تنجح في إثبات مثل هذه العلاقة بين نتائج معمل النوم ومستوى القلق عند مرضى سوء استخدام الأفيونات.

وقد توصلت هذه الدراسة إلى أن مرضى سوء استخدام الأفيونات يعانون من اضطرابات في النوم وتستمر هذه الاضطرابات لفترة من الزمن بعد التوقف عن

التعاطي وأظهرت نتائج معمل النوم أن هذه الاضطرابات تظهر في المرحلة الأولى، الثانية، الثالثة والرابعة من النوم دون وجود علاقة بين هذه التغيرات ومدة التعاطي، فترات العلاج أو نوع الأفيونات.

نقد الدراسة:

وإن كان يحسب للبحث دراسته لمثل هذا الموضوع التي تندر فيه الدراسات إلا أن هناك بعض أوجه القصور ومنها.

- اقتصار البحث على عينة من الذكور دون الإناث.
- قلة عدد الأفراد عينة الدراسة.
- عدم دراسة بعض العوامل الأخرى المؤثرة في النوع ككمية الكافيين والنيكوتين بالإضافة إلى العوامل البيئية.

التوصيات:

التوصيات البحثية:

- تكرار هذه الدراسة على عينة أكبر وأكثر تمثيلاً.
- تكرار هذه الدراسة لتتضمن الإناث.
- عمل دراسات مشابهة لبحث اضطرابات النوم المرتبطة المواد الأخرى ذات التأثير النفسي.
- دراسة نمط النوم في مرضى سوء استخدام الأفيونات بعد فترة أطول من التوقف عن التعاطي لبحث الآثار بعيدة المدى لسوء استخدام الأفيونات.
- عمل دراسات لقياس فاعلية الأساليب العلاجية المختلفة لاضطرابات النوم عند مرضى سوء استخدام الأفيونات

التوصيات الإكلينيكية:

- الاهتمام بعلاج اضطرابات النوم كجزء من علاج الإدمان.
- تقييم حالة النوم عند مرضى سوء استخدام الأفيونات في المراحل العلاجية المختلفة
- وضع مقاييس علاجية واضحة لعلاج اضطرابات النوم عند مرضى إدمان الأفيونات.
- تدريب المرضى على أساليب والحصول على النوم الصحي.

RECOMMENDATIONS

Research Recommendations:

- Future research should be conducted studying sleep profile in other substances of abuse. This will lead to more specific analysis to sleep complaints and better management of the problem.
- Researches should be done to examine the sleep profile of opioid dependent patients after long period of abstinence (protracted abstinence phase). Egyptian researches in this subject will be beneficial as most of the international literature researches were performed on long term Methadone maintained patients so comparative studies on patients not using Methadone will be of great value.
- Replication of the study at a larger sample
- Performing a similar study that includes both sexes.
- There is a need to perform researches assessing and comparing the efficiency of various pharmacological and behavioral tools managing sleep disturbances in opioid abuse patients.

Clinical recommendations:

- Sleep hygiene counseling should be included in all treatment programmes dealing with substance of abuse. They should include patients' education and training for management of sleep problems all over the recovery period.
- Assessment of sleep of opioid abuse patients during phases of follow up as sleep problems may last longer than the period of withdrawal and early recovery.
- Proper management of sleep disturbance starting from withdrawal and all through the stages of recovery as it causes marked distress to the patients.
- Developing clinical guidelines for the assessment and proper management of sleep disturbance in opioid abusers including when to use polysomnography as an objective tool to diagnose sleep disorder.

Sleep Physiology

Sleep is a universal behavior that has been demonstrated in every animal species studied from insects to mammals. It is one of the most significant human behaviors occupying nearly one third of human life **(Benca et al., 2005)**. It is worth mentioning that sleep is not just a basic human need. It is essential for good health, good quality of life as well as performing well during the day **(WHO, 2004)**.

Definition of Sleep

Sleep is defined as a reversible behavioral state of decreased responsiveness and interaction with the environment **(Carskadon & Dement, 1989)**. It differs from coma by its relative rapid and easy reversibility **(McDonald, 2006)**. Another difference lies in the fact that people who are sleeping – unlike those in coma- recognize the beginning of the sleep episode (by feeling sleepy) and are aware that they were sleeping after the termination of the episode **(Benca et al., 2005)**.

Structure of Sleep:

In 1953, **Aserinsky, Kleitman, and Dement** demonstrated the occurrence of periods of sleep characterized by conjugate rapid eye movements with an activated, low amplitude EEG pattern. This led to the description of rapid eye movement (REM) sleep that recurs in a cyclic fashion throughout the night, interspersed by periods of non-rapid eye movement (NREM) sleep **(Castronovo & Butkov, 2007).**

Since then, further attempts were done to specify and describe various sleep stages. Monitoring physiological variables such as brain activity, muscle activity and eye movements during sleep gives information about the different stages of sleep and their pattern of occurrence **(Wilson & Nutt, 2008)**. Recording of the brain activity is done using electroencephalography (EEG), ocular movement detected by occulography (EOG) and muscular activity detected by electromyography (EMG) **(Eltaweel et al., 2005)**.

Stages of Sleep:

Before thorough discussion of physiological variables during stages of sleep, the characteristics of these parameters during wakefulness should be highlighted **(Smolley, 2007)**. Throughout wakefulness, EEG shows low

voltage fast activity or activated pattern. Voluntary eye movements and eye blinks are obvious. The EMG has high tonic activity with additional phasic activity related to voluntary movements **(Benca et al., 2005)**.

The Transition from Wakefulness to Sleep

The exact onset of sleep has been difficult to pinpoint because specific alterations in EEG, EMG, or EOG patterns are not consistently linked to a person's perception of the beginning of sleep. Also, subjects may report they remain awake while they manifest behavioral changes indicative of sleep **(Smolley, 2007)**. EMG amplitude may decrease as a person becomes sleepy but there is no precise level that demarcates sleep onset, especially in view of the fact that a relaxed person may have an EMG indistinguishable from definite sleep. EOG during relaxed wakefulness shows rapid movements and blinks while the eye is opened and few or no eye movements while the eyes are closed **(Russo, 2005)**. Moreover, during eye closure in preparation for sleep, alpha activity (8-13 cycles per second) becomes prominent especially in the occipital region **(Pivik, 2000)**.

NREM Sleep:

NREM sleep accounts for 75% to 80% of sleeping time in normal adults. NREM is divided into four stages (stages 1, 2, 3, and 4) defined by typical waveforms of the EEG which show a tendency to slowing as do the eye movements on the EOG. The stages are generally related to a depth of sleep increasing from stage 1 through stage 4, with the depth of sleep determined by the EEG and the intensity of the stimulus needed to cause arousal. The threshold for arousal is lowest in the first stage and highest in the fourth **(Smolley, 2007)**.

Stage I:

Stage I is considered a transition between wakefulness and sleep. It usually forms about 3% to 6% of total sleep time in normal adults. During this stage, aroused subjects describe being half awake rather than sleeping **(Stores, 2003)**.

EEG shows mainly mixed frequencies in the range of 4 to 7 cps of low to moderate voltage of about 50 to 75 microvolt (Theta waves) that replaces the alpha waves of wakefulness. Staged I of sleep is recorded when alpha waves drops to less than 50% of the record **(Eltaweel et al., 2005)**.

The appearance of the Vertex waves is another important EEG finding that is recorded during Stage I of

sleep. A Vertex wave is a compound potential formed of a small spike discharge of a positive polarity, a large negative, a large negative wave followed by another positive spiky discharge **(McDonald, 2006)**.

EOG records slow and rolling eye movements.

EMG activity is moderate-to-low denoting muscle relaxation. Occasionally, individuals may experience hypnic jerks (Sudden muscle contractions associated with sense of falling, dream-like imagery or both).

Stage II:

After a few minutes of stage I, sleep usually progresses to stage II. Stage II and the subsequent stages of NREM and REM sleep are all subjectively perceived as sleep **(Benca et al., 2005)**.

Then the transition from stage I to stage II is signed by the occurrence on the EEGs of characteristic burst of 12 to 15 cps waves, lasting for one-half to two seconds, with a global shape of spindle. These "sleep spindles" are accompanied by sharp spikes of high-voltage brain activity present on the different EEG leads and called "K complex" **(Muzet, 2004)**.

After some minutes, the electroencephalogram shows large undulations and those characteristic wave forms, occurring at about one-half to 2 cycles per second, are called "delta" waves. The amount of delta waves during the scoring

period determines the current sleep stage. If less than 20% of the period is occupied by delta waves, sleeper is considered as being still in stage II **(Ropper & Samuels, 2005)**.

EOG records no eye movements yet infrequent eye movements may persist briefly after the appearance of the sleep spindles.

EMG records low tonic activity **(Eltaweel et al., 2005)**.

Stage III:

Particularly in the beginning of the night, stage II of sleep is followed by a period of Stage III and VI. The slow background EEG activity moves into the foreground and dominates the picture. Delta waves are particularly prominent especially in the anterior region Stage III is defined when the delta waves constitute not less than 20% of the recordings not also not more than 50% of it **(Ropper & Samuels, 2005)**.

EOG records no eye movements yet if the eye lid is raised, pupils appear smaller than before with intact light reflex.

EMG records low tonic activity and generally muscle tone decreases gradually from stage II to stage VI **(Benca et al., 2005)**.

Stage VI:

In this stage, delta waves forms more than 50% of the recordings of the EEG. EOG records no eye movements and EMG records low tonic activity **(Wilson & Nutt, 2008)**.

Stage III and VI are called Slow Wave Sleep (SWS) or Delta Sleep due to the prominence of slow waves (delta waves) in the EEG recordings in these stages of sleep. It is worth mentioning that Stages III and VI are also called Deep Sleep as the threshold of arousal is high at these stages of sleep. When people are aroused at these stages of sleep, they are usually disoriented and full arousal may take up to 5 minutes or more **(Higgins & George, 2007)**.

REM Sleep:

REM sleep accounts for 20% to 25% of sleeping time in normal adults.

In contrast to NREM sleep, the entry to REM sleep is rapid and fairly sudden. REM sleep is distinguishable from NREM sleep by changes in physiological states, including its characteristic rapid eye movements after which this stage of sleep was named **(Wilson & Nutt, 2008).**

EEG recording show low voltage mixed frequency activity. It is similar frequency yet lower amplitude compared to stage I of NREM sleep **(Smolley, 2007)**. Saw tooth waves appear in short bursts over frontal leads or

vertex. These are periods of alpha waves that are slightly slower than wakefulness with frequencies 2-6 cps and notched morphology **(Eltaweel et al., 2005)**.

EOG reveals paroxysmal relatively sharp contoured high amplitude activity occurring in all eye leads simultaneously representing clusters of rapid jerky eye movements that are usually lateral **(Castronovo & Butkov, 2007)**.

As for EMG recordings, the prominent feature of REM sleep is the tonic suppression of the skeletal muscle tone and reflexes resulting in atonia of skeletal muscles except for the extra ocular muscles and diaphragm. Superimposed on this background of tonic muscle inhibition, episodes of muscle twitches can be detected **(Benca et al., 2005)**.

Therefore, REM sleep is rather described in two components rather than stages. These components are tonic and phasic periods. During the tonic periods, which account for the majority of REM sleep, muscle tone is decreased and the EEG is similar to that seen during stage 1 NREM sleep. These tonic periods are interrupted by intermittent phasic REM events. During these periods, the eye movements characteristic of REM sleep occur in bursts, which are followed by the tonic periods of EOG

quiescence. Coupled with the bursts of eye movements are phasic muscle twitches, typically involving peripheral muscles, although the reduced muscle tone (i.e., atonia) characteristic of the tonic periods continues in most muscle groups **(Timothy & Thomas, 2001; Shalaby et al., 2005).**

Table (1.1): Sleep stage scoring criteria

Stage	EEC	EOG	EMG
Wakefulness	Eyes closed; alpha prominent in the occipital region. Alpha attenuates with concentration Eyes open; low voltage mixed frequency, beta activity	Voluntary control; blinks, Rapid eye movements, Slow eye movements if drowsy	Tonic activity, relatively high, voluntary movement
NREM Stage I	Low voltage mixed frequency, theta activity, vertex sharp waves	Slow eye movements	Tonic activity, slight decrease from wakefulness
Stage II	Relatively low voltage mixed frequency background. Sleep spindles and/or K complexes	Occasionally Slow eye movements near sleep onset; otherwise, reflects EEG activity (mostly, no eye movements)	Tonic activity
Stage III	20 to50% delta waves, 0.5 to 2 Hz; greater than 75 uV in amplitude	Reflects EEG activity (mostly, no eye movements)	Tonic activity
Stage IV	> 50% delta waves, 0.5 to 2 Hz; greater than 75 uV in amplitude		
REM	Relatively low voltage mixed frequency, possible saw tooth waves, theta activity	Phasic Rapid eye movements	Tonic suppression, phasic twitches

*Adapted from**: Castronovo and Butkov (2007)***
Fundamentals of Sleep Technology, 1st Edition
Sleep Stages and Sleep Architecture

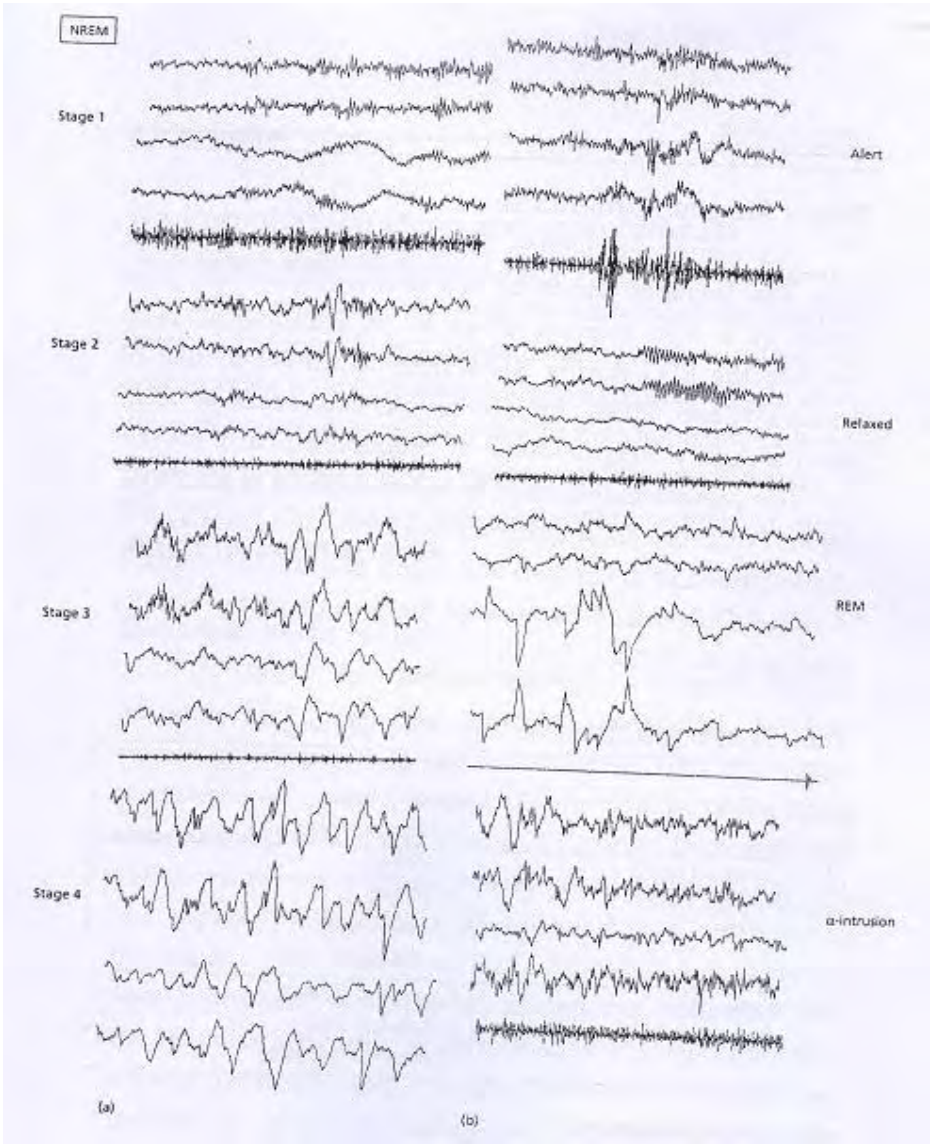

Fig.1.1: EEG waveforms during sleep and wakefulness.

Adapted from: ***Shneerson 2005 , Sleep Medicine: A Guide to Sleep and its Disorders***

Sleep stages nomenclature:

As mentioned before, REM sleep drives its name from the frequent bursts of eye movement activity that occur. It is also referred to as to as Paradoxical sleep because the EEG during REM sleep is similar to that of waking **(Chen, 2006)**. In infants, the equivalent of REM sleep is Active Sleep because of prominent phasic muscle twitches present in this stage in infants **(Davis et al., 2004)**. As for NREM sleep, it is also called Orthodox sleep as it is characterized by decreased activation of EEG. In infants, it is called Quiet sleep because of the lack of motor activity **(Benca et al., 2005)**.

Table (1.2) Nomenclature of sleep states and stages

NREM	Quiet sleep (infants) Orthodox sleep Synchronized sleep
NREM stages 1 and 2	Light sleep
NREM stages 3 and 4	Deep sleep Slow-wave sleep Delta sleep
REM sleep	Active sleep (infants) Paradoxical sleep Desynchronized sleep

Adapted from ***Shneerson 2005***
Sleep Medicine: A Guide to Sleep and its Disorders

Neurobiology of sleep and wakefulness:

Sleep and wakefulness are governed by separate yet interacting systems. Although the activity of the cerebral cortex is critical in determining whether sleep or wakefulness occurs, it does not generate the drive to enter sleep or wakefulness. This is due to the interaction of many influences, some of which are localized to specific areas of the central nervous system and others which are more diffuse **(Benca et al., 2005)**.

Historical background:

In 1949, the Italian neurophysiologists **Horace Magoun** and **Giuseppe Moruzzi** discovered the first circuits governing sleep and wakefulness. They found that stimulating a group of neurons in the midline of the brain stem aroused a sleeping animal. Likewise, lesions of this region resulted in persistent sleep. Anatomically, this area is composed of a mixture of cell nuclei and nerve fibers that form a reticulum (from the Latin word rete, meaning "net"). Moruzzi and Magoun named this brainstem area the reticular activating system (RAS) and proposed that it is responsible for sleep– waking behavior. This discovery initiated a variety of studies that eventually lead to the knowledge and understanding ascending reticular activating system (ARAS) and other areas of the brain

related to sleep and wakefulness **(Higgins & George, 2007)**.

Some of the most important anatomical structures concerned with sleep–wake regulation will be discussed together with their main neurotransmitters of action.

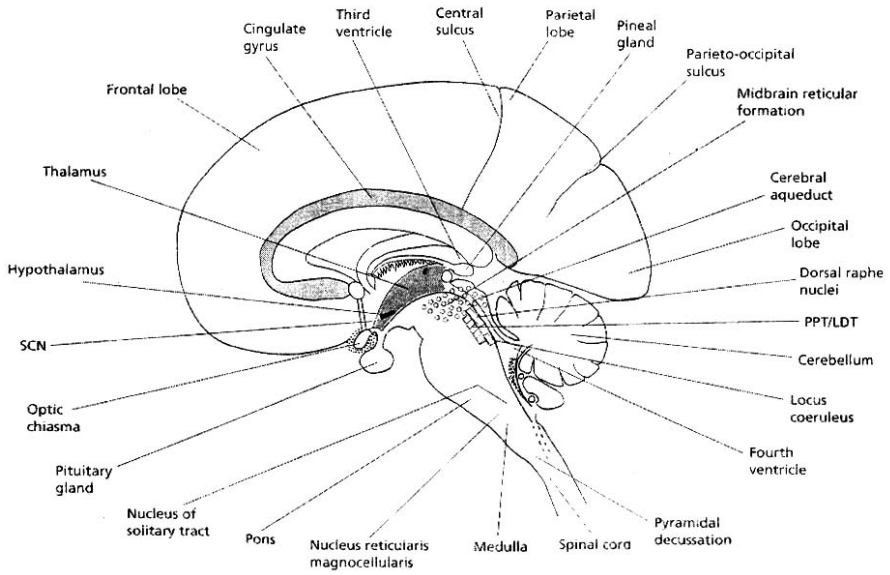

Fig.1.2: Neuro anatomy of sleep-related structures. SCN suprachiasmatic nuclei; LDT, laterodorsal tegmental nuclei; PPT, pedunculopontine nuclei

Adapted from ***Shneerson 2005***
Sleep Medicine: A Guide to Sleep and its Disorders

Ascending reticular activating system (ARAS)

The ascending reticular activating system is a physiological entity which promotes wakefulness when it is active and allows sleep when it is inhibited or inactive. It was originally thought to be a homogeneous system, but the complexity of its structure and function is now realized. It governs the homeostatic drive and many of the reflex components of the adaptive sleep drive, and is closely connected to the circadian sleep rhythms **(Espana & Scammell, 2004)**.

The ascending reticular activating system is largely contained in the brainstem reticular formation which is a loosely connected structure with small groups of cells and nuclei, large numbers of short interneurones and complex ascending and descending interconnecting tracts. Most of the reticular formation lies in the central core or tegmentum of the pons and midbrain, but it also extends into the medulla, hypothalamus and thalamus. It has a complex microstructure and GABA is secreted at most of its synapses. It has an extensive influence over the sensory input to the brainstem, motor function of the cranial nerve nuclei and spinal cord, and the state of sleep or wakefulness **(Bazzett & Kolb, 2005)**.

Locus ceruleus

This is situated in the upper dorsal pons and is noradrenergic. It has widespread connections in the brainstem, thalamus and basal forebrain. It is most active in wakefulness, partially suppressed in NREM sleep and inactive in REM sleep. It inhibits the activity of the LDT/PPT and is itself inhibited by GABA-ergic neurones **(Shneerson, 2005)**.

Raphe nuclei

These are situated in the midline in the midbrain and are serotonergic. The most important is the dorsal raphe nucleus. The raphe nuclei are most active in wakefulness, partially suppressed in NREM sleep and inactive in REM sleep **(Leonard, 2003)**.

Laterodorsal tegmental and pedunculopontine tegmental (LDT/PPT) nuclei

These are situated in the dorsal pontine tegmental reticular formation and their neurones are cholinergic. They are inhibited by the locus ceruleus, raphe nuclei and tubero-mammillary nuclei. They connect to widespread areas in the brainstem and to the thalamus. They fire at high rates when the EEG is activated, that is in wakefulness and REM sleep but reduce their firing during NREM sleep. They are the primary REM sleep generator and when

active inhibit both the locus ceruleus and the raphe nuclei. They are also involved in generation of REM sleep atonia and contribute to visual components of dreams and hallucinations **(Espana & Scammell, 2004)**.

Tubero-mammillary nuclei (TMN)

These nuclei are situated in the posterior hypothalamus and are histaminergic. They only receive afferent input from the ventrolateral preoptic nucleus (VLPO) and the Orexin system in the lateral hypothalamus. They inhibit particularly the VLPO and the LDT/PPT.

The TMN are most active in wakefulness, partially suppressed in NREM sleep and inactive in REM sleep. The TMN promote wakefulness and suppress both NREM and REM sleep **(Shneerson, 2005).**

Perifornical nuclei

These are located in the lateral hypothalamus and their neurones secrete orexins (hypocretins). They project to the brainstem aminergic centres, particularly the locus ceruleus, but also the raphe nuclei and areas of ARAS. They are excitatory at these sites, but lead to inhibition of the LDT/PPT. They are most active in wakefulness, which they promote, and they limit the duration of REM sleep, but have direct effect on the VLPO. Deficiency in the

Orexin system is closely related to narcolepsy **(Beine, 2007)**.

Ventrolateral preoptic nuclei (VLPO)

These are situated inferiorly to the SCN and lateral to the third ventricle, adjacent to the ventromedial preoptic nuclei (VMPO). Their neurones secrete both GABA and galanine which are inhibitory neurotransmitters.

They inhibit all the aminergic brainstem arousal nuclei, including the locus ceruleus, raphe nuclei, mesolimbic system and also the tubero-mammillary nuclei **(Nishino et al., 2004).**

The dorsal part of the VLPO promotes NREM sleep, and its medial extension, which projects particularly to the LDT/PPT, induces REM sleep. The VLPO activity is not related to circadian rhythms, but increases with sleep deprivation. The VLPO is active in sleep and inactive during wakefulness. Its widespread inhibitory connections give it the potential to cause a synchronized reactivation of the sleep promoting centres, but it is inhibited by the aminergic arousal systems, particularly the tubero-mammillary nuclei, as well as the cholinergic basal forebrain **(Higgins & George, 2007).**

Thalamus

The thalamus is the final common path for most of the information reaching the cortex from receptors, apart from olfaction, and from the brainstem. The thalamus modifies these inputs, in effect acting as a gate determining which of the stimuli reach the cortex and in what form, although thalamic activity is itself regulated by the cerebral cortex. As the homeostatic drive to sleep wanes, the ability of the thalamus to block transmission to the cortex weakens and arousals occur **(Benca et al., 2005)**.

The thalamic reticular nucleus is especially important in interacting with the cerebral cortex and determining the state of arousal. It has groups of excitatory neurones, which release glutamate, and inhibitory neurones, which release GABA at their synapses. Intrathalamic relay neurones modify the thalamic activity whereas other neurones form the thalamocortical projection fibres **(Shneerson, 2005).**

Synchronization of cortical activity initiates and maintains the state of NREM sleep. It effectively disconnects the cerebral cortex from brainstem and other influences, although this is reversible through the mechanism of arousal. The thalamus not only protects the cortex from other incoming electrical impulses, but also, through its GABA secreting neurones, it inhibits brainstem

centres that are capable of leading to an arousal. It also influences REM sleep through its projections to the LDT/PPT **(Russo, 2005).**

Neurochemistry of sleep and wakefulness

Noradrenaline (norepinephrine)

This promotes wakefulness and inhibits REM sleep through its alpha adrenergic actions. Neurones in the locus ceruleus release noradrenaline and project widely throughout the brainstem and to the hypothalamus and thalamus. They inhibit the LDT/PPT nuclei and the VLPO and also reach the limbic system where they influence mood and behavior **(Benca et al., 2005)**.

Acetylcholine

There are two main groups of cholinergic neurones:
LDT/PPT nuclei in the pontine reticular formation

These promote REM sleep and wakefulness through their ability to induce thalamocortical desynchronization. They also project to the hypothalamus and basal forebrain. They contribute to loss of skeletal muscle activity in REM sleep **(Webster & Stanford, 2001).**

Basal forebrain cholinergic neurones

These are located in the basal nucleus of Meynert and radiate to the whole cerebral cortex. They promote REM sleep and wakefulness. They are inhibited by local extracellular accumulation of adenosine. Disorders of cholinergic activity within the central nervous system are important factors in narcolepsy and REM sleep behavior disorder **(Espana & Scammell, 2004)**.

5-Hydroxytryptamine (5HT, Serotonin)

Around 15 5HT receptors have been identified of which 5HT 1A and 5HT 2A have most impact on sleep. Stimulation of 5HT 1A receptors reduces the duration of REM sleep, elevates the mood and reduces anxiety. 5HT 2A reduces the duration of stages 3 and 4 NREM sleep, promotes awakenings from sleep, and also leads to vasoconstriction **(Webster & Stanford, 2001).**

The actions of 5HT are complex, not only because of the large number of receptors, but also because of their multiple and often mutually antagonistic interactions. In general, however, they promote wakefulness rather than sleep and are involved with sensory processing and motor activity, particularly related to mood. On the other hand, serotonergic systems promote sleep by producing a sated, quiet waking state that precedes and facilitates SWS. They

may also be involved in the control of respiration and in thermoregulation and hallucinatory states. 5HT-secreting neurones are most active in wakefulness, partially suppressed in NREM sleep and inactive in REM sleep **(Shneerson, 2005)**.

Therefore, 5HT can be considered as a neuromodulator that may normally facilitate the onset to sleep yet plays minimal role in maintaining sleep and major role during awakening.

Most serotonergic neurones are in the raphe nuclei, particularly the dorsal raphe nuclei. These inhibit the LDT/PPT nuclei in the pons, promote wakefulness through excitation of the thalamic reticular nucleus and also inhibit the VLPO. They project to the SCN, basal forebrain, medulla and spinal cord **(Espana & Scammell, 2004)**.

Dopamine

Dopamine has complex effects on sleep and wakefulness because of its multiple interactions with other neurotransmitter systems in many areas of the brain. Dopaminergic neurones arise in the midbrain ventral tegmental area and form two systems.

Nigro-striatal pathway Neurones from the substantia nigra radiate to the striatum, nucleus accumbens, and indirectly to the prefrontal cortex. They increase alertness, modify motor activity and have sympathetic-like effects, including an increase in heart rate and blood pressure, *Mesolimbic tract (mesocorticolimbic pathway)*

This projects to the prefrontal cortex and limbic cortex, particularly the amygdala and hippocampus, and is associated with arousal, cognitive and emotional function **(Webster, 2001)**.

Although Dopamine (DA), like noradrenaline, is principally a wake-promoting transmitter/modulator; however, unlike noradrenaline, it is particularly associated with the pleasurable and rewarding emotional states that may also occur during sleep. Moreover, During REM sleep, the monoaminergic neurons become silent except for the Dopaminergic neurons. The maintained discharge of dopamine during REM contributes to the cognitive correlate of delusions and hallucinations (dreaming) of that state **(Benca et al., 2005)**.

Disorders of dopamine activity within the central nervous system are important factors in the restless legs syndrome, in excessive daytime sleepiness **(Russo, 2005).**

Histamine

There are H1, H2 and H3 receptors within the central nervous system, but the latter are the most important. Like noradrenergic neurons, presumed histaminergic neurons discharge at their maximal rate during waking, decrease their rate during SWS and cease firing during REM **(Stahl, 2008).**

Consequently, it is now understood that histamine promotes wakefulness and arousal and inhibits both NREM and REM sleep. It is released from neurones in the tubero-mammillary nucleus of the posterior hypothalamus, which project widely, particularly to the VLPO, locus ceruleus, raphe nuclei and LDT/PPT. The mutual inhibition of the VLPO and TMN is responsible for the oscillation between sleep and wakefulness. Histaminergic inhibition of LDT/PPT inhibits REM sleep. The histaminergic neurones that project to the cerebral cortex not only promote arousal but also planning and creative cognitive functions **(Shneerson, 2005)**

Glutamate

Glutamate promotes wakefulness and is the main excitatory neurotransmitter in the central nervous system. It is the transmitter of the thalamocortical projection fibres which are responsible for synchronizing cortical activity

during NREM sleep, and of the cortico-spinal pathway which arises from the pyramidal cells in the cerebral cortex. Glutamatergic neurones are also present particularly in the ascending reticular activating system of the brainstem, projecting to the LDT/PPT nuclei and to the basal forebrain. Glutamate seems to be critically involved in the generation of REM sleep and muscle atonia. Glutamate agonists can stimulate REM sleep when injected into the ponto-mesencephalic tegmentum **(Webster & Stanford, 2001).**

Gamma amino butyric acid (GABA)

GABA is the most common inhibitory amino-acid transmitter in the central nervous system and, as such, is involved in almost all inhibitory processes that occur during different states. In addition to suppressing discharge of neurons, GABAergic neurons can pace the activity of neurons in fast or slow rhythms **(Shneerson, 2005)**.

The activity of particular GABAergic neurons is similarly important for pacing slower sleep rhythms while inhibiting activating systems. Through a bursting discharge, GABAergic neurons of the thalamic reticular nuclei play a critical role in the generation of thalamo-cortical spindle activity, by both inhibiting and pacing the thalamic relay neurons in association with the spindles and

then slower delta activity through SWS. These GABAergic neurons appear to be responsible for closing the afferent gateway through the thalamus to the cerebral cortex during SWS.

In addition, GABA is contained in locally projecting neurons within the basal forebrain that may inhibit the cholinergic neurons during SWS. Moreover, GABA release from the VLPO inhibits the aminergic wakefulness promoting nuclei **(Webster & Stanford, 2001; Eltaweel et al., 2005)**.

Galanine

This is an inhibitory peptide secreted by neurones of the VLPO. It promotes sleep.

Glycine

This is located mainly in the brainstem and spinal cord, where it is released at synapses of the reticulospinal tract with alpha motor neurones. These are inhibited and this leads to the muscle atonia of REM sleep **(Shneerson, 2005).**

Peptides

This important group of chemicals includes most of the sleep factors and cytokines which, like melatonin, also have an important influence on the immune response.

Hypocretins (orexins)

Hypocretins are peptides derived from a pre-hypocretin protein which splits to form two related peptides, hypocretin 1 and hypocretin 2 (orexin A and B). These are located in the synaptic vesicles of neurones in the perifornical area of the lateral hypothalamus. They are excitatory neurotransmitters with specific hypocretin 1 and 2 receptors, although hypocretins appear to interact with noradrenaline, dopamine and acetylcholine **(Siegel et al., 2001)**.

The neurones in the lateral hypothalamus project widely, particularly to the aminergic brainstem arousal centres, especially the locus coeruleus and the LDT/PPT. They also connect to the limbic system, thalamus and

cerebral cortex, but not significantly to the VLPO. Hypocretin-containing neurones tend to stabilize wakefulness and limit the duration of REM sleep. They also increase motor activity, particularly to increase food intake and for defense, and alter the blood flow to skeletal muscles. In REM sleep hypocretins appear to enhance motor inhibition rather than activity **(Ganjavi & Shapiro, 2007).**

Narcolepsy is associated with loss of hypocretin secreting neurones, but the hypocretin level is raised in the restless legs syndrome, where there is an increase in motor activity **(Siegel et al., 2001).**

Cannabinoids

There are two types of endogenous cannabinoid receptors, CB1 and CB2, both of which are coupled to G proteins. CB1 receptors are widespread within the central nervous system. Anandamide, a fatty acid, is the best recognized endogenous cannabinoid. It appears to promote NREM sleep but its effects are blocked by interleukins.

Oleamide

This is an endogenous sleep-producing polyunsaturated fatty acid which is synthesized from arachidonic acid, and has similar actions to anandamide, an endogenous cannabinoid. It promotes NREM sleep and reduces motor activity. Its concentration in the cerebrospinal fluid increases during sleep deprivation **(Shneerson, 2005).**

Adenosine

This is a purine nucleoside which is produced from adenosine triphosphate (ATP) and adenosine diphosphate (ADP) and is converted into inosine and then to hypoxanthine. There are A1, A2A, A2B and A3 adenosine receptors. A1 receptors are antagonized by xanthines.

Adenosine is a vasodilator. It promotes NREM sleep, especially stages 3 and 4, by inhibiting the basal forebrain cholinergic neurones. It may also have an effect on the pontine cholinergic neurones. Adenosine accumulates extracellularly during wakefulness as a result of the metabolic activity of brain cells, particularly astrocytes. Astrocytes provide a readily available supply of glucose for local neurones from their glycogen stores, but their metabolic activity consumes ATP and releases adenosine. This binds particularly to the A1 receptor, leading to

inhibition of basal forebrain cholinergic neurones. During sleep the concentration of adenosine falls and this enables the neurones to become active again and promote wakefulness. These cyclical changes in adenosine concentrations probably contribute to the homeostatic sleep drive **(Higgins & George, 2007).**

Opioid peptides

These interact with endorphins, enkephalins and dynorphins, which are located particularly in the medulla, hypothalamus, thalamus, basal ganglia and limbic system. They tend to inhibit REM sleep partly through their action on the LDT/PPT nuclei **(Shneerson, 2005).**

Table (1.3): Effect of Neurotransmitters on Sleep

Neurotransmitter	*Promotes*	*Inhibits*	*Other actions*
Noradrenaline (norepinephrine)	Wakefulness	REM	—
Acetylcholine	Wakefulness, REM	—	Motor inhibition in REM
Serotonin	Wakefulness	REM	facilitate the onset to sleep
Dopamine	Wakefulness	—	contributes to the cognitive correlate of delusions and hallucinations (dreaming)
Histamine	Wakefulness	REM NREM	—
Glutamate	wakefulness		—
GABA	NREM	Wakefulness, REM	—
Cannabinoids	NREM	—	—
Oleamide	NREM	—	—
Adenosine	NREM	wakefulness	—
Opioid peptides	—	REM	—

Opioids and control of sleep

There are four major classes of endogenous opioid receptors in the central nervous system: μ (mu), κ (kappa), δ (delta) and N/OFQ (nociceptin/orphanin FQ) receptor. Each of these receptor subtypes has a distinct profile in terms of its pharmacology as well as its distribution within the brain and spinal cord. Three classes of opioid peptides have been identified: the enkephalins, endorphins and dynorphins **(Gutstein & Akil, 2005)**

These have been shown to have a role in sensory modulation and analgesia and may be important in the onset and maintenance of sleep, and therefore be involved in attenuation of arousal and waking. Enkephalin is contained in neurons that are widely distributed through the brain and regions involved in slow wave sleep (SWS) such as the solitary tract nucleus, the preoptic area and the raphe, where it is co-localized with serotonin receptors. Enkephalin containing fibres innervate the locus coeruleus noradrenergic neurons which are inhibited by locally delivered opioids and produce decreased awakenings and increased SWS. β-Endorphin is derived from prepro-opiomelanocortin (POMC) which is also processed into the non-opioid peptides adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (α-MSH) and β-lipotropin (β -LPH) hormone. ACTH is the hormone closely related to stress and α -MSH has been suggested to

induce sleep and increase SWS. The association of sharing the same precursors implies a close physiological linkage between stress, sleep and the opioid systems **(Wang & Teichtahl, 2007).**

The mechanism of opioid peptide action on sleep control remains unclear. It has been hypothesized that opioid peptides in conjunction with the peptide neurohormone vasopressin are involved in the induction and maintenance of the sleep state through a complex and modifiable circadian mechanism driven by the suprachiasmatic nuclei (SCN). Vasopressin, one of the neurohormones in the circadian pacemaker SCN, has been shown to have a close relationship to circadian rhythms.

Vasopressin causes the secretion of endorphins into the cerebro–spinal fluid (CSF), while pain and opioids stimulate the secretion of vasopressin from the pituitary. In the supraoptic and paraventricular nuclei, vasopressin is stored with the opioid peptide dynorphin which also shows circadian variability of its blood levels. It is possible that both vasopressin and the opioids are part of the neurochemical mechanism driven by SCN to maintain the daily sleep and wake rhythm.

Moreover, some studies attribute the opioids role in sleep–wake regulation by the direct central opioid inputs to the VLPO. The VLPO was discovered to have μ and κ receptors which are likely involved in mediating the hypnotic response to high levels of opioid analgesics **(Greco et al., 2008).**

Neurophysiology of sleep

Mechanism of NREM sleep:

NREM sleep is controlled by complex initiating and maintenance mechanisms, the extent of which is not fully elaborated. Probably no single sleep-generating center exists. A more likely mechanism is sleep-generating circuits with inputs from brainstem and hypothalamic neuronal groups **(Siegel, 2005)**. Within these circuits, the "switch" for sleep is considered to be the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus. This area becomes active during sleep and uses the inhibitory neurotransmitters GABA and galanine to initiate sleep by inhibiting the arousal regions of the brain **(Kryger et al., 2005)**. The VLPO innervates and can inhibit the wake-promoting regions of the brain including the tuberomammillary nucleus, lateral hypothalamus, locus ceruleus, dorsal raphe, laterodorsal tegmental nucleus, and pedunculopontine tegmental nucleus. The hypocretin

(orexin) neurons in the lateral hypothalamus help stabilize this switch **(Siegel et al., 2001).**

The tuberoinfundibular region projects rostrally to the intralaminar nuclei of the thalamus and to the cerebral cortex. Inhibition of the tuberoinfundibular region is a critical step toward falling asleep because it results in functional disconnection between the brain stem and the more rostral thalamus and cortex. A decrease in ascending thalamic cholinergic transmissions occurs in association with decreasing cortical responsiveness. In addition to inhibiting higher cortical consciousness, the tuberoinfundibular tract projects caudally into the pontine reticular system and inhibits afferent transmissions from ascending cholinergic tracts **(Espana & Scammell, 2004)**.

NREM is an active state that is maintained partly through oscillations between the thalamus and the cortex. The 3 major oscillation systems are sleep spindles, delta oscillations, and slow cortical oscillations. Sleep spindles, a hallmark of stage II sleep, are generated by bursts of hyperpolarizing GABAnergic thalamic reticular neurons. These bursts inhibit thalamocortical projection neurons. As deafferentation spreads, corticothalamic projections back to the thalamus synchronize. As hyperpolarization of the thalamic reticular neurons progresses, delta waves are

produced by interactions from both thalamic reticular and cortical pyramidal sources. Slow cortical oscillations are produced in neocortical networks by cyclic hyperpolarizations and depolarizations (**Stevens, 2008)**.

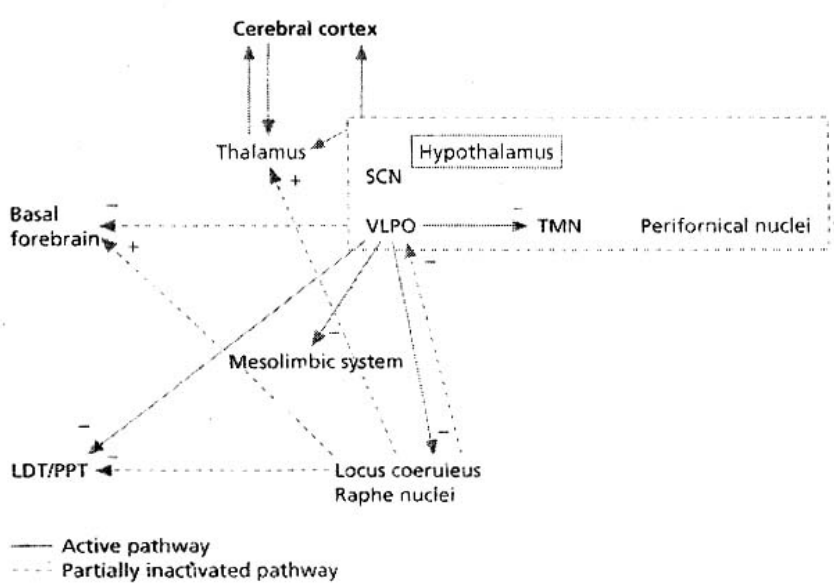

Fig 1.3 Main pathways involved in NREM sleep

Adapted from ***Shneerson 2005***

Sleep Medicine: A Guide to Sleep and its Disorders

Mechanism of REM sleep:

REM sleep is generated by the cholinergic mediated "REM-on neurons" in the mesencephalic and pontine cholinergic neurons. The pedunculopontine tegmental nucleus (PPT) and the lateral dorsal tegmental (LDT) neurons use acetylcholine to trigger cortical desynchrony

via the thalamus. Cortical desynchrony (also described as low voltage mixed frequency) is the EEG hallmark of REM sleep. An additional EEG hallmark of REM sleep is "sawtooth waves." A pharmacologic offshoot of the cholinergic mediation of REM sleep is stage R increasing with cholinergic agonists and decreasing with anticholinergics **(Russo, 2005).**

"REM-off neurons" are the monoadrenergic locus ceruleus and serotonergic raphe neurons. The REM-off neurons use norepinephrine, serotonin, and histamine to inhibit the REM-on cholinergic cells and stop REM sleep. These REM-off neurons become inactive during REM sleep. Medications, such as antidepressants, that increase the amount of norepinephrine or serotonin can cause a pharmacologic suppression of REM sleep **(Saper et al., 2005)**

REM is characterized by muscle atonia, cortical activation, low-voltage desynchronization of the EEG, and rapid eye movements. REM may be considered to have both tonic and phasic characteristics. Tonic muscle atonia is present throughout REM sleep. It results from inhibition of alpha motor neurons by clusters of peri–locus ceruleus neurons, which are referred to collectively as the

dorsolateral small cell reticular group **(Nishino et al., 2004).**

Projection of the presumed cholinergic dorsolateral small cell reticular group is through the medullary reticular formation, which projects through the ventrolateral reticulospinal tract to inhibitory spinal and bulbar interneurons. Glycinergic interneurons produce postsynaptic inhibition and hyperpolarization of the spinal alpha motor neurons. Tonic cortical activation with EEG desynchronization is promoted by projections from cholinergic lateral dorsal tegmental and pedunculopontine tegmental neurons to the thalamic nuclei. Other projections through brainstem reticular formation neurons are likely to be involved as well **(Russo, 2005).**

Phasic rapid eye movements are composed of lateral saccades generated in the paramedian pontine reticular formation and vertical saccades thought to be generated in the mesencephalic reticular formation. REM density is a term used to describe the frequency per minute of the eye movement bursts **(Stevens, 2008)**.

During NREM sleep, the metabolic demand of the brain decreases. This is supported by oxygen positron emission tomography (PET) studies, which show that,

during NREM sleep, the blood flow throughout the entire brain progressively decreases. PET studies also show that, during REM sleep, blood flow increases in the thalamus and the primary visual, motor, and sensory cortices, while remaining comparatively decreased in the prefrontal and parietal associational regions. The increase in blood flow to the primary visual regions of the cortex may explain the vivid nature of REM dreaming, while the continued decrease in blood flow to the prefrontal cortex may explain the unquestioning acceptance of even the most bizarre dream content **(Desseilles et al., 2008).**

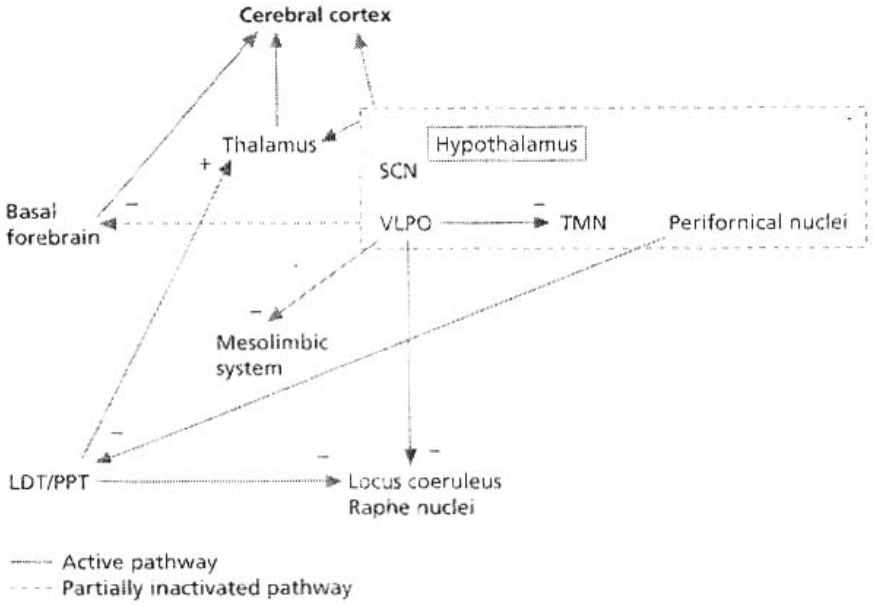

Fig 1.4 Main pathways involved in REM sleep

Adapted from ***Shneerson 2005***

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