Psychiatry Research 273 (2019) 37–41

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

# Depression is differently associated with sleep measurement in obstructive sleep apnea, restless leg syndrome and periodic limb movement disorder

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ARTICLE INFO

*Keywords:*
Depression
Obstructive sleep apnea
Restless leg syndrome
Periodic limb movement disorder

ABSTRACT

Depression causes sleep disturbance and is associated with various sleep-related disorders. However, how depression affects the symptomatic presentation of different sleep-related disorders is unclear. In this study, we investigated the sleep parameters of different sleep-related disorders between depressive and non-depressive patients. A total of 785 patients underwent polysomnography in a mental hospital from Jan 2012 to Jun 2013. We first analyzed variables between the depressive and non-depressive groups. The patients were then divided into four groups: obstructive sleep apnea (OSA, $n = 339$), restless leg syndrome (RLS, $n = 51$), periodic limb movement disorder (PLMD, $n = 58$) and comorbid group (OSA and RLS, $n = 46$). We next compared sleep measures between the depressive and non-depressive subjects within each groups. The patients with OSA and depression were significantly associated with a higher periodic limb movement index. Significantly more patients with RLS patients and depression had initial insomnia complaints. However, significantly more patients with PLMD and depression middle insomnia. Compared with non-depressive population, depressive patients had higher comorbidity with RLS and PLMD. Depression may have different association with the sleep parameters in different sleep-related disorders. Further investigations are needed to investigate how these findings may affect patients' awareness and clinicians' diagnosis and management of sleep-related disorders.

## 1. Introduction

Despite the emerging evidence of the bidirectional causal relationship between depression and insomnia (Sivertsen et al., 2012), the multifaceted interplay and associated neurobiological pathways are still hypothetical (Baglioni et al., 2010; Manber and Chambers, 2009). For clinicians and sleep experts, it is important to understand the association between depression and related sleep symptoms and parameters of different sleep-related disorders.

The difficulty in clinical decision making lies in the fact that sleep-related disorders and depression share common neurobiological risk factors (Atlantis and Baker, 2008; Gao et al., 2009; Reynolds et al., 1997), overlapping symptoms and comorbidities. A bidirectional causal relationship between depression and sleep disturbance is known, however how depression affects or is associated with the symptomatic presentation and parameters of different sleep-related disorders is not fully understand. In this study, we focused on three sleep-related disorders, obstructive sleep apnea (OSA), restless leg syndrome (RLS) and periodic limb movement disorder (PLMD).

OSA is the one of the most common breathing-related disorders and is diagnosed according to obstructive breathing symptoms or events detected by polysomnography (PSG). Some researchers have reported a comorbid relationship between depression and OSA, and also that this relationship may be underestimated (BaHammam et al., 2016; Harris et al., 2009). Björnsdóttir et al. reported that middle insomnia is the most prevalent subtype of insomnia among patients with untreated OSA, but that the prevalence of initial insomnia was the same as in the general population (Björnsdóttir et al., 2013, 2012; Chung, 2003). OSA and depression share common risk factors such as obesity and being overweight. The risk factors for depression in patients with OSA were recently studied by Hein et al. (2017a), however associations among depression and the symptoms and parameters of breathing-related

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https://doi.org/10.1016/j.psychres.2018.12.166
Received 16 August 2018; Received in revised form 14 December 2018; Accepted 29 December 2018
Available online 31 December 2018
0165-1781/ 

disorder have not been thoroughly investigated.

RLS is diagnosed based on symptoms, including with an urge to move the legs, an unpleasant sensation relieved by movement, or symptoms worsening at night. Researchers used to debate the relationship between RLS and depression (Peterson and Benca, 2008), however, ever emerging evidence had shown that a comorbid relationship may be common and bidirectional (Cuellar et al., 2007; Szentkiralyi et al., 2013). In addition, a recent study demonstrated that RLS patients with severe depression may have difficulty falling asleep, difficulty maintaining sleep, early morning awakening and excessive daytime sleepiness (Cho et al., 2017).

Periodic limbs movements at sleep (PLMS) is the leg moving symptom frequently coexisting among different sleep disorders and is mainly diagnosed according to elevated Periodic Limbs Movement Index (PLMI) in PSG. Another similar disorder, periodic limbs movement disorder (PLMD) is a disorder combining PLMS, sleep disturbance and exclusion of other disorders. PLMS is closely related to OSA and RLS. An elevated PLMI is a frequent finding in patients with disordered breathing. Chervin, 2001, Roux, 2013, and PLMS has been reported to have a high prevalence among patients with RLS patients (Gupta et al., 2016). In addition, PLMS and RLS have been reported to be prevalent in certain subjects, such as those who are pregnant and those receiving dialysis (Atekeh et al., 2018; Rijsman et al., 2004; Wilson et al., 2017). PLMS impacts both physical and sleep health, and it may be associated with obesity (Gao et al., 2009) and an increased risk of cardiovascular/cerebrovascular disorder (Barone et al., 2017; Cuellar, 2013; Zhang et al., 2016). It has also been reported to and leads to sleep architecture changes in patients with OSA (Mancebo-Sosa et al., 2016). It is therefore important to study the interactions between RLS, OSA and PLMD/PLMS.

In this study, we investigated associations among depression and the presentation of OSA, RLS and PLMD. Most previous research has established a causal relationship between depression and insomnia according to depressive symptoms or self-report questionnaires (Hedman et al., 2013; Neckelmann et al., 2007; Ohayon and Roth, 2003). In this study, the patients with mood disorders were diagnosed clinically.

## 2. Methods

### 2.1. Subjects

We retrospectively reviewed the medical records and PSG of 785 patients at the sleep center of a mental hospital in central Taiwan, between January 2012 to June 2013. All of the patients were older than 18 years old. A diagnosis of depression was established by an experienced psychiatrist after reviewing the medical records antd coded according to the International Classification of Diseases, 9th Revision (ICD-9). Demographic data, physical measurements, and subjective/objective sleep measures were collected before PSG.

### 2.2. Measures

#### 2.2.1. Demographic and physical variables

Possible confounding factors were collected. Age and gender, which are known risk factors for depression (Krystal, 2004; Lehtinen and Joukamaa, 1994; Wittchen et al., 1994), were collected.

Blood pressure was recorded as mean arterial pressure (MAP, mmHg), body mass was presented using the body mass index (BMI, kg/$m^2$), and cervical circumference was measured in centimeters (cm).

#### 2.2.2. Diagnosis of depression

Psychiatric and biological factors associated with sleep disorders were recorded on the medical records before referral. Patients with ICD-9 codes 296.2, 296.3, 300.4 and 311 were defined as having depressive disorders. Past research has demonstrated that patients with bipolar disorder may have a different PSG pattern (Nofzinger et al., 1991), and therefore they were excluded from this study. The sample size was 736 after excluding the patients with bipolar disorder. Data on anxiety and schizophrenia were also collected. Other general medical conditions such as heart disease and diabetes mellitus were not recorded.

#### 2.2.3. Sleep measurements

Several instruments were applied to assess the types and severity of sleep disturbance.

*Subjective measures*: We collected data on initial insomnia, middle insomnia, daytime sleepiness/fatigue and restless leg symptoms. Initial and middle insomnia were assessed by self-reported questions of “Do you have trouble falling asleep?” and “Do you have trouble staying asleep?” We measured daytime sleepiness/fatigue using the Epworth Sleepiness Scale (ESS). All of our patients completed the questionnaire before undergoing out PSG. An experienced sleep expert reviewed chart records to code the patients with RLS according to the International Classification of Sleep Disorders-II criteria, which include an urge to move the legs, symptoms beginning or worsening during periods of rest or inactivity, symptoms partially or totally relieved by movement and symptoms worsening in the evening or night or only occur in the evening or night.

*Objective measures*: PLMI and the apnea–hypopnea index (AHI), which is an index used to indicate the severity of sleep apnea, were calculated from the PSG reports. Patients with an AHI > 5 were defined as having OSA, and the severity was categorized into three levels: mild (5 < AHI < 15), moderate (15 < AHI < 30) and severe (30 < AHI). Patients with a PLMI > 15 were defined as having PLMD after the exclusion of OSA and RLS in this study.

### 2.3. Analysis strategy

All continuous variables were presented as mean and standard deviation, and categorical variables were presented as relative frequencies (%). In the univariate analysis, we used the Student's *t*-test, chi-square test or Fisher's exact test to compare differences between the patients with and without depression. In order to clearly understand the effects of depression on each sleep measurement and to control for confounding factors, we used multivariate analysis of covariance (MANOVA) to examine differences in subjective and objective sleep measures (ESS, PLMI, and AHI) with gender, initial insomnia, and depression as grouping variables and age, BMI, cervical circumference, MAP, anxiety and schizophrenia as covariates. All data were analyzed using IBM SPSS Statistics software for Windows, version 22.0 (IBM Corp., Armonk, NY). *P*-values < 0.05 were considered to be statistically significant.

### 2.4. Ethics of the study

The study was designed according to the Human Research Protection Program, and was approved by the Office for Human Subject Protection at Changhua Christian Hospital (IRB serial number: 170415).

## 3. Results

### 3.1. Participant characteristics

From January 2012 to June 2013, 736 patients were enrolled, of whom 212 had depression. The mean age was 47.2 years, and 60.2% were males. Of the 736 patients, 46.1%, 6.9%, 7.9% and 6.3% of patients were classified into the OSA, RLS, PLMD and comorbid groups. Of the 212 patients with depression, 25.5%, 15.1%, 12.7% and 7.1% were classified into the OSA, RLS, PLMD and comorbid groups; of the 524 patients without depression, 54.4%, 3.6%, 5.9%, 5.9% were classified into the OSA, RLS, PLMD and comorbid groups, respectively.

**Table 1**
Demographic, physical, psychiatric and sleep measurements.

| | Total Sample ($n$ = 736) | Presence of depression | | $P$-value |
|---|---|---|---|---|
| | | Non-depression ($n$ = 524) | Depression ($n$ = 212) | |
| Demographic | | | | |
| Age (years), mean (SD) | 47.2 (13.9) | 46.2 (14.2) | 49.5 (12.6) | 0.003 |
| Male, % | 60.2 | 67.0 | 43.4 | <0.001 |
| Physical | | | | |
| BMI (kg/m$^2$),mean (SD) | 26 (4.8) | 26.7 (4.9) | 24.2 (3.9) | <0.001 |
| MAP (mmHg), mean (SD) | 112.3 (15.8) | 113.4 (15.8) | 109.8 (15.4) | 0.007 |
| Cervical circumference (cm), mean (SD) | 36.6 (4.2) | 37.2 (4.2) | 35.1 (3.6) | <0.001 |
| Psychiatric characteristics | | | | |
| Anxiety, % | 24.5 | 20.8 | 33.5 | <0.001 |
| Schizophrenia, % | 2.9 | 3.6 | 0.9 | 0.048 |
| Subjective sleep measures | | | | |
| Initial insomnia, % | 46.2 | 37.9 | 66.5 | <0.001 |
| Middle insomnia, % | 47.3 | 41.2 | 62.0 | <0.001 |
| ESS score, mean (SD) | 7.6 (5.2) | 8.1 (5.2) | 6.4 (5.0) | <0.001 |
| Objective sleep measures | | | | |
| AHI, mean (SD) | 14.8 (20) | 17.91 (21.4) | 7.1 (11.8) | <0.001 |
| AHI severity | | | | |
| 5–15, % | | 25.2 | 20.3 | <0.001 |
| 15–30, % | | 15.5 | 6.6 | |
| > 30, % | | 21.9 | 6.1 | |
| PLMI, mean (SD) | 9.3 (22) | 7.6 (17.3) | 13.5 (30.2) | 0.009 |
| OSA (%) | 46.1 | 54.4 | 25.5 | <0.001 |
| RLS (%) | 6.9 | 3.6 | 15.1 | <0.001 |
| PLMD (%) | 7.9 | 5.9 | 12.7 | 0.004 |
| Comorbid OSA + RLS (%) | 6.3 | 5.9 | 7.1 | 0.397 |

$P$-value using the Student's $t$-test for continuous variables (age, BMI, MAP, cervical circumferences, ESS, PLMI, AHI) and the chi-square test or Fisher's exact test for nominal variables when appropriate (gender, initial insomnia, middle insomnia, OSA, RLS, PLMD, comorbid OSA + RLS)
BMI: body mass index
MAP: mean arterial pressure
ESS: Epworth Sleepiness Scale
AHI: apnea–hypopnea index
PLMI: Periodic Limbs Movement Index
OSA: obstructive sleep apnea
RLS: restless leg syndrome
PLMD: periodic limb movement disorder

The demographic variables, physical condition and objective/subjective sleep measurements between the patients with and without depression are summarized in Table 1. Among the demographic variables, the patients with depressive disorders were older (mean = 49.5 years, $p = 0.003$) and more were females (56.6%, $p = 0.003$). Among the physical measurements and comorbid psychiatric conditions, the patients with depressive disorders had a lower MAP (mean = 109.8 mmHg, $p = 0.007$), lower BMI (mean = 24.2 kg/m$^2$, $p < 0.001$) and a lower cervical circumference (mean = 35.1 cm, $p < 0.001$).

Among the subjective sleep measurements, the patients with depressive disorders had a higher proportion of initial insomnia (66.5%, OR = 3.251, $p < 0.001$), a higher proportion of middle insomnia (62%, OR = 2.327, $p < 0.001$), lower ESS score (mean = 6.4, $p < 0.001$) and a higher proportion of RLS (22.9%, OR = 2.701, $p < 0.001$). Among the objective sleep measurements, the patients with depressive disorders had a higher PLMI (mean = 13.5, $p = 0.009$) but a lower AHI (mean = 7.1, $p < 0.001$). The patients with OSA and depression had a lower severity of OSA.

### 3.2. Subjective and objective sleep measures within each group

Table 2 presents the sleep measurements in the depressive and non-depressive patients in each diagnostic group. The OSA patients with depression had a higher PLMI (15.6, $p = 0.001$), lower ESS score (7.1, $p = 0.017$) and higher rate of insomnia (55.6%, $p = 0.001$). The difference in PLMI between the OSA with and without depression was significant ($p = 0.013$, adjusted by age, BMI, cervical circumference, MAP, anxiety and schizophrenia). However, there was not significant difference in ESS ($p = 0.139$, adjusted by age, BMI, cervical circumference and MAP).

The patients with depression and RLS patients had a higher rate of middle insomnia (84.4%, $p = 0.014$), and the patients with depression and PLMD had a higher rate of initial insomnia (77.8%, $p = 0.001$).

## 4. Discussion

This is the first study to assess the associations among objective and subjective sleep measures of different sleep-related disorders and depression. The patients in this study were mostly middle aged (mean = 47.2 years), male ($n$ = 293, 60.2%) and obese (64.8% of the patients had a BMI > 25 kg/m$^2$). The patients with depression had different characteristics, including and older age, female predominance and a lower BMI, and were analyzed further.

The comorbidity phenomena between depression and sleep-related disorders is known until recent years (Staner, 2010), however little is known about how this comorbidity may affect each disorder and the related measurements. Physiological evidence has shown that depression itself can cause sleep disturbance (Peterson and Benca, 2008). It is possible that depression affects various sleep measures in different sleep-related disorders, and, that the effects of depression may differ according to the type of sleep disorders. In this study, we demonstrated that depression may have different association with different sleep measurements in OSA, RLS and PLMD.

We found an elevated PLMI in OSA patients with depression. Other researchers have reported that PLMS is associated with breathing-related disorders (Exar and Collop, 2001; Manconi et al., 2014), and recent research has shown that PLMS and breathing disorders result in greater cumulative changes to sleep architecture, than individual disorders alone, and that the interactions is complex (Mancebo-Sosa et al., 2016). Earlier research also reported an association between depression and PLMS (Aikens et al., 1999; Al-Alawi et al., 2006; Saletu et al., 2002), and several recent studies have demonstrated that certain antidepressant or antipsychotic agents may worsen PLMS or be associated with an increased risk of RLS (Fulda et al., 2013; Goerke et al., 2013; Yang et al., 2005; Zhang et al., 2013). In this study, it was unclear whether the elevated PLMI was caused by depression itself or mediated by the side effects of medications, and further studies are needed to elucidate this issue, such as mediation analysis. We speculate that there may be an additive effect of OSA and depression on the leg movement symptoms, however further studies may be warranted to investigate how this additive effect impacts sleep and physical health.

In the current study, PLMI was not significantly higher in the patients with depression and RLS, PLMD and comorbid groups, although an additive effect of depression may have existed. The small number of patients in the RLS, PLMD and comorbid group may have affected our results. A recent study reported that Korean patients with RLS had different prevalence rates and characteristics of PLMS compared to Western patients (Shin et al., 2016). Ethnic factors may be another explanation for our study results, and the characteristics or genetic factors of different Asian populations may warrant of further investigations.

We found a preliminary but noteworthy phenomenon that depression may be associate with RLS and PLMD in different ways. For

**Table 2**
Subjective and objective sleep measures among the four group in terms of depression.

| | OSA Depression | | | RLS Depression | | | PLMD Depression | | | Comorbid with RLS and OSA Depression | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No ($n$ = 285) | Yes ($n$ = 54) | $P$-value | No ($n$ = 19) | Yes ($n$ = 32) | $P$-value | No ($n$ = 31) | Yes ($n$ = 27) | $P$-value | No ($n$ = 31) | Yes ($n$ = 15) | $P$-value |
| Insomnia | | | | | | | | | | | | |
| Initial, % | 31.7 | 55.6 | **0.001** | 66.7 | 68.8 | 0.880 | 34.5 | 77.8 | **0.001** | 54.8 | 60.0 | 0.741 |
| Middle, % | 41.1 | 50.0 | 0.224 | 52.6 | 84.4 | **0.014** | 34.5 | 50.0 | 0.244 | 48.4 | 60.0 | 0.460 |
| ESS, mean (SD) | 9.0 (5.4) | 7.1 (4.9) | 0.139 | 7.0 (4.6) | 6.4 (4.6) | 0.436 | 7.0 (4.9) | 6.6 (4.4) | 0.566 | 7.2 (4.6) | 8.8 (5.6) | 0.086 |
| AHI, mean (SD) | 27.7 (21.8) | 18.5 (14.6) | 0.252 | 1.3 (1.6) | 1.6 (1.4) | 0.703 | 1.8 (1.6) | 2 (1.7) | 0.187 | 26.6 (21.4) | 20 (16) | 0.583 |
| PLMI, mean (SD) | 6.7 (13.4) | 15.6 (36) | **0.013** | 4.7 (8.6) | 11.7 (17.7) | 0.275 | 37.8 (20) | 41 (24) | 0.706 | 15 (38.4) | 8.7 (13.8) | 0.467 |

*P*-values of nominal variables using the chi-square test or Fisher's exact test when appropriate.
*P*-values of continuous variables by using multivariate analysis of covariance controlling for covariates (age, BMI, cervical circumference, MAP, anxiety and schizophrenia).
OSA: obstructive sleep apnea
RLS: restless leg syndrome
PLMD: periodic limb movement disorder
ESS: Epworth Sleepiness Scale
AHI: apnea–hypopnea index
PLMI: Periodic Limbs Movement Index

example the patients with depression and RLS tended to have a higher rate of initial insomnia, whereas those with depression and PLMD tended to have a higher rate middle insomnia. However, there were no significant differences in the middle insomnia complaints of the RLS patients and initial insomnia complaints of the PLMD patients. These findings are different to past research. In Cho and Kim's research (Cho et al., 2017), RLS patients with severe depressive symptoms had both difficulty falling asleep and suffered from broken sleep. There may be two explanations for this discrepancy. One may be the small number of patients in these two groups in our study. Another may lie in the study design. Our study was not based on depressive symptoms/questionnaires but clinical diagnoses, which may imply that the types or symptoms severity of depression symptoms may have different effects on sleep disturbance. However, how these factors may affect the patients' awareness of their condition and self-reporting is still unknown. Since sleep lab services are not available in every clinical setting and depression is frequently comorbid with sleep disorders, understanding the symptomatic differences between different sleep disorders in patients with depression may be an important issue for clinicians.

The depressive patients tended to have higher proportions of RLS and PLMD in our study population. The prevalence of any RLS symptoms during a year is about 7% in European and American populations (Allen et al., 2005). The prevalence in Taiwan is 1.57% (Chen et al., 2010) according to Telephone survey and 10.4% among pregnant women (Chen et al., 2012). Although the prevalence rate in patients attending a sleep center may involve referral bias, our results are compatible with a recent report that RLS and comorbid depression (Rana et al., 2016; Szentkiralyi et al., 2013). Higher rates of PLMD and RLS have been reported in depressive patients receiving dialysis, and similar EEG patterns between have been reported PLMD and RLS patients. Elevated PLMI is both a criterion for PLMD and the associated symptoms of RLS. Since RLS criteria are comprised mainly of subjective sensory phenomena and the PLMD criteria are based mainly on objective motor findings with exclusions, it may be possible that RLS and PLMD are like two side of a coin in certain clinical condition. There may be coexisting factors which decrease or enhance the patients' perception of limb movement or the urge to move a leg. If a patient's sensory process is enhanced by some mechanisms, such as due to sleep disturbance caused by psychotropic agents or hyperarousal of depression (Hein et al., 2017b; Kwan et al., 2018; Ulke et al., 2017), the patients would be more likely to report subjective sensory symptoms, and a diagnosis of RLS may be made. However, if a patients' sensory process is disturbed due to hypnotic medications or other factors, such as benzodiazepines (Manconi et al., 2012), it may be difficult for the patients to report subjective symptoms. In this case, the diagnosis may tend to be PLMD, because motor phenomena are easily detected using instruments. More research is needed in this area.

There are several limitations to this study with may limit the generalizability of the results. First, as this was a retrospective study, we could only include major demographic, physical and psychiatric conditions, and risk factors, such as substance use, socioeconomic status and other conditions such as diabetes mellitus and renal disease were not included. In addition, the number of patients may not be large enough to study all comorbid physical and psychiatric conditions. Variables including anxiety and schizophrenia were statistically controlled rather than being excluded because of the relatively small case numbers among subgroups. Second, the cross sectional design reflects only an association but not a causal relationship. Third, due to the limitation of retrospective review, the PLMD group in our study was established by ruling OSA and RLS, and not by incorporating associations with impairments in mental, physical, social, occupational, educational, or behavioral wellbeing. Other disorders which may lead to PLMS were not included. Further, the diagnoses were established by clinical interview but not structured interview, although this approach may be more closely related to a clinical scenario.

We recommend that future research should include a prospective design, different risk factors such as education, socioeconomic status, other general medical conditions and medications, and a larger sample size. Because depression frequently comorbid with other psychiatric disorders, two approaches may improve our understanding of the neurobiology in the future. One approach is to collect patient with pure depression, and another is to study both the interaction and the independent effect between depression and other psychiatric conditions.

Our study may have made some contributions to the field. In clinical practice, our findings may broadened our understanding of the complex associations between depression and various sleep measurements of different sleep-related disorders. Since a sleep lab service is not available in every clinical setting, the understanding of how depression may affect the subjective symptoms of insomnia can help facilitate clinicians to make a diagnosis and appropriate treatment decision. Understanding the subjective and objective measures of different sleep-related disorders and depression can also help physicians and researchers to interpret and explore the complex interactions and neurobiology between sleep and depression.

## Conflict of interest

The authors have no conflicts of interest with the work carried out in this study.

## Role of funding sources

Funding was not needed for the study since this is a retrospective study conducted at our unit. There were no specific grants from public, commercial or not-for-profit sectors.

## Acknowledgments

The authors thank all of the members in our study group and especially the corresponding author Ting-Gang Chang for guidance of how to organize teamwork in research.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.166.

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