Clinical and sociodemographic correlates of severe insomnia in psychotropic drug-free, Asian outpatients with major depressive disorder

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Article info
Article history:
Received 21 May 2015
Received in revised form 18 June 2015
Accepted 20 June 2015
Available online 21 July 2015

Keywords:
Asian
Insomnia
Depressive disorders
SCL-90-R
Subjective

Abstract
Background: Little has been known regarding the correlates of severe insomnia in major depressive disorder (MDD). This post-hoc analysis aimed to examine the sociodemographic and clinical correlates of severe insomnia in psychotropic drug-free, Asian adult outpatients with MDD.

Methods: Participants were psychotropic drug-free patients with MDD, aged 18–65 years. By using the Symptom Checklist-90 Items, Revised (SCL-90-R), a score of 4 (severe distress) on any one of three insomnia items was defined as severe insomnia. Other measures included the Montgomery–Asberg Depression Rating Scale (MADRS), the Fatigue Severity Scale (FSS), the nine psychopathology subscales of SCL-90-R, the Physical and Mental Component Summaries of Short Form Health Survey (SF-36 PCS and SF-36 MCS), and the Sheehan Disability Scale (SDS).

Results: Of 528 participants, their mean age being 39.5 (SD = 13.26) years, 64.2% were females, and 239 (45.3%) had severe insomnia. The logistic regression model revealed that low educational qualifications (less than secondary school completion), high SCL-90-R Depression scores, high SCL-90-R Anxiety scores, and low SF-36 PCS scores were independently correlated with severe insomnia (p’s < .05).

Limitations: Insomnia was determined only by the patient’s distress. Middle insomnia was not assessed. Psychotropic drug-free patients with MDD are not commonly seen in psychiatric practice.

Conclusion: Severe insomnia is common in patients with MDD. It is closely related with low educational qualification, subjective depression and anxiety severity, and poor physical health. These findings may implicate the treatment of comorbid MDD and severe insomnia, for example, sleep hygiene education, pharmacological treatment.

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1. Introduction

Insomnia is characterized by difficulty falling asleep (sleep onset disturbance), difficulty staying asleep (sleep maintenance disturbance), or poor quality (nonrestorative) sleep, leading to impairment of next-day functioning, including psychological distress (Walsh, 2004). For patients with major depressive disorder (MDD), it is common, difficult to treat, and associated with poor outcomes. Insomnia can be found in 80–90% of patients with MDD (Park et al., 2013; Soehner et al., 2014; Sunderajian et al., 2010; Sung et al., 2014). In spite of achieving remission with fluoxetine treatment, almost half of these patients still have insomnia.
Disorders and Schizophrenia, O’Brien et al. (2011) found that 24.7% of rating from 0 to 5 of the insomnia item of Schedule for Affective such as congestive heart failure (Katz and McHorney, 2002). Last, of life to almost the same extent as chronic physical conditions, is independently associated with worsened health-related quality chosocial functioning (McCall et al., 2000). Third, severe insomnia of adult outpatients with MDD had severe insomnia (score of 4 or more) (Park et al., 2013). Univariate analysis, compared with mild insomnia stressed insomnia (Committee on Safety of Medicines, 1998), such limited bene- for example, selective serotonin reuptake inhibitors, not only have complicated than usual. Antidepressants commonly used in practice, for example, motor incoordination, increased risk of falls, etc. There have been many studies on insomnia in depression, but the evidence specific for severe insomnia in MDD is still limited. Based on the multivariate analysis, compared with mild insomnia in MDD, the more severe one is associated with increased age, gastrointestinal somatic symptoms, poor insight, high levels of anxiety, and more severe illness (Park et al., 2013). Univariate findings of another study also supported the association between severe insomnia and poorer psychosocial functioning (O’Brien et al., 2011). However, due to the statistical limitation that could not rule out the coincidence of depression and poorer psychosocial functioning, this later finding might only reflect the association between severe insomnia and depression. Another limitation of both the studies was that some participants might be taking hypnotic medications (e.g., hypnotic medications) during the assessment periods, which might affect the sleep results. In addition, it is not yet known if several factors associated with insomnia in MDD are also correlated with the severe one. Examples of those are being female (Sung et al., 2014), severe depression (Sunderajan et al., 2010), suicide ideation (McCall et al., 2010), and poorer physical health (Sunderajan et al., 2010). Due to these reasons, we proposed to examine the clinical and sociodemo- graphic correlates of severe insomnia in psychotropic-free outpatients with MDD.

2. Methods

This is a post-hoc analysis of data obtained from the Study on Aspects of Asian Depression (SAAD). The SAAD was a multi-country, cross-sectional, observational, clinical study of depression, carried out between 2009 and 2010. Because its details have already been presented (Srisurapanont et al., 2013; Sulaiman et al., 2014), only the key methods are presented here. This study examined outpatients with depression who were attending psychiatric practices in China, Korea, Malaysia, Singapore, Taiwan, and Thailand. All the sites are tertiary psychiatric care settings. After the study details were explained, all the participants provided written informed consent prior to participation in the study. The study protocol was approved by the Institutional Review Board or the Ethics Committee of each site.

2.1. Participants

Inclusion criteria were age between 18 years and 65 years, and meeting the DSM-IV criteria for MDD, confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Exclusion criteria included unstable medical condition, mood disorder due to medical conditions and/or substance abuse, psychotic or bipolar disorder, clinically significant cognitive impairment, treatment with a long-acting antipsychotic medication within the previous three months, treatment with an oral psychotropic medication within the previous month, and treatment with a benzodiazepine within the previous week. All other psychi- atriatic and co-morbid conditions were permitted.

2.2. Assessment

2.2.1. Insomnia and the Symptom Checklist-90, Revised (SCL-90-R)

Each of the participants assessed their behavioral symptoms by using the SCL-90-R (Derogatis, 1977). This questionnaire is a 90-item self-report symptom inventory designed primarily to collect the psychological symptom patterns of psychiatric and medical patients. It is a measure of perceived, current psychological symptoms during the previous week. Based on the subjective distress, each item is rated as 0 (no distress), 1 (a little bit distressed), 2 (moderately distressed), 3 (quite a bit of distress), and 4 (extremely distressed). The SCL-90-R consists of nine primary symptom dimensions and a group of additional items. Each of the nine symptom dimensions comprises 6–13 items. The score on each dimension is the mean of the scores derived from all items of such dimension.

Three insomnia items of the SCL-90-R inquire about sleep as follows: How much were you distressed by trouble falling asleep, awakening in the early morning, or sleep that is restless or disturbed? These three items measure the distress on initial insomnia, terminal insomnia, and restless sleep. Based on the original factor analysis, none of them is a part of any SCL-90-R symptom dimensions (subscales). Together with disability, one may use distress to establish disorder thresholds (American Psychiatric Association, 2013). In this study, insomnia and severe insomnia were defined, respectively, by a score of 2 or more and a score of 4 on any of the three SCL-90-R insomnia items.

2.2.2. Sociodemographic and clinical characteristics

Other than sociodemographic characteristics, we collected the data relevant to age at onset of MDD, history of hospitalization, and duration of index episode. The SCL-90-R items were clustered into nine dimensions (or subscales), including somatization, obsession–compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. We used the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Fatigue Severity Scale (FSS) (Krupp et al., 1989) for assessing the severity of depression and fatigue. The higher scores on the SCL-90-R subscales, the MADRS, and the FSS indicate, the more severe psychopathology.

Items 15 and 59 of the SCL-90-R inquire about the respondent’s distress on “thought of ending your life” and “thoughts of death or dying,” respectively. The presence of suicidal ideation was defined by a score of 2 or more on any of these two items.
2.2.3. Health status, psychosocial functioning, and social support

We measured the physical and mental health statuses by using the Short Form Health Survey (SF-36). This is a 36-item questionnaire that measures self-perceived general health across eight health status domains (or subscales): physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health (Ware and Sherbourne, 1992). Each subscale is scored from 0 to 100, with higher scores indicating better health state. The eight subscales are hypothesized to form physical and mental health components. While the first four domains highly correlate with the physical component (Physical Component Summary, PCS), the later four domains correlate most highly with the mental component (Mental Component Summary, MCS).

We used the Sheehan Disability Scale (SDS) to assess psychosocial functioning. This three-item scale can assess perceived disability in three areas, including work/school, social life/leisure, and family/home life (Sheehan et al., 1996). Each item can be rated from one (no disability) to ten (extreme disability), and the total scores range from 3 to 30.

We measured social support by using the Multidimensional Scale of Perceived Social Support (MSPSS). This is a 12-item scale that measures perceived social support from three sources (or subscales): family, friends, and significant other. The subscale scores can be averaged to give the mean total score, with higher scores indicating greater perceived social support (Zimet et al., 1990).

2.3. Statistical analysis

Educational qualifications were divided into high (completion of secondary school or higher) and low (less than secondary school completion). We computed the numbers and percentages of those having insomnia and those having severe insomnia. For categorical variables, we compared the proportions between those with and those without severe insomnia by using the Chi-square (χ²) test.

For the stepwise binary logistic regression analysis, we applied the Forward Likelihood Ratio (LR) method to identify the independent factors significantly correlated with severe insomnia. The regression model included all variables significantly associated with severe insomnia in the univariate analyses (p < .05). The odds ratios (OR) and the corresponding 95% confidence intervals (CIs) were used to observe the associations. We determined the model goodness-of-fit by using the Hosmer and Lemeshow (H–L) test. A p-value of 0.05 or higher of the H–L test would indicate that the model fitted well with the data. All reported p values and 95% confidence intervals are two-sided. The analyses were done using the software SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Participants

Of the 556 participants in the SAAD, 547 met the DSM-IV diagnostic criteria for MDD, confirmed by using the MINI. Of these, 19 MDD patients did not complete the three items of SCL-90-R. This post-hoc analysis, therefore, included the data of 528 patients with MDD from China (n = 113, 21.4%), Korea (n = 97, 18.4%), Malaysia (n = 88, 16.7%), Singapore (n = 37, 7.0%), Taiwan (n = 91, 17.2%), and Thailand (n = 102, 19.3%). Their mean age was 39.5 (SD = 13.26) years, and 339 of them (64.2%) were female.

Of the 528 participants, 439 (83.1%) and 239 (45.3%) had, respectively, insomnia and severe insomnia. For the 239 patients with severe insomnia, 191 (36.2%) had severe initial insomnia, 96 (18.2%) had severe terminal insomnia, and 161 (30.5%) had severe restless sleep.

3.2. Correlates of severe insomnia

Based on the univariate analyses, the sociodemographic and the clinical characteristics significantly associated with severe insomnia included country, low educational qualifications, suicidal ideation, the MADRS score, the FSS score, all nine SCL-90-R subscale scores, the SF-36 PCS and the MCS scores, and the SDS score (p’s < .05) (see Tables 1 and 2). Although the MADRS scores were

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Socio-demographic and clinical differences between and among groups of 289 MDD patients without severe insomnia and 239 MDD patients with severe insomnia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108 (57.1%)                                                                                                                      81 (42.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>181 (53.4%)                                                                                                                     158 (46.6%)</td>
</tr>
<tr>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>79 (69.9%)                                                                                                                       34 (30.1%)</td>
</tr>
<tr>
<td>Korea</td>
<td>52 (53.6%)                                                                                                                       45 (46.4%)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>37 (42.0%)                                                                                                                       51 (58.0%)</td>
</tr>
<tr>
<td>Singapore</td>
<td>20 (54.1%)                                                                       17 (45.9%)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>51 (56.0%)                                                                                                                       40 (44.0%)</td>
</tr>
<tr>
<td>Thailand</td>
<td>50 (49.0%)                                                                                                                       52 (51.0%)</td>
</tr>
<tr>
<td>Work status</td>
<td></td>
</tr>
<tr>
<td>Unemployed/retired</td>
<td>55 (53.0%)                                                                                      45 (45.0%)</td>
</tr>
<tr>
<td>Homemaker</td>
<td>58 (53.2%)                                                                     51 (46.8%)</td>
</tr>
<tr>
<td>Employed/student</td>
<td>176 (55.2%)                                                                    143 (44.8%)</td>
</tr>
<tr>
<td>Educational qualification</td>
<td></td>
</tr>
<tr>
<td>High (complete secondary school)</td>
<td>229 (57.5%)                                                                                      169 (42.5%)</td>
</tr>
<tr>
<td>Low (less than secondary school)</td>
<td>60 (46.2%)                                                                      70 (53.8%)</td>
</tr>
<tr>
<td>Living with family</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>233 (55.6%)                                                                                                                     186 (44.4%)</td>
</tr>
<tr>
<td>No</td>
<td>56 (51.4%)                                                                                                                       53 (48.6%)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98 (43.9%)                                                                                                                       125 (56.1%)</td>
</tr>
<tr>
<td>No</td>
<td>191 (62.6%)                                                                                                                      114 (37.4%)</td>
</tr>
</tbody>
</table>
significant correlated with the SCL-90-R Depression scores, they were not highly correlated ($r^2 = .528$, $p < .001$). The scores of both measures were therefore allowed to be included in the following regression analysis.

The forward LR stepwise logistic regression analysis was conducted to predict severe insomnia among 528 patients with MDD. The variables significantly associated with severe insomnia, presented in Tables 1 and 2, were included as the predictors. A test of the full model against the constant-only model was found to be statistically significant ($\chi^2 = 101.931$, $df = 4$, $p < .001$), indicating that low educational qualifications ($p = .018$), the SCL-90-R Depression score ($p = .001$), the SCL-90-R Anxiety score ($p = .006$), and the SF-36 PCS score ($p = .011$) as a set reliably distinguished between patients who had and patients who did not have severe insomnia (see Table 3).

For the H–L test, its $p$-value of .919 suggested that the model fitted well with the data. The prediction success overall was 67.6% (73.4% for those having no severe insomnia and 60.7% for those having severe insomnia). The included variables – but those that were not in the equation – were country ($p = .069$), suicide ideation ($p = .136$), severity of depression (MADRS score) ($p = .190$), fatigue (FSS score) ($p = .351$), obsessive–compulsive level (SCL-90-R Obsessive–compulsive score) ($p = .112$), interpersonal sensitivity level (SCL-90-R Interpersonal Sensitivity score) ($p = .833$), hostility level (SCL-90-R Hostility score) ($p = .939$), phobic anxiety level (SCL-90-R Phobic Anxiety score) ($p = .448$), paranoid level (SCL-90-R Paranoid score) ($p = .490$), psychoticism (SCL-90-R Psychoticism score) ($p = .652$), mental health status (SF-36 MCS score) ($p = .339$), and psychosocial functioning (SDS Total score) ($p = .160$).

### Table 3

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>$\beta$</th>
<th>SE $\beta$</th>
<th>Wald’s $\chi^2$</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-939</td>
<td>.485</td>
<td>3.751 ($p = .053$)</td>
<td>N/A</td>
</tr>
<tr>
<td>Low educational qualification (reference group: high)</td>
<td>539</td>
<td>.227</td>
<td>5.617 ($p = .018$)</td>
<td>1.714 (1.098–2.675)</td>
</tr>
<tr>
<td>Depression level (SCL-90-R Depression score)</td>
<td>590</td>
<td>.172</td>
<td>11.800 ($p = .001$)</td>
<td>1.904 (1.288–2.525)</td>
</tr>
<tr>
<td>Anxiety levels (SCL-90-R Anxiety score)</td>
<td>.461</td>
<td>.167</td>
<td>7.576 ($p = .006$)</td>
<td>1.586 (1.142–2.202)</td>
</tr>
<tr>
<td>Physical health status (SF-36 PCS score)</td>
<td>-0.015</td>
<td>.006</td>
<td>6.484 ($p = .011$)</td>
<td>.985 (.974–.997)</td>
</tr>
</tbody>
</table>

MDD = major depressive disorder; SCL-90-R = Symptom Checklist-90 revised, SF-36 = Short Form Health Survey, and PCS = Physical Component Summary. Overall Chi-square test: $\chi^2 = 101.931$, $df = 4$, $p < .001$; Nagelkerke $R^2 = .235$; Hosmer and Lemeshow Test: $\chi^2 = 3.230$, $df = 8$, $p = .919$. N/A: not applicable

### 4. Discussion

The present findings suggest that severe insomnia is common in patients with MDD. Severe insomnia could be found in 45.3% of psychotropic, drug-free outpatients with MDD. For the severe end, initial insomnia and restless sleep were more common than terminal insomnia. Low educational qualifications, higher levels of perceived depression and anxiety, and poorer physical health are independently correlated with severe insomnia in MDD.

The prevalent rate of severe insomnia in the present study of MDD (45.3%) was in line with the previous ones. While the CRESCEND study found the prevalence rate to be 59.1% (Park et al., 2013), another study found the prevalence rate to be 24.7% (O’Brien et al., 2011). Although all studies, including the present one, were carried out in outpatients with MDD, none of them used the same measure to determine the presence of severe insomnia. Moreover, they had different inclusion and exclusion criteria for enrolling the participants, as well. Due to these methodological differences, the prevalent rates obtained from these studies may not be comparable. However, all of the findings confirmed with
each other that severe insomnia is common in patients with MDD. To our knowledge, this is the first study that has found an independent correlation between low educational qualifications (less than secondary school completion) and severe insomnia in patients with MDD. While the CRESCEND study did examine this issue, it did not find the correlation between years of education and high insomnia in Korean patients with MDD (Park et al., 2013). However, the association between low educational qualifications and the increased risk of insomnia has been found in general people living in many countries, for example, Norway, Turkey, and Finland (Laflukka et al., 2012; Paparrigopoulos et al., 2010; Siertsen et al., 2009). It has been hypothesized that higher educational levels may be associated with greater knowledge about sleep hygiene practices and more awareness of the strategies that can be used to improve sleep (Arber et al., 2009).

Several clinical correlates of severe insomnia in MDD found in previous studies were reexamined in the present study. However, only the high levels of anxiety were replicated. While the SAAD used the subjective measure of SCI-90-R Anxiety subscale, the CRESCEND study used the HAM-A without insomnia item, which is an observer-rated measure (Park et al., 2013). In spite of such difference, both studies found that high levels of anxiety independently correlated with severe insomnia.

The present findings further support the association between insomnia and major depressive episodes, which has been constantly reported (Ohayon, 2002). However, as measured respectively by the subjective measure of SCI-90-R Depression subscale and the observer-rated measure of MADRS, only the perceived but not the observed depression severity was found to be correlated. The correlation between the SCI-90-R Depression and the MADRS scores were also low ($r^2 = .524$) These findings might support previous findings that measures for perceived and observed severity of depression did not rate the same thing (Demytenaere et al., 2009).

Poor physical health appears to be correlated with severe insomnia in MDD. For general people, insomnia symptoms, even in the absence of concomitant depression or other mental disorders, are associated with serious health conditions (Blank et al., 2015). In addition, comorbid mental disorders potentiate the effect of insomnia symptoms on physical health. However, such correlation was not found in the CRESCEND studies (Park et al., 2013). The discrepancy between the findings of the present and the CRESCEND studies may be caused by the differences of measures used for assessing physical health. Whereas the SAAD measured physical health by using the SF-36-PMC, the CRESCEND study took into consideration comorbid physical illnesses. In addition, while the CRESCEND included only Koreans, this SADD enrolled patients with MDD from six Asian countries.

We could not find any correlation between age or poorer psychosocial functioning and severe insomnia, which was found in the CRESCEND study. Again, the differences of measures used for assessing insomnia and psychosocial functioning might be the cause of the discrepancy between the results.

The correlation between low educational qualifications and severe insomnia in MDD suggests that sleep misconception and/or lack of knowledge on sleep hygiene should be carefully assessed in patients with comorbid MDD and severe insomnia. Given that sleep misconception is common in individuals with insomnia, sleep hygiene education should be an important part of insomnia treatment (Carney and Edinger, 2010). Although insomnia and depression are closely associated, their cause–effect relationship has not yet been known (Lustberg and Reynolds, 2000). Together with the cross-section study design, the present finding may only confirm the correlation between severe insomnia and depression.

Given that there is no adequate evidence to support the superiority of any one antidepressant for anxiety and insomnia in depressed patients (Thaler et al., 2012), benzodiazepine-antidepressant combination may be a treatment of choice for patients with comorbid MDD and severe insomnia, patients who are also likely to have high levels of anxiety. Non-benzodiazepine hypnotics co-administered with antidepressants may be an alternative for those having only mild anxiety. However, adverse effects of benzodiazepines or other hypnotics, especially falls, should be carefully assessed.

Other than poor physical health (Estrin et al., 2009; Lord et al., 1991), depression (Gassmann et al., 2009; Launay et al., 2013; Tsai et al., 1998), and insomnia (Avidan et al., 2005; Mahgoub et al., 2012), most antidepressants, especially selective serotonin reuptake inhibitors, have long been recognized as a contributory factor to falls (Coupal et al., 2011; Darowski et al., 2009). The use of benzodiazepine or non-benzodiazepine sedative-hypnotics for severe insomnia would also further increase the risk of falling (Diem et al., 2014; Estrin et al., 2009; Obayashi et al., 2013). A convergence of these factors would synergistically increase the risk of falls in patients with comorbid MDD and severe insomnia.

There were some limitations of the present study. First, the severity of insomnia was determined only by the patient’s distress. Due to the lack of polysomnography, the actual insomnia was not known. In addition, functional impairment, another aspect of sleep disturbance, was not considered. Second, none of the three SCI-90-R insomnia items can assess middle insomnia. Last, while the study of insomnia in psychotropic drug-free patients with MDD is the major strength of this study, these patients are not commonly seen in psychiatric practice. However, they would be a considerable proportion of patients with MDD in primary care settings.

In conclusion, severe insomnia is common in psychotropic drug-free Asians with MDD. It is correlated with low educational qualifications, high levels of perceived depression and anxiety, and poor physical health. Sleep hygiene education should be underscored. Pharmacotherapy for MDD with severe insomnia may be complex, and several harms and benefits commonly found in these patients (e.g., high levels of anxiety, poor physical health, falls) should be taken into account.

Contributors
The member of Mood Disorders Research: Asian & Australian Network (MD-RAN), except RUSH, designed and collected the data of the original study (the Study on Aspects of Asian Depression). Srisurapanont and Likhitsathian conceived the research ideas, managed the literature searches, and analyzed the data. Srisurapanont prepared the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source
The original study (the Study on Aspects of Asian Depression, SAAD) was supported by an unrestricted research grant from Lundbeck A/S. No funding support for the present study. Lundbeck A/S has no role for research conception, study design, data analysis, or study report.

Conflict of interest
The authors have no conflicts of interest to report.

Acknowledgments
The authors would like to thank the members of Mood Disorders Research: Asian & Australian Network (MD-RAN) and all study site personnel for contributing to the Study on Aspects of Asian Depression.