ชนิดการนอนไม่หลับและผลของการนอนไม่หลับต่อการรักษาผู้ป่วยโรคซึมเศร้า

Insomnia Subtypes in Depressive Disorders and their Relationship to Clinical Outcomes

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บทคัดย่อ

วัตถุประสงค์ เพื่อศึกษาชนิดและการเปลี่ยนแปลงการนอนไม่หลับในผู้ป่วยโรคซึมเศร้า (Dysthymia หรือ Major depressive disorder) ในกลุ่มที่อาการของโรคซึมเศร้าสงบและอาการไม่สงบ

วิธีการศึกษา การศึกษานี้เป็นส่วนหนึ่งของ “โครงการวิจัยผลการรักษาโรคซึมเศร้าของผู้ป่วยจิตเวชในโรงพยาบาล: การศึกษาแบบติดตามไปข้างหน้า” มีผู้ป่วย 224 คนที่ได้รับการประเมินการนอนไม่หลับชนิดต่างๆ โดยใช้ 3 ข้อคำถามจาก Hamilton depressive rating scale-17 (HAMD-17) ในครั้งแรกของการรักษาและหลังจากได้รับการรักษาไปแล้ว 3 เดือนเปรียบเทียบความแตกต่างของความรุนแรงของการนอนไม่หลับแต่ละชนิดในกลุ่มที่อาการของโรคซึมเศร้าสงบและไม่สงบ

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วารสารสมาคมจิตแพทย์แห่งประเทศไทย 2560; 62(1): 47-58

ผลการศึกษา ความชุกของการนอนไม่หลับในผู้ป่วยโรคซึมเศร้าจากการประเมินด้วย HAMD-17 เท่ากับร้อยละ 93 การนอนไม่หลับที่พบมากที่สุดคือชนิดsimultaneous insomnia (มีทั้ง initial, middle และ terminal insomnia) ซึ่งพบร้อยละ 52 เมื่อเริ่มรักษา, ร้อยละ 15 เมื่อรักษาไปแล้วเป็นเวลา 3 เดือน และค่าคะแนนเฉลี่ยลดลงในกลุ่มอาการสงบมากกว่ากลุ่มที่อาการยังไม่สงบ (mean difference = -1.76, 95% Confidence Interval = -0.24 ถึง -1.19) การนอนไม่หลับทั้ง initial, middle และ terminal เป็นปัจจัยสำคัญในการทำนายค่าคะแนน HAMD-17 ตลอดระยะเวลาการรักษา (p<.0001)

สรุป การนอนไม่หลับชนิด simultaneous insomnia พบมากที่สุดในผู้ป่วยโรคซึมเศร้าและเมื่อทำการรักษาไปแล้วยังพบ simultaneous insomnia มากที่สุดเช่นกัน อย่างไรก็ตาม ความรุนแรงของการนอนไม่หลับนั้นลดลงในกลุ่มที่อาการสงบมากกว่ากลุ่มไม่สงบอย่างมีนัยสำคัญทางสถิติ

คำสำคัญ นอนไม่หลับ ชนิด โรคซึมเศร้า อาการสงบ การรบกวนการนอนหลับ

ABSTRACT

Objective : To investigate the insomnia subtypes found in patients with depressive disorders, those in both remission and non-remission groups.

Methods : This report describes the insomnia subtypes found in outpatients with depressive disorders after 3 months of treatment. Two hundred and twenty-four participants with depressive disorder were evaluated using the Hamilton Depressive Rating Scale (HAM-D) insomnia subscale at the baseline and at a three-month follow-up. The insomnia subtypes found at each of these points were compared. Clinical Global Impression was applied to define the presence or not of remission, and the influence of each insomnia subtype on HAM-D scores over time analyzed.

Results : Ninety-three percent of the participants were found to have insomnia. The most common subtype was simultaneous initial, middle and terminal insomnia, with 52% showing this subtype at the baseline, and 15% at the 3-month follow-up. The mean score for simultaneous early, middle and terminal insomnia decreased more among those in the remitted group than in those from the non-remitted group (mean difference = -1.76, 95% CI = -0.24 to -1.19). All three subtypes were significant predictors of HAM-D scores over time ($p < .0001$) and the initial and terminal subtypes also appeared to have an effect when interacting with time.

Conclusions : The most common subtype is simultaneous early, middle and terminal insomnia, the decrease in insomnia severity is related to remission among depressive disorders.

Keywords : insomnia, subtypes, depressive disorder, remission

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Introduction

Depressive disorder is a common mental health problem that can have a significant impact on people's lives, due to the disability it causes[1]. Around three- quarters of patients with depression experience insomnia symptoms[2]. Those with insomnia symptoms have difficulty sleeping, and insomnia patterns are often related to its etiology[3]. Chronic insomnia is a strong risk factor in the development of depression, a prognostic indicator of the requirement for a clinical course of treatment to be carried out, as well as a predictor of relapse in non-remitted depression patients[4-8]. The effective management of insomnia symptoms is important when wishing to achieve remission from depressive disorders;[9-11] however, insomnia symptoms in patients with depression are often not detected and so may be left untreated.

There are three insomnia subtypes. Initial insomnia (difficulty falling asleep at the beginning of the night) is often associated with anxiety disorder[12] while middle insomnia (difficulty maintaining sleep) and terminal insomnia (early morning awakening) are often associated with disorders causing pain, adverse general health and depression[13,14]. Some investigators have found that terminal insomnia is more closely related to depression than the other insomnia subtypes,[12,13] while some have found that persistent depression is related to middle insomnia[15]. However, recent studies have found that the most common insomnia subtype in those with depressive disorders is simultaneous early, middle and terminal insomnia[16,17]. Changes in insomnia subtypes after treatments have rarely been reported upon, including differences in insomnia subtypes found among remitted and non-remitted patients. The key aim of this study was; therefore, to investigate the insomnia subtypes found in a group of depressive disorder patients. In addition, it aimed to explore any 3 changes that took place in insomnia patterns after treatment, and in particular, any differences in the subtypes of insomnia experienced by those with remitted and non-remitted depressive disorders.

Methods

This study was part of the Thai Study of Affective Disorder (THAISAD) research project; a prospective, one-year follow-up study of Thai people with depressive disorder and receiving treatment at 11 hospitals across Thailand. The THAISAD project has over time provided extensive epidemiological data on depressive disorders and their treatment outcomes. The entire study was conducted between March 2011 and August 2012 at each site. Details regarding the THAISAD project can be studied elsewhere[18].

The Joint Research Ethics Committee of Thailand and the Ethics Committee of the Ministry of Public Health of Thailand provided ethical approval for the study (COA-JREC 061/2009, 11 August 2009). All of the participants provided written informed consent before the study began.

Eligible participants were aged 18 years or older and had presented their symptoms to an outpatient clinic. The participants were diagnosed with Major depressive disorder (MDD) and/or dysthymic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)-as conducted by psychiatrists using the Mini International Neuropsychiatric Inventory (MINI-version 5)[19,20].

The exclusion criteria included: 1) the presence of co-morbidity, 2) pregnancy and lactation, 3) a history of severe substance abuse, 4) cognitive impairment as established by the Mini-Mental Status Examination,[21] 5) a history of schizophrenia or bipolar disorder, and/or 6) a failure to provide written, informed consent.

The patients were also assessed for depression by trained clinicians and psychiatric investigators. Demographic data and psychosocial variables, as reported by the participants, were then collected by research assistants. The participants were followedup at three-month intervals over a one-year period (five assessments, including one at the baseline). The 17-item Hamilton Depression Rating Scale (HAMD-17) and Clinical Global Impression (CGI) were used by investigators at each visit.

Insomnia symptoms were evaluated using a three-item insomnia subscale of the HAMD-17[22,23]. These three items were rated on a scale of 0 to 2, addressing the inability to fall sleep (initial insomnia), waking up during the night (middle insomnia) and waking too early (terminal insomnia). The substantial agreement between HAM-D insomnia subscale scores and sleep diary data has validated the HAM-D subscale as a global measure of insomnia severity among those with depressive disorders[24]. The presence of insomnia was indicated by a score of ≥ 1 on the HAMD-17 insomnia subscale, while insomnia severity-based on the total score of all the insomnia subtypes-was reported using a 0 to 6 scale. The insomnia items of the HAMD were defined as the main outcome variables which inpatients with depressive disorder patients may have many subtypes simultaneously. It can be divided into 7 insomnia subtypes as follows 1) initial only 2) middle only 3) terminal only 4) initial + middle 5) initial + terminal 6) middle + terminal and 7) initial + middle + terminal (simultaneous initial, middle and terminal insomnia).

The CGI-Severity (CGI-S)[25] clinician-rated tool is widely used to measure the severity of psychiatric disorders, both in clinical practice and in research. The CGI-S asks clinicians about their experiences with mentally ill patients at any given time. The tool can be rated using a 7-point rating scale as follows: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. In this study, a score of 1 was considered to represent remission.

When using the HAMD-17 scale; meanwhile, and regarding depressive disorder, remission in this study was defined as a score of ≤ 7.[22,23] The

internal consistency coefficient scores generated to represent insomnia severity-for those in the non-remitted and remitted depressive disorder groups-were 0.68 and 0.73 respectively. Since insomnia scores were generated through the use of HAMD-17, then in order to avoid the HAMD-17 confounding problem when exploring remission statuses and their association with insomnia scores, a Clinical Global Impression-Severity (CGIS) score of 1 (normal, not at all ill) was used to define remission during the follow-up period[26].

Statistical analyses were performed using IBM SPSS 22.0 for Windows. Descriptive analysis was used for the socio-demographic and clinical data. Insomnia and depression scores at the baseline were compared with those obtained at three months using the paired t-test. A comparison of the optimal dose of antidepressant was carried out across all those participants in and out of remission, using the chi-square test, whereas t-test statistics were used to compare medication doses between the remitted and non-remitted groups. In the study of predicting factors, linear regression was used for the total score of insomnia as the outcome variable, while ordinal regression analysis was used for the ordinal type of CGI-S. Significance was set at $p < 0.05$ (two-tailed) for all the tests.

Results

Of the 3,167 outpatients being treated for all kinds of depressive disorder across the 11 study hospitals, 371 (11.7%) patients displaying new or recurrent episodes of unipolar MDD, dysthymic disorder and/or double depressions, gave their consent and 6 were recruited to the project. In total, 25 patients were excluded due to the presence of co-morbidity, meaning that 346 (10.9%) patients were eventually enrolled on the THAISAD study. After three months' treatment, 224 patients were followed-up. There was no significant difference in patient characteristics between the studied group and dropouts (35%), except for their age. The mean age of those dropouts was 43.1 (SD 16.1) significantly younger than those in the studied group ($p = .02$).

Among the 224 patients with MDD or dysthymia, the mean age (SD) was 47.2 (15.2), and most of the patients were female (77.2%), cohabitating or married (44.6%) and employed (76.3%). The mean score (SD) on the HAM-D scale was 22.1(6.6) and the remission rate-according to HAM-D ≤ 7 scores at the three-month follow-up, was 114 (50.9%), but only 33 (16.3%) using CGI-S criteria

In terms of medication used, the most common anti-depressant used was Serotonin Selective Reuptake Inhibitor (73.6 %), while benzodiazepine was the most commonly used hypnotic (76.3%) (Table 1). Seventy-two percent of patients were prescribed only one antidepressant. There was no significant difference found between the remitted and non-remitted groups regarding the types of anti-depressant and hypnotic-sedatives used ($\chi^2 = 1.1$, $p = 0.29$; $\chi^2 = 3.5$, $p = 0.06$, respectively).

Table 1 Socio-demographic and clinical characteristics (n = 224)

Variables	Mean ± SD (min-max) or N (%)
Age; mean ± SD (min-max)	47.2 ± 15.2 (18-82)
Sex, N (%)	
Male	51(22.8)
Female	173 (77.2)
Education, N (%)	
Less than elementary	27 (12.1)
Elementary to junior	70 (31.3)
High school	57 (25.4)
Bachelor or higher	70 (31.3)
Marital status, N (%)	
Single	72 (32.1)
Cohabitated or married	104 (46.4)
Lived alone (Widowed/divorced/separated)	48 (21.4)
Employment, N (%)	
Yes	171 (76.3)
No	53 (23.7)
HAMD score, mean ± SD (min-max)	20.7 ± 7.3 (8-39)
Remission rate (HAMD score ≤ 7)	
Remitted	114 (50.9)
Non-remitted	110 (49.7)
Remission rate (Clinical Global Impression-Severity = 1)	
1-Normal, not at all ill	33 (16.3)
2-Borderline mentally ill	63 (31.0)
3-Mentally ill	48 (23.6)
4-Moderately ill	34 (16.7
5-Markedly ill	20 (9.9)
6-Severely ill	5 (2.5)
Antidepressant	
Serotonin Selective Reuptake Inhibitors (SSRIs)	165 (73.6)
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	14 (6.3)
Noradrenergic and specific serotonergicantidepressants (NASSAs)	17 (7.6)
Tricyclic	8 (3.6)
Others (e.g. tetracyclic, Serotonin selective Reuptake Enhancer)	20 (8.9)
Hypnotic-sedatives	
Trazodone	32 (14.3)
Benzodiazepine	171 (76.3)
Others	21 (9.4)

Notes:

Abbreviations: SD, Standard deviation; HAMD, Hamilton Rating Scale for Depression

We found that 78.9% of all cases used optimal doses of antidepressants; 83.2% in the remitted group and 78.3% in the non-remitted group, and that there was no statistically significant difference between the groups ($\chi^2 = 0.02$, $p = 0.09$). Also, there was no difference found in the benzodiazepine doses and doses of other hypnotic drugs (e.g.Trazodone) used across the two groups.

Among the 7 insomnia subtypes, the most common one found was a simultaneous early, middle and terminal insomnia which occurred in 52.2% of patients at the baseline and in 14.7% at three months. Terminal insomnia only was present in only 2.7% of patients at the baseline (Table 2).

At the baseline, insomnia was found in 92.9% of the patients, but this rate had decreased to 60.7% three months later. The mean (SD) scores for insomnia severity-7 using the total scores for the insomnia sub-scale of HAMD-17-were 3.6 (1.9) at the baseline and 1.5 (1.8) at the three-month follow-up (Table 2).

After three months of treatment, there were significant reductions in initial insomnia, middle insomnia, terminal insomnia, and all subtypes, with each type of insomnia showing a large to very large effect size (Table 3).

When comparing each insomnia subtype against instances of no insomnia, these were significantly less common in the remitted group than in the non-remitted group ($\chi^2 = 13.3$, df =1, $p < .0001$).

Table 2 Comparison of insomnia subtypes at the baseline and the 3 months follow up: remitted and non-remitted depressive disorder

Insomnia subtypes	At baseline	At 3 month follow up		
		Over all	Remitted group	Non-remitted group
	N (%)	N (%)	N (%)	N (%)
No insomnia	16 (7.1)	104 (46.4)	29 (12.9)	75 (33.5)
Initial only	17 (7.6)	22 (9.8)	2 (0.9)	20 (8.9)
Middle only	10 (4.5)	13 (5.8)	1 (0.4)	12 (5.4)
Terminal only	6 (2.7)	10 (4.5)	1 (0.4)	9 (4.0)
Initial+middle	36 (16.1)	23 (10.3)	3 (1.3)	20 (8.9)
Initial+terminal	11 (4.9)	8 (3.6)	0 (0)	8 (3.6)
Middle+terminal	11 (4.9)	11 (4.9)	1 (0.4)	10 (4.5)
Initial+middle+terminal (Simultaneous insomnia)	117 (52.2)	33 (14.7)	3 (1.3)	30 (13.4)
All	224 (100.0)	224 (100.0)	40 (17.9)	184 (82.1)

Table 3 Mean differences among insomnia scores after treatment

Insomnia subtypes	At Baseline (Mean ± SD)	At 3 months follow-up (Mean ± SD)	Mean difference	95% CI Upper	95% CI Lower	Effect size
Initial	1.4 ± 0.8	0.6 ± 0.8	-0.3	-0.5	-0.2	1.1
Middle	1.1 ± 0.7	0.5 ± 0.7	-0.4	-0.5	-0.3	1.0
Terminal	1.1 ± 0.9	0.5 ± 0.8	-0.4	-0.5	-0.2	0.8
All (severity)	3.5 ± 1.9	1.5 ± 1.8	-1.8	-2.4	-1.2	1.1

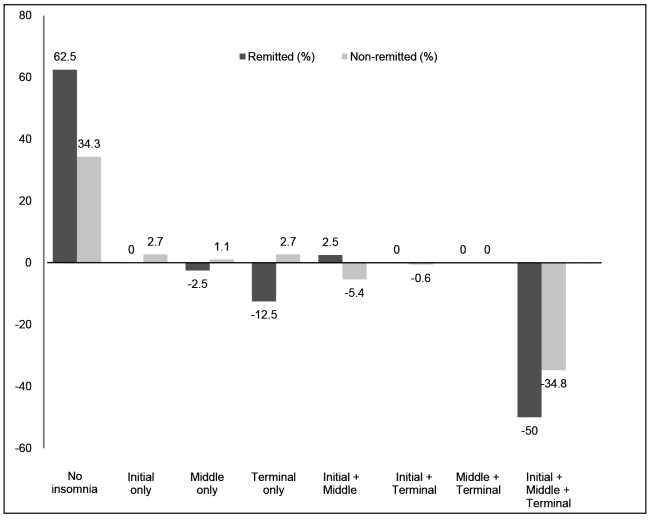

Figure 1 Percentage of change in insomnia subtypes at the 3-month follow-up, among both remitted and non-remitted depressive disorders

The most common insomnia subtype found in the non-remitted group was simultaneous early, middle and terminal insomnia, while no differences were found in remitted group (Table 2). Regarding the changes seen after three months' treatment, the largest change was seen among the simultaneous early, middle and terminal insomnia patients in both groups, though more in the remitted than in the non-remitted group (50% vs. 34.8%) (Figure 1).

Having further exploring influences on the simultaneous early, middle and terminal insomnia score at the 3-month follow-up, we found that only the baseline simultaneous early, middle and terminal insomnia score predicted the subsequent scores, while gender and age did not ($F(1,224) = 5.3$, $p = 0.022$). When examining the impact of insomnia on follow-up remission statuses using CGI-S, it was found that the mean total score for insomnia at the 3-month follow-up significantly predicted the CGI-S score, while the baseline total score for insomnia did not (Wald 58.81, df 1, $p < .001$). This model was fitted and explained by 36% of total variances.

Discussion

Overall, the evidence and findings in this study suggest a link between insomnia and poor depressive disorder treatment outcomes, but there was a difference found here between the subtypes of insomnia in this regard. A decrease in the insomnia subscale was associated with a reduction in the severity of depression, and vice versa. However, some investigators believe that insomnia may not be a necessary part of depression, but a separate co-morbid illness, which means it may not improve even as depression does[9,10,27,28]. Both insomnia and depression have been shown to significantly predict each other's onset[29]. The present study; however, was unable to demonstrate this association, as a history of insomnia prior to the depression diagnosis was not recorded. It is interesting to note that there was no difference found in terms of antidepressant and hypnotic-sedative use between the remitted and non-remitted groups. This suggests

that, for clinicians, insomnia problems may require greater levels of intervention-and not only in terms of the medication prescribed[11].

It is also interesting to note that between the remitted and non-remitted groups, no difference was found in this study in terms of either antidepressant or hypnotic medication dosages, implying that other non-pharmacological factors may play a role in ameliorating insomnia symptoms. Insomnia may be improved by the use of antidepressants, but there can also be side effects when using such drugs,[30] and particularly middle insomnia[15]. Physiological and cognitive-behavioral factors can also play a part after the onset of depression, helping to perpetuate chronic insomnia.

In terms of insomnia subtypes, inthis study the prevalence of insomnia among those with depressive disorders was high, with early, middle and terminal forms of insomnia being the most common forms of insomnia seen (as simultaneous early, middle and terminal insomnia). Interestingly, terminal insomnia was shown to have the lowest prevalence (2.7%) in this study, the same result found by the CRESCEND17and STAR*D studies[16].

Among the three subtypes, initial insomnia was found to be the most potent predictor of depression when measured using the HAM-D scale. These results are inconsistent with previous studies, e.g. the CRESCEND study and McClintock et al.'s study, which revealed that the most common insomnia subtype experienced during the depression is middle insomnia (81.6%). Meanwhile, Rodin et al.'s study with elderly patients found terminal insomnia to be more closely related to depression than other subtypes.[13,15] In contrast, Yokoyama et al.[31] found that terminal insomnia has no statistically significant relationship with depression. These differences in insomnia subtypes found in depression studies might be linked to the varying characteristics of the studied samples such as the age groups used, as well as the criteria used for responses or for establishing remission, or due to varying levels of perceived stress, pain and anxiety among the patients. For example, high levels of anxiety may be related to the predominance of initial insomnia, as was found in the present study[32-35].

Assessing the role of insomnia subtypes in depression might help clinicians better manage the condition. As found in this study, a high prevalence of initial insomnia might encourage clinicians to look for and work on psychosocial issues, using psychotherapy and other non-pharmacological interventions. As revealed recently in Ma, et al.'s extensive review of insomnia research trends over the past two decades, the use of drugs in therapy, and so their adverse side-effects, has decreased for most of the last five years, while non-pharmacological therapy such as psychosocial treatment and alternative methods, has a greater potential for advancement in the future[36]. All in all, there are several reasons which might account for the high prevalence of residual insomnia found in patients with major depression. Insomnia, regardless of what the cause is, can lead to poor treatment outcomes and relapse[2,30,37]. Depression can be related to any of the insomnia subtypes, depending on the pathological conditions co-occurring around it, and this suggests clinicians should pay attention to these subtypes when treating depression. The key strength of this study is that, to our best knowledge, it is the first study to focus on insomnia subtypes, how they change and their effect on treatment outcomes (such as remission or improvement, using either the HAM-D

or CGI scales). The present study has some limitations. First, since the participants who dropped out before the 3-month assessment were younger than the rest of the study group, this may have affected the results. Second, even though the data suggest a validity of HAMD insomnia items, a more specific method such as sleep diaries, which provide quantitative data that is not possible to infer from the HAM-D scale, should be encouraged. In addition, prospective quality of sleep can be traced easier and more accurately by the use of technology such as electronic monitoring devices or wearable technology that are synced to a wireless computer or smartphone for long-term data tracking. In addition, a recent study of insomnia phenotypes by Pillai, et al.[38] might have provided a more up-to-date description of insomnia subtypes, and this might be used in any future study. Finally, data analysis was only performed between the baseline and the three-month follow-up period, and this might not have been long enough to demonstrate the correlation between insomnia and treatment outcomes.

Conclusion

Insomnia is common in patients with depressive disorders. The most common subtype is simultaneous early, middle and terminal insomnia, which in this study was found both at the baseline and after three months' treatment. Insomnia is related to poorer outcomes in terms of depression treatment, and this study showed that any decrease in insomnia severity is related to remission among depressive disorders. It was found that initial insomnia is the most influential in terms of aiding recovery among the three subtypes. Any subtype that might be related to comorbid factors other than depression will need to be explored further.

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