

The Relationship Between Insomnia and Major Depressive Disorder: A Chicken and Egg Situation?

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ÖZET:

Uykusuzluk ve majör depresif bozukluk arasındaki bağlantı: Bir tavuk ve yumurta durumu mudur?

Majör depresif bozukluk (MDB) çok yaygın, şiddetle güçsüz düşürücü ve sıklıkla da yineleyicidir. MDB'li bireylerin önemli bir kısmı uyku düzensizliklerinden yakınlar. MDB aynı zamanda çeşitli uyku bozukluklu kitleler arasında fazla miktarda temsil edilmektedir. Uyku düzensizlikleri MDB'nin tipik özelliklerinden olsa da, böyle belirtiler bazen bir MDB döneminden önce ortaya çıkarlar. Uyku düzensizliği, özellikle de uykusuzluk ile MDB arasındaki çift yönlü ilişkiler, aralarındaki neden-sonuç bağlantılarının kurulmasını güçleştirmektedir. Uzunlamasına çalışmalar uykusuzluğu sürekli olarak yeni başlangıçlı ya da yineleyici bir MDB gelişimi için bir risk etmeni olarak tanımlamışlar ve bu ilişki genç, orta yaşlı ve hatta yaşlı erişkinlerde gösterilmiştir. Araştırmalar uykusuzluk ve depresyon birlikteliğinin aynı zamanda dönem şiddeti ve süresi yanında alevlenme oranlarını da artırarak MDB'nin seyrini etkilediğini gözlemlemiştir. Ancak yakın tarihli çalışmalar uykusuzluk için gerek ilaç gerekse de ilaç dışındaki müdahalelerin MDB'yi uygun bir şekilde azaltabileceği ve belki de önleyebileceğini göstermişlerdir. Bu bulguların tümü birden uyku ile ilişkili belirtilerin ister bir MDB dönemi öncesinde, isterse de sırasında ve/veya sonrasında olsunlar, düzelme halinin sağlanması ve sürdürülmesinde önemli bir rol oynayabilecek büyük olasılıkla da değiştirilebilir etmenler olduklarını ileri sürülmüştür.

Anahtar sözcükler: uykusuzluk, uyku, depresyon, depresif, bağlantı, ilişki

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ABSTRACT:

The relationship between insomnia and major depressive disorder: a chicken and egg situation?

Major Depressive Disorder (MDD) is highly prevalent, severely debilitating, and often recurrent. The majority of individuals with MDD experience sleep disturbances. MDD is also over-represented in populations with a variety of sleep disorders. Although sleep disturbances are typical features of MDD, such symptoms sometimes appear prior to an episode of MDD. The bidirectional association between sleep disturbance, especially insomnia and MDD, increases the difficulty of differentiating cause-and-effect relationship between them. Longitudinal studies have consistently identified insomnia as a risk factor for the development of a new-onset or recurrent MDD, and this association has been identified in young, middle-aged, and even older adults. Researches have also observed that the combination of insomnia and depression influences the trajectory of MDD, increasing episode severity and duration, as well as relapse rates. Fortunately, recent studies have demonstrated that both pharmacological and non-pharmacological interventions for insomnia may favourably reduce and possibly prevent MDD. Together, these findings suggest that sleep-related symptoms that are present before, during, and/or after a major depressive episode are potentially modifiable factors that may play an important role in achieving and maintaining remission of depression.

Key words: insomnia, sleep, depression, major depressive disorder, relationship, association

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Major Depressive Disorder

Major depressive disorder (MDD) is a severe, recurrent, and disabling medical illness that is highly prevalent worldwide and often associated with a negative impact on medical health, quality of life, and productivity (1). MDD, according to the DSM-IV-TR (American Psychiatric Association, 2000), is diagnosed by the presence of a constellation of symptoms including psychological (e.g. sadness), behavioural (e.g. suicidality), cognitive (e.g. concentration), and somatic/physical

symptoms (e.g. sleep, energy, psychomotor, and appetite disturbances). The lifetime risk of developing MDD is as high as 25% in women and 12% in men (2). According to the WHO, depressive disorders are the fourth leading cause of disability-adjusted life years worldwide, and by year 2020 they are estimated to be the second only to ischemic heart disease (3). A recent analysis on the effect of mood disorders on work performance conducted by Kessler and colleagues revealed that MDD is associated with 27.2 lost work-days per ill worker per year (4). This is of great concern and constitutes a major public health

issue, since the incidence of depression is expected to increase as a result of prolonged life expectancy and social and demographic changes (5).

Definitions of Specific Terms used in Evaluating and Treating Major Depressive Disorder Clinically

Response

The American College of Neuropsychopharmacology (ACNP) Task Force agreed with the widely held concept that response represents a clinically meaningful degree of reduction in depressive symptoms, and restated the commonly accepted criterion of a $\geq 50\%$ reduction in baseline severity, assessed by a symptom severity rating scale (6).

Full remission

Similarly, the recommendation of the ACNP Task Force is to use a score of ≤ 7 or ≤ 5 on the HAMD-17 scale as criteria for full remission (6). Full remission is obtained where clinical improvement is such that the patient becomes almost asymptomatic.

Partial remission

Partial remission is defined as a period of time with some improvement of symptoms, but not of enough magnitude as to achieve full remission, and with the persistence of some residual symptoms. This state corresponds to a score of 8 to 15 on the HAMD-17 (7).

Recovery

Recovery from depression was defined as a period of at least 2 months during which there were no significant symptoms of depression, which was defined operationally as 8 consecutive HAMD-17 scores of 7 or less within 6 months of beginning medical treatment and subsequent confirmation of the absence of major depression by diagnostic re-evaluation (8).

Relapse

Relapse was viewed as a return of the index major

depressive episode (MDE) following the onset of full or partial remission but before fulfilling the criteria for recovery. So, relapse can be defined as the re-appearance or aggravation of symptoms to score 18 or more on the HAMD-17 scale for at least 2 consecutive weeks in the partial or full remission period (6).

Recurrence

Recurrence referred to the development of a new MDE following the recovery. In other words, a new MDE which fully met diagnostic criteria must emerge during the recovery period for the term of recurrence according to The ACNP Task Force (6).

The Significance of Full Remission and The Role of Residual Symptoms

In recent years, the ACNP Task Force has established remission as the goal of treatment for patients with MDD (6). The most widely used criterion for remission is a Hamilton Rating Scale for Depression (HAMD-17) score of ≤ 7 , which corresponds to a HAMD-7 score of ≤ 3 (9). However, the recommendation of the ACNP Task Force is to use a score of ≤ 7 or ≤ 5 on the HAMD-17 scale as criteria for remission (6). Furthermore, although the goal of treating MDD is to achieve full remission, it is common for many patients to continue suffering from residual symptoms after they respond to treatment (10). The consequence of not achieving remission is that patients with residual depressive symptoms (i.e., partial- and non-responders to antidepressant medications) have an increased risk for MDD and a shorter time to relapse of symptoms (3). Increasingly, researchers and clinicians have advocated the importance of treating residual symptoms and of exploring their neurobiological basis to develop better treatment options and to improve MDD outcome (11).

The Importance of Sleep Disturbance as a Residual Symptom

Whether all previously mentioned diagnostic depressive symptoms weigh equally with regards to their adverse impact on functioning, morbidity, mortality, and treatment outcome or whether some symptoms are more

relevant than others remain, as of yet, undetermined. However, several studies published to date suggest that sleep disturbance may represent such a symptom that weighs more heavily with regards to its adverse impact on a number of outcomes (12). For instance, complaints of poor sleep are reported in up to 90% of people with diagnosed depression (13,14). Among the residual symptoms, disturbed sleep is also the most prevalent (15). Nierenberg and his colleagues assessed the prevalence of residual symptoms in a sample of 215 patients taking open-label fluoxetine 20 mg for 8 weeks; of the original sample, 108 achieved remission (HAMD-17 score ≤ 7), yet 44% continued to complain of problems with sleep (16). Of all sleep-related complaints, insomnia (and resultant daytime sleepiness) is the most frequent (5). In a recent study the patients in remission after completing at least 20 weeks of therapy, 22%, 26%, and 17% still suffered from initial insomnia, middle insomnia, and terminal insomnia, respectively (17). More than 40% of patients reported symptoms of fatigue and sleepiness/sedation even they were in partial or full remission (18).

The Consequences of Insomnia in Terms of Major Depressive Disorder in Presently Healthy Individuals

Insomnia and depression are also bi-directionally related (19). So, insomnia is a risk factor for developing depression and residual insomnia symptoms after a major depressive episode increase the risk of relapse and recurrence. In the National Institute of Mental Health Epidemiologic Catchment Area study sample, individuals with persistent insomnia (present at both baseline and 1-year follow-up) were much more likely to develop a new depressive episode at follow-up compared with individuals whose insomnia resolved by follow-up (20). Subsequent analyses revealed that 14% of those who had insomnia at the first interview had developed new major depressive disorder a year later and those with sleep problems had the highest relative odds (7.6 times) of developing a new-onset major depressive episode during the next year compared with those without sleep problems (21). The data have been augmented by several more recent reports of increased risk. In a longitudinal study of 979 young adults, insomnia increased the relative risk for depression fourfold over a 3-year period, even after controlling for baseline depression symptoms (22). One

study followed over 1000 male medical students for a median of 34 years (range 1–45). The physicians in this prospective study who had complained of insomnia during medical school in the 1950s and 1960s were twice as likely to have developed depression at follow-up in 1990s (23).

The association between insomnia and depression has also been reported in more recent studies. Sleep disturbance appears to be one of the important risk factors for depression among elderly community subjects (24). Another review, consisting of 8 longitudinal epidemiological studies, showed that the presence of insomnia symptoms at baseline significantly predicted an increased risk of depression at follow-up 1–3 years later (25). There was a 3-fold higher risk of new depression if subjects had reported one sleep problem occurring “on most nights” a year earlier in a questionnaire survey of adults over 18 in the UK (26). The longitudinal study of Buysse and his colleagues showed the increased risk of subsequent depression among individuals with insomnia (27). Similarly, LeBlanc et al. found that compared to good sleepers and insomnia symptoms incident cases, the insomnia syndrome incident cases presented a premorbid psychological vulnerability to insomnia, characterized by higher depressive and anxiety symptoms (28). In light of these studies, it is possible to conclude that insomnia may mediate the development of depression. If this would be true, treating insomnia may have important implications for preventing the onset or recurrence of depression.

The Risk of Ongoing or Re-Emerging Insomnia for Subsequent Relapse or Recurrence of Major Depressive Episode

As mentioned, residual symptoms are predictors of relapse or recurrence and may be associated with residual psychosocial impairment (29). This relationship also was demonstrated in previous studies. Continued insomnia following the acute phase of antidepressant therapy poses a significant risk for relapse. For instance, 67% of patients with persistent insomnia at the end of treatment with nortriptyline and interpersonal psychotherapy relapsed within one year after switching to placebo pill. In contrast, 90% of the patients with improved sleep quality remained well, compared to 33% of patients with persistent

insomnia who remained well (30). Residual symptoms of insomnia after a major depressive episode also increase the risk of recurrence. So, there are indications that insomnia may be a first-occurring prodromal symptom in previously depression-remitted persons. In one small study of patients with recurrent MDD who were currently in remission for at least 4 weeks, progressively greater levels of subjective sleep disturbance preceded the recurrence of a depressive episode (31).

The association between insomnia and major depressive relapse or recurrence has also been reported in more recent studies (32,33,34). Armitage stated that persistent sleep problems, insomnia specifically, elevate the risk of relapse and recurrence, as well as the need for augmenting medications (32). Additionally, Ohayon and Roth showed that insomnia appeared before (>40%) or in the same time (>22%) than mood disorder symptoms in most cases of mood disorders (33). So, chronic insomnia can be a residual symptom of a previous mood disorder and put these subjects to a higher risk of relapse. Subjective sleep problems, including insomnia, were also found to be predictors of early recurrence in a study of "remitted" patients maintained on an SSRI and psychotherapy (34). Very recently, we have assessed the frequency and types of ongoing or re-emerging subjective insomnia symptoms and their relationship to subsequent depressive relapse or recurrence in a group of full/partial remitters or recoverers (35). Majority of the participants had subjective sleep disturbance, insomnia prior to relapse or recurrence. Repeated measures of ANOVA were used to evaluate changes in scores of depression and sleep scales over time between recurred and non-recurred groups. Differences between means were calculated with post hoc Bonferroni comparison test. The changes in scores of entire clinical scales over time between recurred and non-recurred groups were statistically significant. As a consequence, our data suggest that patients who suffer recurrence exhibit greater levels of sleep disturbance several weeks prior to recurrence and the subjective sleep complaints may precede the series of symptoms that comprise the syndrome of major depression. These findings are consistent with the studies of previously mentioned authors. The data from these studies provide strong evidence that self-reported sleep disturbance not only can predict incidence of MDD in the longitudinal course, but also represents the vulnerability to MDD. Therefore,

regular monitoring of sleep status may allow for treatment intervention prior to the development of the full clinical syndrome. Such early intervention may delay, diminish the intensity of, or possibly prevent recurrent depressive episodes. Insomnia-specific interventions (e.g., hypnotic drugs, sleep hygiene, and cognitive behavioural psychotherapy) may therefore lead to remission that is more stable, extending the time between depressive episodes and possibly lowering relapse and recurrence rates.

Furthermore, we have encountered similar results with bipolar depression. Sleep disturbance is also a common feature during depressive episodes in bipolar disorder. Even the interepisode bipolar individuals exhibit greater sleep disturbance than the healthy controls (36,37). Recently, Sylvia and her colleagues (38) investigated prevalence of such symptoms among euthymic bipolar patients and their association with risk for depressive episode recurrence. They found that sleep disturbance at study entry was significantly associated with risk for depressive episode recurrence. Also, disturbed sleep appears to be an early symptom of the first mood episode of bipolar disorder (39). Additionally, sleep disturbance may be associated with a more severe course of illness. In line with this inference, Gruber et al. (40) demonstrated that greater sleep variability was associated with increased depression severity in bipolar disorder. And, more variable sleep efficiency was also found to be associated with more lifetime depressive episodes (41). All these suggest that sleep disturbance is an important prodromal symptom of bipolar disorder and should be considered a target for pharmacological and/or psychosocial maintenance treatment.

CONCLUSIONS

MDD has been increasingly prevalent worldwide. It has severe consequences and is associated with increased rates of disability, morbidity, and mortality. Despite numerous therapeutic options and recommendations of current guidelines, a great number of depressed patients cannot achieve full remission. So, majority of the patients continue to suffer from residual symptoms even after they respond to treatment partially. In addition, despite good short-term outcomes, long-term therapeutic results still remain disappointing and are associated with a poor

prognosis, raising significant public health concerns. Impaired sleep, especially insomnia may be at least partly responsible for this problem. Very close relationships between MDD and sleep disorders have been observed. In particular, residual symptoms of sleep disturbance in a remitted patient may predict a relapse or recurrence of the disease. However, most currently available antidepressants do not always take into consideration the sleep disturbances of depressed patients; some agents long used in clinical practice (e.g., SSRIs) even appear to worsen them by their sleep-disrupting properties. But some other new medications (e.g., agomelatine) were shown to relieve early sleep disturbance in addition to alleviating other depression-related symptoms. This

positive impact should promote compliance with medication and psychological treatments and increase daytime performance and overall functioning. The complete remission of MDD appears therefore to depend on the relief of sleep disturbance, a core symptom of MDD that should be taken into consideration and treated early in depressed patients.

In summary, there are evidence that sleep strongly influences both the development and trajectory of depression and impacts episode frequency, severity and duration in depression. Hence sleep-related symptoms may be important and modifiable risk factors to prevent depression and/or achieve and maintain remission in treatment of depression.

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