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Insomnia and Depression - Bidirectional Cause and Effect: A Literature Review

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ABSTRACT

Insomnia is a health problem that is very often experienced by patients and can have an impact on the emergence of psychiatric problems, such as depression. On the other hand, patients with depression may develop insomnia during this phase of the illness. This shows that there is a bidirectional relationship that must be described in order to understand the diagnosis and management of the two cases. Through the review of this article, a theoretical review of the relationship between the two in general and theoretical in order to understand each aspect is presented because the management of the two is closely related to each other.

1. Introduction

Insomnia is defined as an acute or chronic sleep disorder that can have symptoms in the form of difficulty initiating and maintaining sleep, waking up too early and having difficulty falling back asleep, and/or subjective complaints of poor sleep quality as well as disturbances or complaints in daytime activities. Currently, insomnia has become a concern because of its high prevalence and long-term physical and mental complications in the form of mood, concentration, and memory disorders.^{1,2}

Forms of insomnia can include poor sleep quality, difficulty initiating sleep, difficulty maintaining a good night's sleep, and getting out of bed too early. All forms of insomnia are risk factors for depression.³ On the other hand, depression is also a risk for insomnia, where sleep disturbances are the most frequent symptom of depression, around 80%.⁴

In everyday practice, it is often said that sleep

disturbances are a cardinal sign of major depressive disorders, ranging from disturbances in sleep continuity, sleep framework, to EEG abnormalities during sleep.⁵ Patients with depression have sleep disturbances in the form of disturbances in sleep initiation (initial insomnia), maintaining sleep (mid insomnia), or waking up too early (terminal insomnia). Abnormalities experienced can include shortening the interval between sleep initiation and the first REM sleep, lengthening the REM phase, and decreasing delta waves in the EEG.⁴

Symptoms of depression increase with age, where these symptoms can lead to low quality of life, increased morbidity, loss of autonomy, and suicidal tendencies. REM sleep disorders are often one of the causes of depression, especially in the elderly. In sleep disorders, it is suspected that there is a disturbance in monoamine activity associated with hyperactivity of

the hypothalamic-pituitary-adrenal axis.³

This shows that there is a reciprocal relationship between insomnia and depression. Patients with insomnia may experience complications in the form of depression, while depressed patients may develop insomnia. So it is very interesting to see the relationship between these two aspects, whether insomnia causes depression or depression causes insomnia because this is closely related to the principles of diagnosis and treatment.

Insomnia and depression, which one is cause and which one is effect?

Insomnia is defined as complaints resulting from disturbances in the initiation or maintenance of sleep that are related to the consequences of daytime activities and are not caused by environmental factors or lack of opportunity to sleep⁶. In addition, it can also be defined as a sleep disorder that is not sufficient and not restorative.⁷ This disease is called chronic if it has occurred for more than 3 months and with a frequency of at least 3 times per week. If the complaint meets the diagnostic criteria but is less than 3 months, it is called short-term insomnia. The prevalence of insomnia is quite high, especially in the elderly, with a prevalence of about 5-10% for chronic insomnia and 30-50% for short-term insomnia. This insomnia disorder is a significant risk factor for psychiatric disorders, depression, and alcohol abuse.⁶

All living things have circadian cycles that influence biological and personality processes. This cycle is regulated naturally in the body with its center in the suprachiasmatic nucleus in the hypothalamus which acts as the body's natural clock. Melatonin is a hormone produced at night by the pineal gland that is involved in the circadian cycle and sleep. This hormone will come out 2 hours before bedtime in response to dim light. In conditions of depression, there will be a delay in the release of melatonin, making it more difficult for patients with depression to sleep. Approximately 40-60% of patients with depression also have impaired hormone release in the hypothalamic-pituitary and adrenal axis which causes

impaired cortisol release at night, which can lead to sleep disturbances.^{4,8}

The existence of disturbances in the circadian cycle is believed to be the cause of insomnia, especially in old age. However, most are also caused by medical disorders such as chronic pain, psychiatric disorders (depression and anxiety), nervous and respiratory disorders, and drugs (anticholinergics and antidepressants). In old age, insomnia is part of the multifactorial geriatric syndrome. The combination of medical, psychiatric, cognitive, and social disorders in sleep disorders makes the management of insomnia must cover all these aspects.⁷ Insomnia management generally includes treatment of comorbid and psychiatric conditions, medications to interfere with sleep, and maximizing the patient's environment. Specific therapy includes the use of hypnotic and sedative drugs.⁶

Depression is characterized by WHO as sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration. Depressive disorders include two main sub-categories: major depressive disorder/depressive episode and dysthymia.⁹ In addition, depression leads to impairment in social, occupational, and interpersonal function, often manifesting in several symptoms including impaired concentration, fatigue, alteration to weight, hopelessness, and disturbed sleep.² Depression consists of a disease with decayed mood as its main symptomatology. There are also painful feelings, bad humor, anguish and panic attacks, performance decay of various psychic and cognitive functions, a tendency to isolation, demotivation, apathy, abulia, difficulty to enjoy, hopelessness, motor inhibition, hypotonia, and negative thoughts, including possible delusions in cases of serious severity.¹⁰ Depression has been suggested as a risk factor for insomnia in various age groups.¹

In the literature, a relationship between depression and EEG abnormalities during sleep has been suggested, while its relationship with sleep continuity has not been widely studied. Insomnia itself should be

considered as a comorbid of depression that can exacerbate morbidity, not as a symptom. Nearly 80% of patients with depression experience sleep disturbances in the form of insomnia. However, the two can be separate and unrelated to each other, this is seen from about 25% of patients with insomnia who do not have symptoms of depression⁵. In a study, it was said that patients with insomnia tended to be accompanied by at least 1 psychiatric disorder with an odds ratio of 5.0 for severe insomnia, 2.6 for moderate insomnia, and 1.7 for severe insomnia.¹¹

If we measure when the patient sleeps using polysomnography, it will be found that depressed patients experience abnormalities in their sleep in the form of increased sleep latency, reduced duration, increased wake time, and decreased sleep efficiency. On average, depressed patients take 15-40 minutes to fall asleep, wake up 15-30 minutes after falling asleep, and wake up too early, resulting in a decrease in average sleep efficiency of up to 85-95%. While patients with pure insomnia usually have more severe measurement abnormalities. Primary insomnia patients have more severe polysomnographic scores than insomnia patients in the context of depression.⁵

Depressed patients tend to have shorter REM latency cycles (the time between the onset of sleep and the onset of REM), increased REM density and duration⁵, as well as a decrease in the duration and proportion of slow-wave sleep.¹² The average normal person has a REM latency of 70-110 minutes. While patients with depression tend to be lower about <65 minutes. In addition, depressed patients also spend longer in REM cycles than normal adult patients. Meanwhile, patients with primary insomnia did not have consistent REM abnormalities. The brain waves of primary insomnia patients with depression-related insomnia are also different, wherein pure insomnia there are more beta and gamma waves than normal and depressed people.⁵ This explains that the pattern of sleep disturbances in pure insomnia is different from insomnia related to depression.

Impressively, both types of insomnia cause increased central nervous system metabolic activity

during NREM, but only depressed patients with insomnia have increased metabolism in brain regions that regulate REM cycles. These regions include the brainstem, limbic system, anterior paralimbic cortex, and executive cortex.⁵

The best way to look at the relationship between insomnia and depression is to determine whether insomnia acts as a predisposing, precipitating, or perpetuating factor for depression. It is said to be a predisposing factor if insomnia temporarily becomes a risk for developing depression, in other words, insomnia causes depression. It is said to be precipitation if insomnia precedes and then continues along with depression. Finally, it is said to be perpetuating if insomnia is related to unresponsiveness to treatment, resistance, or reduced degree of remission, in other words, insomnia is a complication of depression.⁵ Insomnia may precede depression in about 41%, along with depression in about 29%, and after depression in about 29%¹¹.

Insomnia also has 3 factors as above. Predisposing factors or that increase the risk of insomnia include childhood or interpersonal trauma, chronic mental conditions such as depression, shift work that interferes with sleep, and chronic pain. Precipitation factors/events that cause sleep disruption include events that cause physical injury, divorce or death, or job changes. Perpetuating factors / habitual and cognitive factors that cause continuous sleep disturbances include watching TV before going to bed, anxiety, or lying on bed in the long term¹³.

Patients with insomnia have a 3-5-fold higher risk of developing depression than those without insomnia symptoms. This condition is more common in elderly patients with a risk of up to 3 times. So it can be concluded that insomnia is one of the risks for depression. On the other hand, insomnia can also be a prodromal symptom of depression and can trigger or trigger new depressive episodes. On the other hand, depressed patients with insomnia also have a lower cure or remission rate than non-insomniacs, so it can be said that insomnia is comorbid with depression.⁵

If we examine more deeply, psychologically

insomnia has an impact on a person's mood and cognitive disorders in dealing with social and interpersonal stressors that increase negative experiences in life. This can lead to reduced hope and enthusiasm, which can lead to depression. Persistent insomnia can lead to endocrine disorders such as hypercortisolism and serotonin deficiency. This disorder can indirectly trigger symptoms of depression.⁵

On the other hand, depressed patients who do not initially have insomnia may develop insomnia. It is believed that insomnia occurs in response to depression to increase serotonin as a compensatory mechanism for depression and act as an antidepressant effect. Depressed patients experience the increased activity of the central nervous system and somatic which will naturally be balanced with a systemic response in the form of insomnia to increase system homeostasis to the point of fatigue and sleepiness.⁵ The existence of this two-way relationship explains that depression can cause disturbances in sleep patterns, while sleep disorders can increase the risk of depression.¹⁴

In-depth perspective: Bidirectional causality

Sleep disturbances are the most common symptom experienced by depressed patients and are referred to as the second major symptom of depression. But in some literature mentions that insomnia is an independent risk factor for depression in various age groups. The existence of a two-way relationship between depression and insomnia gives rise to a new perspective of the relationship between the two problems.¹⁵

Sleep disorders almost affect many people around the world and those who experience this problem tend to experience mental problems such as bipolar disorder, generalized anxiety, depression to suicidal ideation. Depression is also the most common mental illness, accounting for 16% of the population. In depressed patients, sleep disturbance patterns can occur.¹⁵

In the past, we thought that sleep disturbances

were part of depression and would disappear when depression was resolved. However, in recent years it has been recognized that sleep disturbances/insomnia can precede depression. Antidepressant drugs and hypnotics are often used in depressed patients with sleep disorders, but they can cause or exacerbate the sleep disturbance they are experiencing.¹⁵

Patients with insomnia have a higher risk of developing depression, but this relationship is also known to be bidirectional.¹⁶ Almost half of the patients with insomnia, especially chronic insomnia, have psychiatric problems such as depression and most patients with psychiatric problems will experience insomnia.¹³ The study of healthy patients who were made to experience sleep disturbances for 2 days, showed changes in the area of emotional regulation including depression, anxiety, and paranoid disorders.¹¹

Insomnia can cause an increase in the secretion of cortisol and orexin as well as a decrease in adenosine which will cause dysfunction of cognitive and emotional processes and increased cortical activity.¹⁷ On the other hand, in depressed patients, there will be disturbances in brain function that regulates sleep and wake cycles. An example is the increased production of orexin due to disruption of the circadian pattern that causes hypersomnia or insomnia in depressed patients.¹¹ The relationship between insomnia and depression is complex. Whether insomnia is part of depression or is something completely separate is still very difficult to trace.¹⁸

Depression is one of the most common mental disorders and can vary from mild symptoms to severe symptoms. Insomnia is said to increase the risk of developing depression through several mechanisms. Insomnia will cause cognitive, affective, and emotional regulation disorders that disrupt normal nerve function, causing depression. In addition, an increase in the HPA axis is also believed to play an important role in the development of depression in insomnia patients.¹⁹

Depressed patients often experience sleep

disorders in the form of insomnia, narcolepsy, breathing problems during sleep, and restless leg syndrome in up to 90% of cases. Sleep disturbances have been known to be a core symptom of depression. Depression is also said to be a risk factor for insomnia. In several studies found that insomnia can cause depression in both young and old age. While depressed patients initially have no sleep problems, when depression occurs, it can cause REM sleep disturbances resulting in disturbances in sleep parameters and quality. This suggests that there is a two-way complex relationship, where depression causes insomnia and insomnia causes depression.¹⁵

Potential mechanism

Insomnia can cause an increase in the number of melatonin which plays an important role in the initiation of sleep. So this circadian cycle is very important for the inflammatory cytokines (IL-6 and TNF) in a matter of days. In more detail, sleep deprivation causes an increase in inflammatory markers through activation of the sympathetic nervous system and beta-adrenergic signals that will increase levels of Nuclear factor kappa- B (Nf-kB) and activation of inflammatory trigger genes. This process will cause an increase in the amount of IL-6 and TNF, which in the end can trigger depression. On the other hand, depressed patients also experience an increase in inflammatory markers compared to normal, where these markers will cause sleep disturbances in depressed patients through mechanisms that are not fully understood.¹⁵

Biochemical pathway

Patients with depression will eventually experience REM sleep cycle disturbances. The transition to REM sleep is accompanied by a rapid fall in monoamine levels (serotonin, norepinephrine, and dopamine) with increased cholinergic activity. Of the various theories of depression, one of which is the effect of monoamine, wherein depressed patients there is a disturbance in the level of monoamine in the body. This is in line with depression medications such as tricyclic

antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) which improve symptoms by increasing monoamine levels. This monoamine disorder also causes REM sleep disorders. In addition, genetic factors are also believed to cause insomnia and depression through the same pattern of gene inheritance.¹⁵

Circadian rhythm

The circadian pattern is a 24-hour physiological rhythm of the body that is regulated by the molecular clock in the suprachiasmatic nucleus. This cycle plays an important role in the wake and sleep cycle, including the duration, continuity, and architecture of sleep. The pineal gland is a projection of the suprachiasmatic nucleus which is important because it secretes melatonin which plays an important role in the initiation of sleep. So this circadian cycle is very important for the continuity of the sleep process until it wakes up later. Disruption of this genetic clock is thought to play a role in depression and insomnia. Sleep disturbances will cause genetic clock changes that can affect mood and cause depression.¹⁵

If we studied more deeply, the relationship between insomnia and depression can be seen from the diathesis-stress model. In this model, stress induced by insomnia can induce the development of depression. Time spent awake at night can trigger negative thoughts about the past or worries about the future, including future responsibilities, which can lead to depression. Conversely, depressed patients during the day full of negative thoughts will increase mental and physiological disorders that trigger insomnia.¹⁴

Patients with insomnia, especially acute insomnia, experience more stress, anxiety, and depression than normal people. In the long term, insomnia disorders will cause a decrease in REM latency and a decrease in the N3 cycle which is a component of depression.²⁰

Treatment

Patients with insomnia and depression tend to have more severe depressive symptoms, longer treatment duration, and lower remissions than either one alone. Depressed patients are often given antidepressants, but actually, some drugs from this class worsen sleep quality such as SNRIs, monoamine oxidase inhibitors (MAOIs), NRIs, SSRIs, and activating TCAs. This is because some medications can increase REM latency periods and disrupt sleep continuity. Meanwhile, sedative antidepressants are considered to be an option because they improve sleep quality. Unfortunately, when insomnia and depression occur together, people only focus on treating depression and forget about insomnia. This causes the symptoms of insomnia to get worse. Non-pharmacological treatment can be in the form of cognitive-behavioral therapy. (CBT).¹⁵ CBT can be in the form of sleep restriction, stimulus control, cognitive therapy, sleep hygiene, and relaxation training¹⁸.

It should be noted that some drugs can cause disturbances in sleep patterns. For example, desipramine and protriptyline reduce sleep time and increase wake time, clomipramine, amitriptyline, doxepin can induce sleep, tricyclic antidepressants can cause blockade of histamine H₁, alpha₁ adrenergic and muscarinic cholinergic receptors, and suppression of the REM cycle and may lead to daytime sleepiness. This is very important to be a concern because the success of therapy and prognosis need to consider the causality of depression and insomnia. If insomnia in patients with depression is not handled properly, it will lead to a relapse of depression.¹²

2. Conclusion

Insomnia and depression are two conditions that are interconnected with each other. Insomnia can trigger depression and depression can trigger the onset of depression. The two are related in the form of causation so it is necessary to improve clinical understanding to see these two components separately, not always a unity. This needs to be observed in daily practice because the treatment of

either depression or insomnia can affect each other and even aggravate each other.

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