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The comorbidity of anxiety-related disorders and insomnia: An analysis of mechanisms

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Abstract. Anxiety is a common epidemiological mental disorder that includes Generalized Anxiety Disorder (GAD), panic disorders (PD), and phobias; its causes include anxiogenic genes and the living environment; insufficient or low sleep quality can trigger and intensify anxiety disorders. Neurotransmitters play an essential role in operating our body's crucial functions, such as emotional regulation and sleep, so much neuroimaging evidence suggests they are critical to forming anxiety and insomnia. Previous longitudinal studies suggest that insomnia is a significant index and predictor of mental health and, therefore, can also be generated from mental disorders due to their comorbidity. This short review will posit the formation of insomnia caused by the presence of anxiety disorders in patients with both insomnia and anxiety symptoms. This review further discusses some therapies that enhance and improve sleep quality among insomnia problems. It mostly debates the thesis that anxiety is the driving factor and precedes insomnia and its related neuropathological developments that can be highlighted from neurotransmitter systems and sleeping models such as the hyperarousal model. Overall, it is significant that individuals with anxiety-related disorders have lower sleeping qualities that cause functional impairment and lower subjective living qualities.

Keywords: Insomnia, anxiety, functional impairment, sleep, comorbidity.

1. Introduction

Anxiety is a common psychiatric disorder thatcauses extra excitations of neuronal activities and decreases the levels of neurotransmitter release; continuous and overwhelming emotions of fear characterize it and worry that are over-concerned to the upcoming danger, with impaired daily functioning and 25% of global prevalence [1]. The co-occurrence of cases of insomnia (a clinical symptom that the patient cannot have standard sleeping quality or usually loses sleep during the night phase.) associated with anxiety is estimated within the range from 20% to 30%, and over thirty percent of populations in the globe reported to have insomnia. It is considered to be highly interactive and comorbid with psychiatric conditions such as generalized anxiety disorders (GAD) and other related mental disorders.

Sleep is one of the essential metabolic activities in mammals; primarily, it serves the internal body function regulations highly associated with circadian rhythms. Therefore, if our body cannot receive a good quality of sleep caused by sleep disturbances in notwithstanding frequency, it will further develop into pathological insomnia that usually corresponds to our mental health. Many epidemiologic studies

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believe insomnia has a complex and interactive relationship with anxiety and recognize it as the risk factor for triggering mental disorders, including anxiety. Whether this is the triggering factor of another will be discussed in the review, but anxiety and insomnia certainly have a solid comorbid relationship that one can affect the other.

This study will focus on the neurobiological mechanisms of insomnia formation under anxiety and how insomnia further worsens anxiety-related disorders (symptoms exclude phobias such as Agoraphobia, etc.). Interventional therapies for insomnia and anxiety disorder will be briefly examined. The narrow review aims to pursue and explain the comorbid relationship between sleep and anxiety-caused insomnia.

2. Possible Triggering Mechanisms of Insomnia by Anxiety Symptoms

The onset of anxiety symptoms precedes insomnia in a neuropathological way. Insomnia involves a bidirectional relationship with anxiety: one's presence will increase the pathological development of the other, and both of their severities correspond to each other [2]. The evidence from previous neuroimaging studies shows brain regions such as limbic systems, thalamus, prefrontal-cortex-amygdala networks, salience detection network, hippocampus, and hypothalamus. Previous fMRI studies investigated individuals who experience anxiety disorders and found that the amygdala and insula activation increased along with the reduced activation of the medial prefrontal cortex, all involving emotional regulation in GAD [3]. Anxiety symptoms are onset from aversive stimuli and emotionally neutral visual clips that activate certain anxiogenic traits and brain regions. Moreover, the activation of particular brain regions, such as the anterior cingulate cortex (ACC), increases with its role in generating fear and anxiety. Therefore, the highly abnormal activations of those neurobiological parts impaired the basal emotional regulation. In patients with anxiety-related disorders, dysregulation of emotions indicates a maladaptive expression of fear and anxious responses that reflect the impaired functions in the amygdala-ACC-dorsolateral prefrontal cortex (DLPFC) networks [4]. A meta-analysis addresses that insomnia precedes anxiety disorder (the first cause of the comorbidity relationship) [1,5]. Total sleep loss generates a metabolic alteration in the functioning of sleep regulation and emotional associating regions—activities of the hippocampus and prefrontal cortex (PFC) decreased alongside the increasing activities of amygdala, ACC, and hypothalamus in aversive emotional processing. The reduced functional connectivity results in an irregular imbalance of emotion regulation due to the activity fluctuations in different brain parts [6]. Furthermore, neuroimaging analyses of GAD and OCD patients show that their hippocampus and DLPFC were hypoactive [7]. Overall, compared with the results of healthy controls and individuals experiencing GAD without insomnia, the comorbidity relationship between insomnia and anxiety reflects that the network segregation increased with a hyperactive posterior cingulate cortex from a fMRI study. The reduced activity in PFC (mainly regulating emotions, executive functions, and thoughts) was highly related to clinical anxiety levels.

Neurotransmitters are essential to the internal metabolic responses, neuronal activities, and emotional regulations; any impairment of their receptor systems is deleterious to sleep and mental health from an epidemiological perspective. This part of the review examines the role of the selected neurotransmitters, including GABA, adenosine, dopamine, glutamate, serotonin, and norepinephrine. Norepinephrine processes and regulates emotions that are produced by LC (limbic system), and its levels metabolically fluctuate within different sleep stages (high during wake and low during NREM sleep) [8]. Regional brain metabolic activities associated with LC, thalamus, and ACC showed hyperactivity in individuals with anxiety disorders that produce autonomic responses. These responses coincided with hyperactivities of metabolic rates. The LC modulates them, and norepinephrine levels correspond to the LC, so that sleep quality can be affected by the abnormalities of norepinephrine fluctuation. Both serotonin and adenosine are mood regulators, arousal, sleep-wake, and anxiety-related conditions. Their receptors reuptake and synthesis of these neurotransmitters in samples of anxiety-related poor sleepers were measured within PET assessments. In individuals with anxiety disorders, 5HT-1A autoreceptors (the other type of serotonin receptor is 5HT-2A) inhibit the synthetization and release of serotonin with its downregulation. The measuring results of serotonin synthesis rate capacity and its transporter

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availability were increased in the amygdala in individuals experiencing GAD compared to normal controls. Serotonin is widely expressed with fear and reward-related brain regions such as the amygdala and thalamus. Both adenosine receptor A1 (ADORA1) and A2A(ADORA2) are linked to the anxiety symptoms. Recovery from total sleep loss resulted in an extensive decrease of ADORA1 in ACC, the limbic system, and the thalamus—serves for regions that associate with fear and anxiety; in individuals experiencing PD, ADORA1 availability in neuronal regions encompassing fear network has shown to be increased [9]. A single night of total sleep loss also showed the increasing trend of ADORA1 availability in the human brain. ADORA2 variations interact with the intake of caffeine and alcohol (conditions related to substance abuse are not examined). Glutamate is one of the major excitatory neurotransmitters also interacting with the LC in CNS. mGluR5 (receptor of glutamate) availability level also indicates anxiety-related disorders (usually appeared to be significantly higher compared to the healthy controls). Its dysfunction is strongly associated with stress psychopathology and can be proved in individuals with PTSD, PD, and GAD [10]. Total sleep loss caused by insomnia indicated pervasively increased mGluR5 availability in the LC and ACC (regions that regulate emotions and fear). Increased binding sites of glutamate cause the retention of fear and stress emotions that disrupt subject's sleeping quality. Dopamine is involved in reward circulation, addiction, and aversive stimuli management. The reduced dopamine release in the amygdala and ACC positively correlates to worsened pathological anxiety. The dopamine levels are affected by insufficient sleep and the presence of anxiety-related disorders (OCD, PD GAD, etc.). The primary inhibitory neurotransmitter in the CNS, GABA, is linked to the occurrence of anxiety-related disorders. In samples of GAD patients, benzodiazepine receptors in the left temporal pole that control fear and anxiety have significantly reduced. Similarly, in samples of PD patients, benzodiazepine binding sites in areas linked to fear and anxiety (insula and orbitofrontal cortex) all showed decreased [11]. Therefore, it is undeniable that GABA has a significant correlation between insomnia and anxiety. Nevertheless, more neurological studies on associated neurotransmitters can be conducted to provide more insightful and persuasive results in clarifying the comorbid relationship between sleep and anxiety and the etiology of anxiety.

3. Debate Over Whether Anxiety or Insomnia is the Inducement

However, from statistical results collected from other studies that also investigated the correlation between poor sleep quality (further worsens to insomnia) and anxiety disorders an entire agreement upon the thesis that insomnia precedes anxiety. According to the sleep quality measurement scale of PSQI (Pittsburgh Sleep Quality Inventory— individual subjective sleep quality measurement including multiple sub—scales), data of anxiety population from the German Health Survey (GHS), and assessment of any anxiety disorders occurred in past—life (past year, past month) is basing on the computerized Munich Composite International Diagnostic Interview (DIA—X/M—CIDI). In comparison with the association of having GAD with poor sleep and poor sleep with the aversive mood disorder in the past month, the population of GAD—diagnosed patients has 8 times higher possibility of being a poor sleeper than the chances of experiencing past—month mood disorder from having poor sleep (the data of Odd Ratio for the association between poor sleep with the presence of GAD is 5.87 with 95% of confidence interval). Also, any anxiety disorders relate to global PSQI scores, further inducing poorer sleeping quality. From a finding conducted by Jansson and Boersma, they hypothesized that the population experiencing severe anxiety significantly developed into diagnostic insomnia over subjects with low insomnia [12]. Thus, according to the analysis of the results from older adults that controlled for other mental health problems and other negative health—related factors, anxiety was found to be the independent predictor of insomnia [10]. A study of the bidirectional relationship between GAD and MDD (major depressive disorder) also provides results that support the hypothesis that anxiety involves the onset and precedes insomnia. In their model of bidirectional analysis, insomnia was set to be the middle mediator as GSQ (global sleep quality) within the "products—of—coefficients approach." T1 predicts the outcome as the variate (whether subjects have GAD or MDD), T2 is the global sleep quality as the mediator, and T3 is the outcome of the other mental disorder. In their first hypothetical model that GAD induces the development of MDD over the mediation of GSQ, they concluded that the

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severity of GAD strongly predicts the poor sleep quality that is associated with diagnostic insomnia (higher GAD index precedes the poorer sleeping quality in T2—the more severe the GAD symptoms, the more likely the subjects have insomnia with a strongly supporting statistical value. In addition, Hyperarousal theory provides several models that can deduce the pathogenesis of insomnia. For example, behavioral models of insomnia propose that classical conditioning to a specific stimulus generates responses that violate sleeping. Biopsychosocial factors contribute to the pathogenesis of acute insomnia that relates to the biological hyperarousal traits (increased metabolic rates, hyperactivity in the hypothalamus), extensive stress and worry generated by the individual's psychological factors, and the social environment that interferes or damages one's normal sleeping circadian rhythms. Besides these aversive or incompatible factors that cause the occurrence of acute insomnia, psychiatric illness plays an essential role as an acute factor in disrupting sleep. Perpetuating these factors further develops pathologically, turning acute insomnia into a chronic state critical to exacerbating mental disorders, including anxiety. The other one is the neurocognitive model; the subjects with anxiety disorder are highly comorbid with sleep—state misperception with more beta EEG activity than healthy sleepers or primary insomnia cases. The cognitive behavioral pattern produced under the negative influence of anxiety symptoms significantly impacts sleeping as an etiological result. Certainly, insomnia is considered to be a risk factor and predictor of the onset of anxiety disorders due to the statistically significant results from cited studies [13]. However, more specific neurobiological mechanisms of how anxiety disorders trigger insomnia require deeper investigation (if another unprevailed factor mediates between insomnia and anxiety).

4. Therapeutic Interventions of Insomnia and Anxiety

Clinicians and therapists have developed and applied many valuable interventions to improve patients' sleeping quality and related anxiety and mental disorders. Cognitive—behavioral therapy and Pharmacotherapy will be shortly introduced as they both proved helpful in treating the comorbidity of anxiety and insomnia.

GABAergic agents are a standard insomnia therapy because they can increase slow wave sleep (SWS) and slow wave activity (SWA) in countering primary insomnia. The agonist of GABAA receptor and GABA reuptake inhibitor facilitates the GABA actions and prolongs the GABA duration at its receptors. Pregabalin is also a widely used structural gabapentin that interacts with the protein subunit of calcium voltage—gated channel, positively affecting SWS and SWA. As good sleep quality can improve mental health and further minimize the effect of anxiety, pharmacological treatment of GABAergic medication is helpful in treating anxiety patients (in a 4—8 weeks period of follow—up of GAD patients, their anxiety scores decreased with pregabalin.

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Cognitive behavior therapy (CBT—I) for insomnia and anxiety are proved to be effective. Including a number of professional relative associations recommend. CBT—I is a sociopsychological treatment that focuses on the reconstruction of cognitive behavior that associates with anxiety symptoms. It has significant possibility in reducing anxiety symptoms in healthy individuals and people that diagnosed as anxiety related disorders. Multiple effective treatments including sleep restriction, relaxation therapy, and stimulus control are effective in improving primary insomnia condition. Thereby improving the comorbidity relationship between the onset of anxiety and the worsen insomnia. Lastly, CBT—I is easier to accept compare to the pharmacotherapy reported by experienced individuals[15, 16].

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5. Conclusion

In conclusion, anxiety is a predictor of secondary insomnia and affect by insomnia in a comorbid relationship. Neurological mechanisms within particular brain regions can reflect the pathological association between anxiety disorders and insomnia. Anxiety symptoms are the driving factor that impair the functions of brain regions that further developing primary insomnia. The chronic sleep—deprivation worsens the anxiety disorders with the decreased SWA and SWS, and the severity of anxiety disorders worsens by the presence of insomnia—higher severity level of the insomnia produces more severe anxiety levels [17, 18]. Therefore, there are two main types of frontline therapy to treat insomnia—cognitive behavior therapy that focusing on the reconstruction of the negative cognitive pattern and the pharmacological intervention of using GABA agents. In the future, a perspective of neuro—molecular study on neurotransmitters that are abnormal under anxiety impact can be conducted to investigate the microscopic mechanisms of the formulation of anxiety disorders. The research lacks the support of primary experimental data and evidence, so this study is mainly based on the secondary results from the referenced relative analysis. Moreover, this study also requires more detailed investigation of neural—pathological development of anxiety. For example, this study can provide the formation of insomnia in GAD patients through neuroimaging evidence (whether particular brain regions having functional impairment) to improve the deficiency of supporting evidence. Thus, future improvement should be provided with primary experimental data to support my claim that anxiety predicts insomnia, and also can give further treatments on either anxiety or the insomnia. In addition, future studies can focus on the neurobiological changes in anxiety patients and find out the triggering mechanisms of secondary insomnia [19, 20]. Specific mechanism of anxiety formation is not completely concluded, there are many unknown factors to be solved, and therefore future studies can also focus on the etiological developments of anxiety through neuroscientific methods. I deduce that there will be more future research on the triggering factors of secondary insomnia, the neurobiological mechanisms of the presence of psychiatric symptoms such as anxiety and depression, and more analysis can be done to decide if anxiety precedes and predicts insomnia or vice versa.

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