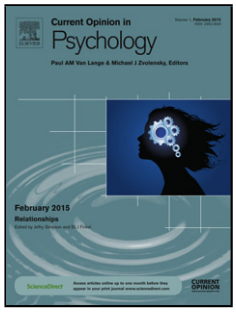

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INSOMNIA AND DEPRESSION: CLINICAL ASSOCIATIONS AND POSSIBLE MECHANISTIC LINKS

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Abstract

Chronic insomnia is highly comorbid with multiple psychological and physical disorders, but most notably depression. While insomnia is now viewed as a risk factor for depression, and not just a "symptom" of the disorder, the reasons for this change in classification (from symptom to risk factor) have yet to be clearly articulated. This is one goal of the present review. Furthermore, efforts to identify the mechanisms by which insomnia is related to increases in depression is a burgeoning area of research. Here, our second goal is to highlight several potential mechanisms that can be targets for future research.

Keywords: insomnia; depression; comorbidity; mechanisms

1. Introduction

Approximately 32 million people in the United States report experiencing insomnia[1], and at a cost of $5,000 per affected individual per year, the estimated annual societal cost of insomnia is $160 billion[2]. Insomnia is a major public health concern, not only because of its prevalence and cost, but because the disorder has been found to be a substantial risk factor for multiple psychological and medical disorders[3], [4] [5]. As a risk factor, the monitoring and treatment of insomnia holds the promise of mitigating the incidence, or diminishing the severity, of new onset morbidity. Beyond this, the comorbidity between insomnia and other disorders may elucidate why and how the disorders tend to co-occur. The goals of the present review are to (1) provide a brief overview of the association between insomnia and depression; and (2) review possible mechanistic links between these disorders.

2. The Association between Insomnia and Depression

The challenge in understanding the association between insomnia and depression is that sleep continuity disturbance (SCD)[1] can represent both a risk factor for, and a consequence of, depression. Until the late 1980s, the focus was on the latter proposition: Insomnia is a symptom of depression and the treatment of the depressive disorder will ameliorate the symptoms of insomnia. Long term management of insomnia, therefore, was thought to be unnecessary. This perspective has since evolved, to where chronic insomnia is now conceptualized, and defined, as an independent disorder. Adopted by the American Psychiatric Association's (APA) diagnostic nomenclature (i.e., DSM-5), "Insomnia Disorder" was and is used to eliminate the concepts (and diagnostic entities) of Primary and Secondary Insomnia [6]. The motivation behind this change in classification is related to a variety of findings including multiple demonstrations that SCD (specifically chronic insomnia): 1) occurs prior to and represents a risk factor for

[1] Sleep continuity refers to the class or set of variables that represent "sleep performance". It is a class term (vs. sleep architecture or sleep microarchitecture) for variables that represent latency to, and duration and efficiency of, the sleep that occurs during the sleep period, i.e., Sleep Latency (SL), Number of Awakenings (NWAK), Wake After Sleep Onset (WASO), Total Sleep Time (TST), and Sleep efficiency (SE). When one or more of these variables are pathological, this is referred to as *sleep continuity disturbance*.

new onset and recurrent depression; 2) often persists following the successful treatment of depression; and 3) targeted treatment of insomnia may substantially affect depressive symptomatology and/or the clinical course of depression, alone or in combination with anti-depressant therapies. In combination, these findings all but mandated the change in perspective on, and diagnostic classification of, insomnia.

2.1. SCD occurs prior to and represents a risk factor for new onset and recurrent depression

The concept of "prior" to new onset can be rendered in one of several ways. The most common conceptualization derives from the epidemiologic literature where long term studies are carried out with interval sampling. For example, assess a large sample of subjects (hundreds to thousands), type them for the presence of insomnia (present or not) and depression (present or not), reassess at later time points (e.g., 3, 6, 12, 24, etc. months), and then compare those that did and did not have insomnia at one or both time points for the new onset depression (recurrent or first episode). Such studies suggest that pre-existing or persistent insomnia confers significant risk for new onset and recurrent depression. A meta-analysis of 21 longitudinal studies identified insomnia as a significant predictor of the onset of a major depressive episode (MDE), such that those with insomnia, compared to those without, were twice as likely to develop depression[7]. A more recent meta-analysis of 34 cohort studies showed similar results (relative risk of developing depression was 2.3 among those with insomnia) [8*]. These rates have been shown to be four times greater in adolescent samples [9]. Similarly, residual insomnia after treatment for depression, is the largest predictor of a subsequent MDE [10], [11], and persistent poor sleep is a known risk factor for relapse after pharmacological [12] and nonpharmacological [13] treatment for depression.

2.2. SCD often persists following the successful treatment of depression.

The second claim in support of the notion that chronic insomnia is independent from depression is that insomnia is the "symptom" most resistant to treatment efforts. That is, even when the overall depressive episode has remitted, the sleep continuity problems often continue. This has been shown to be true when the depression is treated with either anti-depressant medications (i.e., SSRIs) or psychotherapy (i.e., CBT)

[14]–[17]. In fact, the rate of post-treatment insomnia symptoms has been shown to be the same for pharmacotherapy versus psychotherapy[16]. This suggests that insomnia symptoms, at least for some individuals with depression, do not remit with therapies for depression, and that an adjunctive therapy for insomnia may be beneficial. Alternatively, Yon and colleague (2014) demonstrated that following manualized treatment for depression (i.e., cognitive behavioral therapy), there was a significant reduction in insomnia symptoms, but only for individuals with mild to moderate depression (at pre-treatment). Subjects with severe depression did not experience relief in their insomnia despite overall reductions in depression[18]. The association between depression and insomnia is likely more complicated and possibly moderated by depression severity (i.e., mild depression and insomnia may share a common etiology whereas severe depression may be a distinct pathological condition). This second claim has important clinical implications given that the first claim asserts that sleep continuity disturbance is a risk factor for recurrent depression, and therefore, residual SCD should be a specific target for intervention.

2.3. Targeted treatment of SCD may substantially affect depressive symptomatology and/or the clinical course of depression, alone or in combination with anti-depressant therapies.

The third and final claim is supported by research suggesting that depressed patients treated for insomnia, alone or in combination with anti-depressant therapies, experience greater reductions in both insomnia *and* depression[19*]. In one study, not only was the remission rate for subjects who were co-treated with an SSRI (i.e., fluoxetine or FLX) and a sedative (i.e., eszopiclone or ESZ) greater after 8 weeks, but the antidepressant treatment response occurred faster in those taking both medications (24 days in those taking ESZ + FLX vs. 42 days in those taking Placebo + FLX)[20]. CBT-I, in combination with anti-depressant medications, has also been shown to enhance and/or modify the anti-depressant response in patients with comorbid depression and insomnia [21**]–[24**]. In at least one other case, the rate of remission was nearly doubled in subjects who received CBT-I versus a control intervention (quasi-desensitization control). More, in subjects with comorbid insomnia and “mild” depression, CBT-I alone produced a 57%

change in depression symptom severity (more than 85% of subjects were no longer depressed at follow-up)[25]. Internet-based CBT-I was equally as effective in treating depression in subjects with comorbid depression and insomnia relative to internet-based CBT-D [26]. The clinical significance of this research is that CBT-I or other treatments for insomnia, alone or in combination with anti-depressant therapies, offer the possibility to enhance treatment responses or remission rates in patients with comorbid depression and insomnia.

3. Possible Mechanistic Links between Insomnia and Depression

Despite research suggesting that insomnia is more than just a symptom of depression, and indeed, a risk factor, the mechanisms that explain the association between insomnia and depression are still relatively unclear [27]. Staner (2010), for example, proposed that insomnia may directly or indirectly cause a depressive episode [28]. Insomnia and/or insomnia-related daytime consequences may increase depressed mood and other depressive symptoms (e.g., increases in anhedonia, fatigue, and concentration problems). The severity and persistence of these symptoms may ultimately reach a point that is consistent with diagnostic criteria for depression. Other possible mechanistic links have been proposed and are briefly reviewed below.

3.1. Stressful Life Events and Stress Reactivity

Insomnia and depression are considered stress-related disorders. Acute stressful life events can simultaneously lead to the development of symptoms for both disorders (though the insomnia symptoms may manifest first), but also, insomnia may produce additional stress, which may culminate in the development of a depressive episode [29]–[33]. While stressful life events, in general, precipitate the onset of acute insomnia and depressive symptoms, there are also a number of individual and contextual factors that determine the frequency and intensity of these symptoms, such as differences in sensitivity to stress or the severity of the stressor [34]. With respect to individual factors, both insomnia and depression are associated with a greater sensitivity to atypical behavioral[35], cognitive[36]–[38], and

physiological[39], [40] responses to stress. For example, patients with insomnia appraise negative life events as more stressful and use less effective coping strategies to deal with that stress compared to good sleepers[41]. These maladaptive cognitive and behavioral responses may in turn hinder a person's ability to fall asleep during stressful periods. Similarly, individuals with depression have a greater cognitive vulnerability to stress, or a tendency to make more negative attributions following a stressful life event[42]. Some more recent studies have also shown that insomnia and depression are independently related to sleep reactivity, or a greater vulnerability to stress-related sleep disturbances[43]. In sum, one possible explanation for the high comorbidity rates may be a common vulnerability to stress-related disturbances among patients with insomnia and depression. It may be the case that the same maladaptive responses to stress may precipitate symptoms for both disorders.

3.2. Neurobiological factors

A number of neurobiological factors have also been identified as potential mechanisms that explain how insomnia may be a risk factor for depression or at the very least explain why these two disorders are highly comorbid. These neurobiological mechanisms include alterations in: monoaminergic neurotransmission, genetic profiling, and the hypothalamic–pituitary–adrenal (HPA) axis [44], [45]. With respect to monoaminergic neurotransmission, and in particular serotoninergic neurotransmission, it has been documented that greater activation in this system is related to the promotion of wakefulness. In contrast, suppression of the serotoninergic system facilitates sleep onset [46], [47]. Depression has been reported to be associated with decreases in serotoninergic neurotransmission, which may explain why some findings suggest that depression is characterized by short REM sleep latency (the serotoninergic system is offline during REM sleep). This said, the role of serotoninergic neurotransmission in the link between insomnia and depression is likely much more complex and may be better characterized by overall dysregulation in the system (i.e., the system is online when it's supposed to be offline and offline when it's supposed to be online). While much less is known about the role of domaminergic neurotransmission

in the association between insomnia and depression, some have proposed that it may be another common factor that plays a role in the neurobiology of both disorders [48]. However, like all of these proposed mechanisms, further study is needed to elucidate the nature of these alterations.

With respect to the genetic links to insomnia and depression, a number of studies have reported associations with both circadian clock genes[49], [50] and genes related to stress reactivity[51], [52]. For example, overexpression of the genetic variants in two different circadian clock genes were observed in patients with depression and insomnia[49], [50]. In particular, this comorbidity was specific to late insomnia (i.e., early morning awakenings), and in one study, only observed in male subjects. Not surprisingly, alterations in the HPA-axis is likely the most popular candidate for the underlying mechanistic link between insomnia and depression. The HPA-axis regulates a series of neuroendocrine responses to acute stressors that facilitate the mobilization of key adaptive physiological processes such as down-regulating digestive activity and maximizing glucose utilization[53], [54]. While alterations in HPA-axis stress reactivity have long been linked to increases in depressive symptoms[55], [56], the research on the relation between insomnia and HPA-axis functioning, especially in response to stress, is surprisingly much more limited and inconsistent. This said, insomnia is viewed as a disorder of "hyperarousal" and there is some data to support that there are abnormalities in the circadian release of cortisol in patients with insomnia (see [57] for review). The observed hypercortisolemia in depression and chronic insomnia may therefore represent a neurobiologic concomitant for both disorders. The role of these biological mechanisms remains unknown, but what is clear is that these are potential targets for future research.

3.3. Mechanisms of risk for suicide.

Suicide is one of the leading causes of death nationwide. Insomnia and depression are both significant risk factors for suicide-related ideation and behaviors (including death by suicide). A number of psychological and physiological mechanisms by which insomnia and depression lead to suicide have also been proposed

[58], [59], including insomnia-related psychosocial impairments (that may or may not be related to loneliness and lack of belonging); activation of hopelessness and/or helplessness schema; and/or diminished executive function. Potential physiological mechanisms, which may occur as a result of insomnia or a common neurobiologic substrate, include serotonin deficiency; hypercortisolemia; and/or elevated basal metabolic rate. There has also been additional evidence that suicides are disproportionately likely to occur at night suggesting that nocturnal wakefulness itself may represent a risk factor for suicide[60**]. That is, being awake at night, and the associated hypofrontality that occurs during the night or with sleep loss (i.e., decreased frontal lobe function), may be another mechanism by which insomnia increases risk for suicidal ideation[61]. Insomnia increases the likelihood of being awake at night, the time of day in which one's ability to reason, think rationally, and to engage in impulse control may be at its lowest [62], [63]. Being awake at night, especially during times of increased stress or mood disturbance, may therefore increase risk for suicidal ideation.

4. Conclusion

The goal of this brief review was to highlight the change in perspective with regard to the association between insomnia and depression. While insomnia was originally conceived of as a symptom of depression, it is now more commonly categorized as an independent risk factor (for both depression and subsequent suicide). So much so that there is now research showing that the treatment of the insomnia symptoms alone can lead to improvements in depression. While the field's knowledge and understanding of the mechanisms that contribute to the comorbidity between insomnia and depression is still in its infancy, there are a few targets for future research. Among these potential mechanisms, there is a common theme, one that suggests that a critical commonality between insomnia and depression is alterations in stress responding or sensitivity to stress. This has been shown to be the case when evaluating multiple psychologic, physiologic, and genetic constructs.

Declaration of interest

None

5. References

*of special interest
**of outstanding interest

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