LEADING ARTICLE

Insomnia and Depression: Birds of a Feather?

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Over the course of the last 30 years there has been a great deal of research into sleep abnormalities in patients with major depression. However, only a small proportion of this work has focused on sleep continuity disturbance (as opposed to abnormalities in sleep micro- and macroarchitecture), despite insomnia being a defining feature of depression. The lack of work in this area may be attributed to the view that insomnia is nothing more than a symptom of depression. Yet, in recent years, perceptions have shifted to the alternative point of view – that insomnia is less a symptom and more a comorbid disorder. The present article provides an overview of the data and suggests that insomnia and depression are separable entities, insomnia confers a risk for greater depressive morbidity, and targeted treatment for insomnia may influence the clinical course of major depression. *Int J Sleep Disorders* 2007;**1**(3):82–91.

It has often been said that sleep disturbance is a cardinal sign of major depressive disorder (MDD). However, this claim does not refer to a single abnormality but rather to a cluster of signs and symptoms that range from sleep continuity disturbance[1], to abnormalities in sleep architecture, to sleep electro-encephalogram (EEG) anomalies.

The relationships between depression and sleep architecture and/or sleep EEG anomalies have been extensively studied, well delineated, and thoroughly reviewed [1], whereas the relationship between depression and sleep continuity disturbance has not. This may be due to the prevailing assumption that, like headache or fever, insomnia is simply a symptom of an underlying disease process and, as a symptom (even as a defining feature of MDD), it cannot provide information on disease etiology or pathophysiology. In order to challenge this perspective, it is necessary to demonstrate that insomnia is not simply a symptom (i.e. occurs with the disease and is otherwise absent), but is instead a comorbid condition that may interact with the MDD to confer greater morbidity.

To make the case for comorbidity, one would need to demonstrate that insomnia has the following characteristics:

- It occurs in the absence of depression.
- It persists following effective therapy for depression.
- It can be distinguished from depression in terms of sleep and neurobiological abnormalities.

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To determine whether insomnia interacts with MDD to confer greater morbidity, the following must be established:

- Insomnia can exist as a predisposing, precipitating, and/or perpetuating factor for depression.
- Insomnia represents a modifiable factor, which, when subjected to targeted treatment, alters the course of depression.

The present review examines these lines of evidence.

Historical context: is insomnia a symptom or a comorbid disorder?

Up to 80% of patients with depression have sleep complaints consistent with insomnia [2]; this finding, along with the fact that first-generation antidepressants tend to have sedative effects, led to the pervasive point of view that insomnia occurs as a consequence of mood dysregulation.

Insomnia and depression are separable

The evidence that insomnia and depression may be separate, although related, disorders, is provided by the relatively recent observations that:

- Up to 25% of insomnia subjects do not have concomitant depression (or other psychiatric or medical illnesses) [3].

1. Sleep continuity refers to the collection of variables that correspond to sleep initiation and maintenance, including sleep latency, wake after sleep onset, number of awakenings, and total sleep time. While the term is not formally part of the sleep lexicon, it has the heuristic value of being a global term whose meaning may be contrasted with the class of variables that correspond to sleep architecture.

- Second-generation antidepressants (e.g. selective serotonin reuptake inhibitors) often exert their clinical effects without ameliorating the patient's insomnia complaints [4–8].
- Regardless of the type of intervention, it is often the case that insomnia persists and/or becomes chronic, despite successful resolution of the psychiatric illness [9–12].

While not refuting the alternative point of view, these data suggest that insomnia and depression could be considered separate entities or comorbid conditions. This evidence is further strengthened by a series of findings showing the two conditions to be distinct in terms of sleep and neurobiological measures.

Insomnia and depression exhibit different sleep and neurobiological abnormalities

Polysomnographically-measured sleep abnormalities

When sleep is measured using polysomnograpy (PSG), patients with depression reliably exhibit sleep continuity and sleep architectural abnormalities [1,13]. Within the sleep continuity domain, patients with depression tend to exhibit increased sleep latency, increased wake time, and decreased sleep efficiency. Typically, depressed patients take 15–40 min to fall asleep, spend 15–30 min awake after sleep onset, have early morning awakenings that last ≥15 min, and exhibit sleep efficiencies (total sleep time/total time in bed) that range from 85–95% [14,15]. While this profile clearly resembles that which is seen in patients with primary insomnia, the magnitude of the problem tends to be smaller. Patients with primary insomnia usually have more severe PSG-measured sleep continuity problems than those with insomnia in the context of depression [16,17]. However, it should be noted that this may be a selection artifact, as only patients with primary insomnia are selected for study on the basis of the severity of the insomnia complaint.

Sleep architecture refers to two kinds of PSG-defined variables: those related to non-rapid eye movement (NREM) sleep and those related to REM sleep. Within the NREM domain, slow-wave sleep (SWS) is the main variable of interest, and is thought to be related to sleep homeostasis (for a review of sleep homeostasis and insomnia see [18]). While the amount of SWS varies with age, healthy adults (aged, for example, 25–55 years) typically spend 10–15% of total sleep time in SWS (approximately 40–60 min) [19]. Deficiencies in SWS have been observed both in patients with primary insomnia [20–23] and in those with MDD [14,15,24,25], with an exhibited decrease in SWS to 5–10% of total sleep time.

With regard to REM sleep, patients with depression tend to exhibit a shorter REM latency (time between sleep onset and the first epoch of REM sleep), increased REM density (number of REMs during REM sleep), and increased REM sleep time. Typically, healthy subjects have REM latencies of 70–110 min [19]. Between 50% and 70% of patients with MDD have mean REM latencies of ≤65 min [14,15,24,26]. Patients with depression exhibit greater REM density than controls; this is particularly evident during the first REM period [14,15]. Finally, while the amount of REM sleep varies with age, healthy middle-aged adults typically spend 15–20% of total sleep time in this sleep stage [19]. Patients with depression tend to exhibit more than 20% – often as much as 30% – of sleep time in REM [14,15,24]. In contrast, patients with primary insomnia do not show any consistent REM abnormalities.

Quantitative EEG abnormalities

Power spectral analysis (PSA) of EEG activity from PSG recordings confirmed many of the PSG sleep architecture findings, and also produced a number of new results. A variety of studies based on PSA have reported that patients with depression exhibit either reduced NREM delta power (overall) or abnormal distributions of delta activity across the sleep period [27–29]. However, other studies have suggested that these findings are not replicable [30,31], are limited to men [32], and/or are characteristic of depressed cohorts from past, but not present, generations [33]. There have been fewer studies in patients with insomnia than depression, but the finding of diminished delta activity has been observed more consistently within these [20–23,34].

In addition to findings in the slow-wave portion of the EEG spectrum, differences have also been observed within the high-frequency (beta and gamma frequencies) domain. Patients with primary insomnia have been found to exhibit more beta and gamma activity than either good sleepers or patients with insomnia secondary to MDD [17,21,35–39]. Specifically, patients with primary insomnia exhibit more high-frequency EEG activity at sleep onset and during NREM sleep. This kind of activity has also been negatively associated with the perception of sleep quality [40,41], and positively associated with the degree of discrepancy between PSG and sleep diary measures of sleep continuity [39]. The latter finding regarding sleep state misperception is important as this clinical phenomenon is thought to occur with primary insomnia, and is not typically seen in insomnia associated with depression [42].

Taken together, these data suggest that, using PSG and PSA measures, depressed patients with insomnia do not exhibit the same sleep continuity, sleep architecture, or sleep EEG profiles as patients with primary insomnia.

Neuroimaging abnormalities

Using positron emission tomography (PET), Nofzinger and colleagues at the University of Pittsburgh (Pittsburgh, PA, USA)

have shown that depressed patients have a higher degree of activation of structures involved in REM sleep, from waking to REM sleep, than healthy controls [43]. In broad terms, these areas include brainstem structures, the limbic and anterior paralimbic cortex, and the executive cortex. Differences between depressed and normal patients have also been observed in PET studies of NREM sleep: depressed patients showed a higher overall brain metabolism and a smaller decrease in activation across a variety of frontal areas from waking to NREM sleep [44,45]. These findings are consistent with PSG findings of decreased SWS activity and increased REM sleep activity in depressed subjects.

In patients with primary insomnia[2], compared with good sleepers, the same Pittsburgh group found that:

- There was a smaller decline in metabolism from waking to NREM sleep in the ascending reticular activating system, the hippocampus, the amygdala, and anterior cingulate cortex in insomnia patients [47].
- Only the patients with insomnia exhibited elevated whole-brain metabolism across waking and NREM sleep [48].

These data suggest that both forms of insomnia are associated with increased central nervous system (CNS) metabolic activity during NREM sleep (and in structures related to the promotion of sleep and/or wakefulness), but only patients with depression exhibit increased metabolic activity in regions associated with the generation of REM sleep. These differences, while entirely consistent with PSG and PSA findings, await replication by multiple investigators using more standardized groups and procedural criteria in larger samples.

Neuroendocrine abnormalities

When acutely ill, patients with depression exhibited elevated levels of cortisol and adrenocorticotropic hormone (ACTH), both during the night and over the course of the 24-h day, compared with healthy controls [49]. Data from longitudinal studies suggest that these hypothalamus–pituitary–adrenal (HPA) axis abnormalities normalize with the resolution of the acute illness [50]; however, it is unclear from these studies whether the sleep continuity disturbance persists into remission.

Studies of non-depressed young adults who were good or poor sleepers found that the poor sleepers have significantly higher mean 24-h levels of urinary-free 11-hydroxycorticosteroids [51]. Parallel findings have been observed in studies of patients with primary insomnia versus good sleepers. The insomnia patients exhibited significantly higher mean levels of ACTH and cortisol over 24 h, with the largest group differences observed in the evening and first half of the night [52,53]. Correlation analyses show that increased HPA axis activation is associated with increased amounts of Stage 1 sleep, increased wakefulness following sleep onset, and lower sleep efficiency [52]. It should be noted that there is at least one study that has failed to show a difference between patients with primary insomnia and good sleepers with regard to cortisol levels [54].

To date, only one study has concomitantly evaluated EEG sleep and nocturnal plasma levels of catecholamines in patients with primary insomnia, patients with acute major depression, and healthy controls [55]. The insomnia group showed disordered sleep continuity and nocturnal increases in levels of circulating norepinephrine compared with the control group, whereas depressed patients showed no differences in EEG sleep or nocturnal catecholamines (Fig. 1). Sleep efficiency was negatively correlated with nocturnal elevations of norepinephrine in the patients with insomnia, but not in the patients with depression or in the healthy controls.

The finding that hypercortisolemia can occur in the absence of depression suggests that insomnia and depression are separate entities and that it is the insomnia (as opposed to the depression) that appears to account for the HPA abnormalities. Alternatively, there may be a sequential effect, such that stress leads to acute activation of the HPA axis, insomnia, and then depression, but in the long-term the insomnia that persists beyond acute illness leads to a tonic activation of the HPA axis.

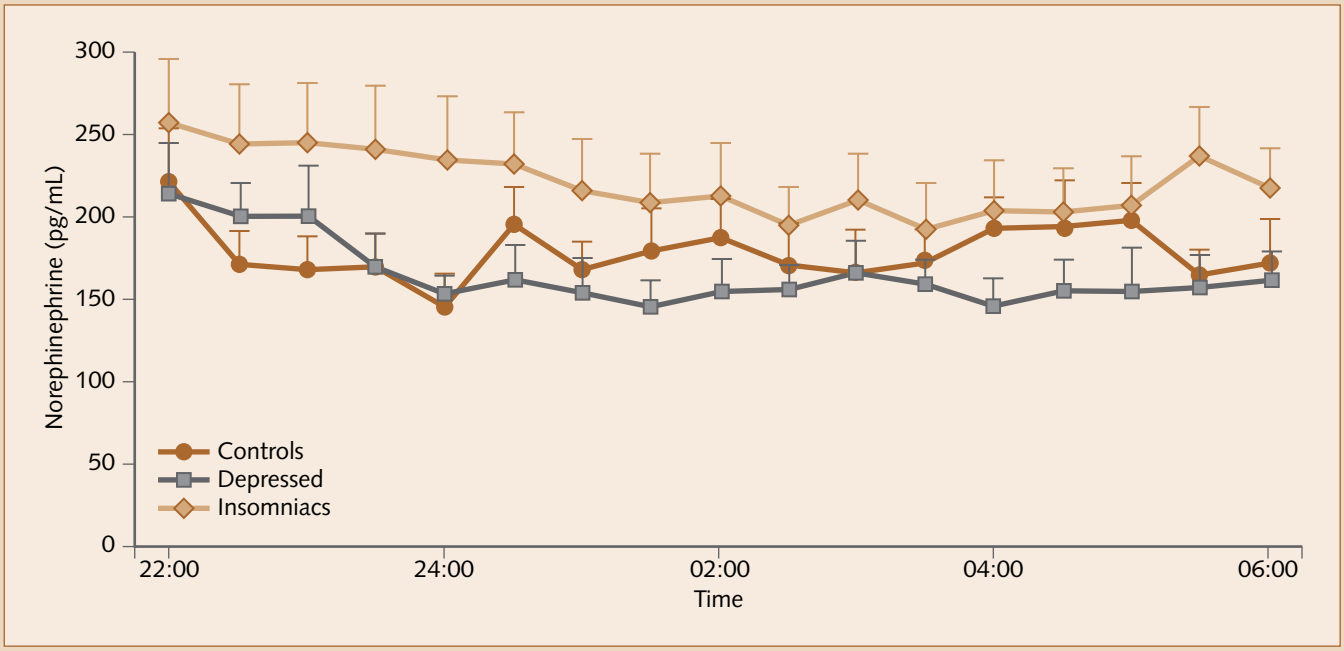
Neuroimmune abnormalities

Depression is associated with diminished cellular immune competence (e.g. lymphocyte proliferation and reduced natural killer [NK] cell activity) and elevated markers of systemic inflammation (e.g. elevated circulating levels of interleukin-6 [IL-6] and C-reactive protein) [56–58]. In a study that assessed both types of measures simultaneously, depressed males had reduced NK cell activity and increased IL-6 levels compared with never-depressed controls [59].

In vitro stimulation of proinflammatory cytokines with lipopolysaccharide (LPS), which tests the ability of circulating white blood cells to produce cytokines (as would occur in an innate immune response to infection), have yielded mixed findings when sampling depressed inpatients and/or outpatients [60]. In non-clinical samples, where depression is measured using validated depression scales, higher scores were associated with greater LPS-stimulated expression of

2. It should be noted that there is one additional imaging study that has been conducted in patients with primary insomnia [46]. In this study, single-photon emission computed tomography (SPECT) was used to assess CNS metabolic activity in patients with primary insomnia and in good sleepers. Patients with insomnia exhibited lower levels of activation following sleep onset, particularly in the basal ganglia. While these results appear entirely inconsistent with the PET findings, numerous methodological differences may account for the differences. The most likely explanation is that the short time resolution of SPECT captured a more transient phenomenon that occurs when subjects first achieve persistent sleep, whereas the PET study, with its longer time resolution, captured a more stable phenomenon that occurs throughout NREM sleep.

Figure 1. Nocturnal catecholamines and immune function in insomnia patients, depressed patients, and control subjects. The bars represent the standard error of the mean.



Redrawn with permission from [55].

tumor necrosis factor-α (TNF-α) and IL-1β (the latter only in men) [61,62]. In contrast, higher depression scores have been associated with diminished *in vitro* production of IL-6 and increased circulating levels of IL-6 [63]. Another study found that higher depression scores were associated with lower *in vitro* stimulated IL-6, IL-1β, and TNF-α, but were not associated with circulating levels of IL-6 or TNF-α [60]. Interestingly, in this latter study, the somatic symptom cluster of depression (including sleep-related items) was most strongly associated with stimulated cytokine production.

Chronic insomnia (as compared with good sleep) tends to be associated with decreased NK activity [55,64,65] and a shift in the circadian distribution of IL-6 and TNF-α from the night to the daytime, despite higher evening levels of IL-6 [53]. Burgos et al. found that IL-6 secretion is inversely correlated with self-reported sleep quality and PSG-measured SWS in patients with insomnia [66].

These neuroimmune findings are less conclusive than the other areas reviewed in terms of whether insomnia and depression are distinct disorders. While some of the findings show that the disorders are associated with similar abnormalities (e.g. decreased NK cell activity, elevated IL-6), there is some indication that these findings may differ when the measurement strategy is *in vitro* stimulation of immune responses [60]. Furthermore, there are no data on whether the neuroimmune findings persist into remission. If, like the neuroendocrine findings, these changes are persistent, it is possible that insomnia (as opposed to depression) accounts for neuroimmune abnormalities. Alternatively, a sequence effect may be responsible.

Taken together, this overall set of neurobiological findings provides evidence for a distinction between insomnia and depression. Given that the two disorders appear to be separate, the nature of their relationship remains in question.

How are insomnia and depression related?

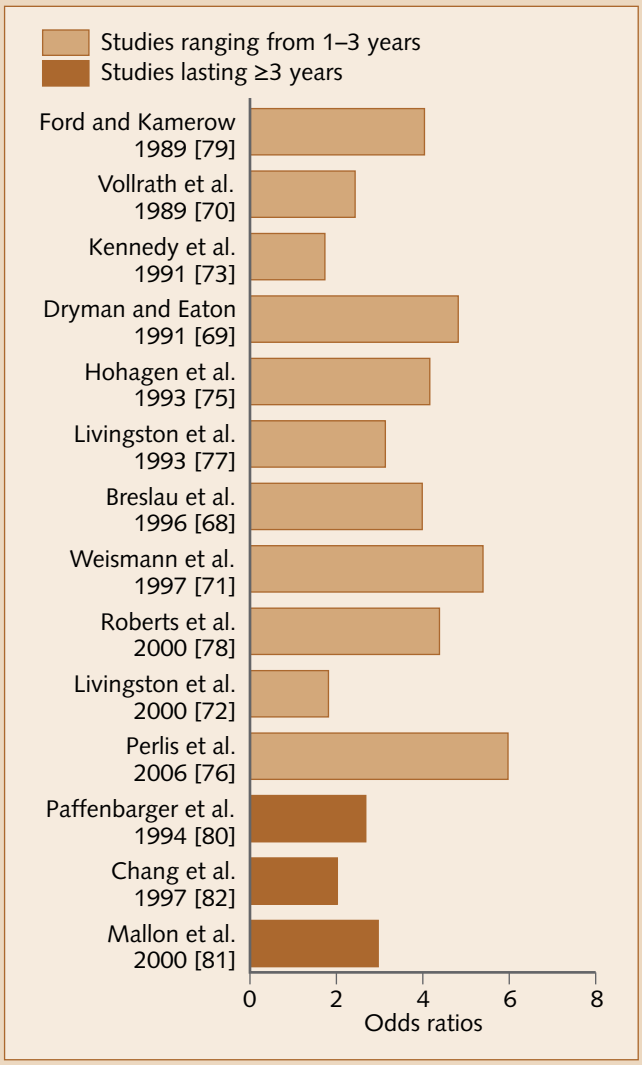
A useful way of assessing the relationship between insomnia and depression is to consider whether insomnia serves as a predisposing, precipitating, or perpetuating factor for depression. This conceptual framework is the basis for Spielman's three factor model of insomnia and is applied here for its heuristic value [67].

In the present context, insomnia would be labeled a predisposing factor if it temporally preceded and conferred risk for the development of new-onset or recurrent depression; a precipitating factor if its occurrence (or increase in severity) preceded, and was immediately contiguous, with new onsets of depression; and a perpetuating factor if its occurrence (or severity) was associated with treatment non-response, treatment resistance, or reduced rates of remission.

Insomnia as a predisposing factor for depression

There are at least 12 longitudinal studies reporting that insomnia carries an increased risk of new-onset and

Figure 2. Odds ratios from longitudinal studies showing the elevated risk for the development or presence of depression when there are symptoms of sleep disturbance consistent with persistent insomnia.



recurrent depression over time frames of between 6 months and 3 years [68–79]. Reports also show that insomnia can confer depression risk for a period that extends over decades [80–82]. In general, these studies show that patients with persistent insomnia have an approximately 3.5-fold increase in the risk of depression compared with subjects without complaints of insomnia. A graphical representation of these data is shown in Figure 2.

Several of these investigations have evaluated insomnia as a predisposing factor for depression in terms of age and gender interactions. In the three studies that focused on older adults [76–78], this trend was found to be characteristic of the elderly; that is, insomnia conferred an approximately three-fold increase in risk of depression. It is difficult to infer age interactions in the remaining investigations as the samples tended to be heterogeneous for age, which was statistically controlled. What was evident from these studies was that the relative risk estimates were reliably higher in the investigations that controlled for age. This suggests that insomnia is not a uniform risk factor for all age cohorts and/or that the effects of persistent insomnia are larger when age effects (which are significantly more predictive than sleep factors) are adjusted for. With respect to gender differences, the majority of the studies calculated odds ratios that were adjusted for gender [68,70,71,77–79], and one study only included men [82]. In the studies that evaluated gender differences [69,81], the association between insomnia and depression was predominantly observed in women.

In addition to these considerations, it should be remembered that the definition of a "risk factor" i.e. how insomnia is measured and how it is defined in terms of type, severity, and chronicity, varies widely between studies. These caveats notwithstanding, data from the above studies strongly support the hypothesis that insomnia represents one of the predisposing factors for MDD.

Insomnia as a precipitating factor for depression

To our knowledge, only one study has examined whether insomnia is a precipitant, or at least a prodromal, sign of MDD [83]. In this, patients with recurrent MDD (remitted) were followed for up to 42 weeks. Subjects were monitored on weekly basis using the Beck Depression Inventory (BDI) and if an exacerbation of their symptoms was noted on this scale, they were formally evaluated for recurrence.

Two groups were identified from this cohort: an index group of subjects who experienced a recurrence and a comparison group of individuals who were matched to the index group with respect to age, gender, and clinical history. Weekly sleep disturbance complaints were evaluated using the single sleep item on the BDI (question 16) for the 5 weeks prior to recurrence in the index group and for a temporally equivalent period in the non-recurrent control group. The time series data from this period showed that the non-recurrent group exhibited an elevated, but stable, level of sleep disturbance and the recurrent group exhibited an increased level of sleep disturbance that began 5 weeks prior to, and was of highest severity at, the week of recurrence.

These data strongly suggest that insomnia may be a prodromal symptom of depression, and lend weight to the possibility that insomnia may trigger or precipitate new depressive episodes. To properly assess the latter, it would be necessary to experimentally manipulate sleep continuity in what would most likely be an ethically challenging and difficult experiment (see Summary and future directions).

Insomnia as a perpetuating factor for depression

We are only aware of one preliminary study that addresses the possibility that insomnia perpertuates depression. In this investigation, data were drawn from a large interventional study of late-life depression that enrolled 1801 elderly patients with MDD and/or dysthymia based on the Structured Clinical Interview for Diagnostic and Statistic Manual-IV edition [84]. MDD subjects from this cohort (n=1221) were assessed for their clinical status at baseline and at 6 months to determine whether insomnia (classified as no insomnia, transient insomnia, and persistent insomnia) was associated with clinical improvement and/or the occurrence of remission. The groups were significantly different in terms of the percentage of subjects who remained ill at 6 months according to two measures of depression (remission and <50% improvement). Overall, patients with persistent insomnia were 10–12-fold less likely to achieve remission or an improvement of ≥50% in depressive symptoms compared with patients with no insomnia. These data, which await replication, suggest that insomnia may perpetuate depression.

There are therefore good data to suggest that insomnia is a significant predisposing factor for depression, although further investigations are required to address the possible precipitating and perpetuating roles of insomnia in the depressive clinical course. In all three cases, it is unclear whether insomnia as a comorbid disorder interacts with other variables for the development of depression, or whether insomnia itself only represents an as yet unknown factor.

Does treatment of insomnia modify the course of depression?

From the historical symptom-only perspective of insomnia, one would predict that treatment of insomnia in the context of depression is either futile in the absence of treatment for the parent disorder, or, if successful, merely an example of good symptom management. Alternatively, if insomnia is a comorbid condition that predisposes, precipitates, or perpetuates depression, then insomnia should be treatable in the context of depression, and the benefits of such treatment should accrue to the depressive condition. There are now two sets of data that refute the former perspective, and support the latter. First, two clinical case series [85,86] and two randomized clinical trials [87,88] have shown that patients with co-occurring psychiatric or medical illnesses derive benefit from standard cognitive behavioral treatment for insomnia (CBT-I), with effect sizes comparable to meta-analytical norms.

Second, in another clinical case series, 56 patients presenting with insomnia and depression were enrolled in a structured, self-help insomnia program [89]. On average, patients not only showed improved sleep parameters, but 57% no longer exceeded depression cut-off scores, and an additional 13% of the total sample had a >40% decrease in depression scores. In a preliminary, uncontrolled study of CBT-I, eight patients with insomnia and mild depression showed improved sleep continuity measures, and seven of eight had depression scores below the cut-off at the end of treatment and at a 3-month follow-up [90].

Finally, in a large clinical trial (n=545), depressed patients with insomnia were randomized to receive fluoxetine with either placebo or eszopiclone. The group receiving eszopiclone not only showed significantly improved sleep continuity, but also had a greater reduction in depression scale scores and a shorter time-to-event for improved depression than the group receiving fluoxetine plus placebo [91].

These data suggest that the treatment of insomnia is feasible and efficacious in the context of current depression, and that successful treatment of insomnia attenuates depressive symptoms beyond those that are sleep-specific. When coupled with data showing that insomnia can persist following otherwise successful antidepressant treatment [4–8], this strengthens the case for considering insomnia not only as a risk factor in the course of depression, but also as a potentially modifiable risk factor for new-onset, episodic, or unremitting depression.

This, in turn, raises two additional questions:

- Can the treatment of insomnia in remitted depression prevent recurrence?
- Can the treatment of primary insomnia, in an at-risk non-depressed group, be protective against new-onset depression?

To our knowledge, there is one ongoing trial regarding the former (Is Insomnia a Modifiable Risk Factor for Insomnia? Primary Investigator: ML Perlis, University of Rochester, Rochester, NY, USA), but there are currently no published data that respond to either question.

Theoretical perspectives: how could insomnia modify the course of depression?

There are two broad perspectives from which to consider how insomnia may affect the development and course of depression. From a psychological perspective, the mood and cognitive consequences of insomnia may diminish the capacity to cope with interpersonal, social, and vocational stressors, thereby increasing the likelihood of negative life events or poor responses to such events. It is also possible that "lack of control" issues related to insomnia may activate other depressive schema related to helplessness and hopelessness.

From a neurobiological perspective, the association of persistent insomnia with neuroendocrine imbalances (e.g. hypercortisolism, increases in aminergic tone, serotonin deficiency), may directly or indirectly predispose the individual to the full clinical syndrome of MDD. These neuroendocrine abnormalities may, in turn, represent some of the biological factors that make insomnia a risk factor for MDD.

These two perspectives are not mutually exclusive. In fact, a surprising marriage of these perspectives comes from evidence revealing that acute sleep deprivation has antidepressant effects [92]. This raises the question of how insomnia can be a risk factor for MDD, when sleep deprivation acts as a form of antidepressant therapy. Clearly, insomnia and sleep deprivation are not the same, especially since insomnia as it presents in MDD is not comparable in magnitude or form to the sleep deprivation that has antidepressant effects. It has been proposed that insomnia initially occurs as a compensatory phenomenon in MDD to increase serotonergic tone but, unlike its sleep deprivation counterpart, cannot reach a level that exerts an antidepressant effect [93–95]. We would add that insomnia may also be an attempt to regulate other features of depression. If part of the pathogenesis of MDD relates to increased somatic arousal and/or to increased CNS arousal, then insomnia may represent a systemic response i.e. insomnia that occurs with MDD may be an attempt to increase homeostatic pressure to a point where the resultant fatigue and sleepiness counterbalance somatic and/or CNS hyperarousal. While such a position is entirely speculative, it is consistent with reports that sleep deprivation results in decreased core body temperature and decreased CNS metabolism in depressed subjects who have an antidepressant response to sleep deprivation [96–98].

In agreement with this perspective, there is a cascade effect that occurs with new onsets of depression. Following the biopsychosocial events that precipitate the initial CNS concomitants of depression (e.g. limbic hyperarousal induced by life stress), insomnia occurs both as a consequence and as a systemic response. The resultant increase in homeostatic pressure diminishes the CNS hyperarousal but also exacerbates or produces a set of "secondary" depressive symptoms. These secondary symptoms (anhedonia, fatigue, and memory and concentration problems) may, in turn, give rise to tertiary symptoms that include interpersonal problems, social withdrawal, and/or cognitive distortions (Fig. 3). When viewed in this way, onset of new episodes of MDD would be expected to unfold over time in such a way that some symptoms of depression reliably occur before others.

In remitted patients, persistent insomnia may indicate that the depression is not entirely resolved. Alternatively, insomnia may persist for reasons other than those that initiated the depressive episode. In keeping with the behavioral model of insomnia [99], an acute episode of depression may initiate insomnia, but the insomnia (as in primary insomnia) may persist due to perpetuating or maintaining factors, such as extending sleep opportunity and staying in bed while awake, which can result in conditioned insomnia. When insomnia exists as a result of behavioral contingencies, it may set the stage for other depressive symptoms. The occurrence of these symptoms, now secondary to a conditioned insomnia, could lower the threshold for the recurrent episodes of depression. This may be true in at least two ways. First, more defining criteria are met because of insomnia, thereby requiring fewer additional symptoms to make the diagnosis. Second, and more importantly, insomnia may increase general psychobiological vulnerability.

If it is true that insomnia represents a failed attempt at somatic and/or CNS homeostatic regulation, then the regulated sleep deprivation that is a cornerstone of both sleep restriction therapy and stimulus control interventions of CBT-I may succeed where the endogenous form fails. This may be because therapeutic sleep restriction, while of a short duration, is of a greater magnitude than the loss of sleep that occurs with natural insomnia. Thus, it may allow for a downregulation of somatic and/or CNS hyperarousal but may not be sufficiently chronic to exacerbate or precipitate the "secondary" depressive symptoms. This perspective suggests that the behavioral treatment of insomnia might exert direct antidepressant effects in addition to prophylactic effects, and bears further scrutiny in controlled trials.

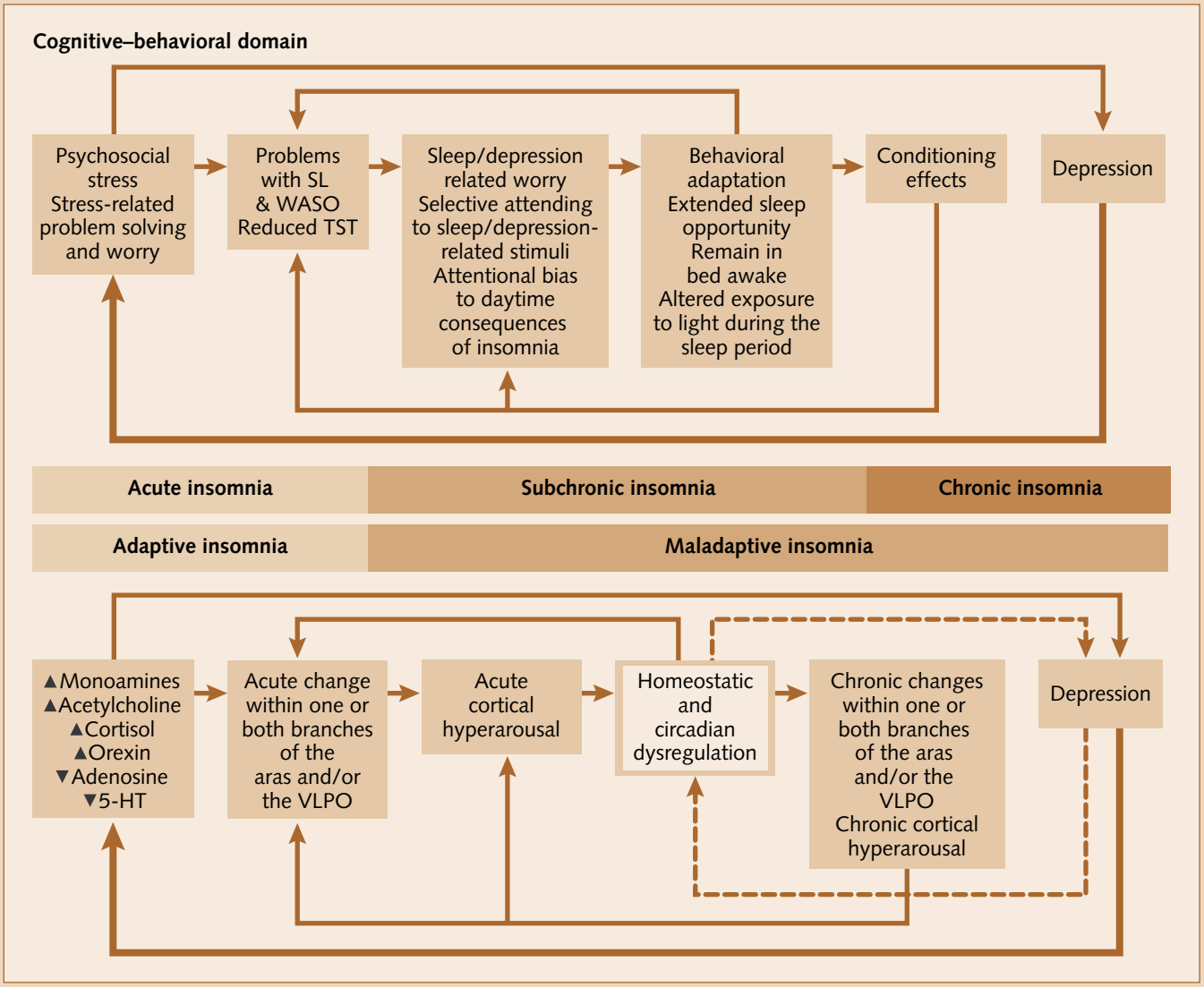
Finally, as has been argued throughout this paper, insomnia may confer risk for new-onset depression in that it may be a normative "first response" to biopsychosocial stress. Such a response, one might argue, is likely to be adaptive to the extent that the stressor appropriately and acutely activates the fight-or-flight system. If, however, the insomnia response continues beyond the biopsychosocial stress event, one might expect this form of insomnia (i.e. chronic insomnia) to represent a risk factor for the development of new-onset depression in a manner that is similar to the sequence (kindling) effect described above. For a graphical representation of this idea, see Figure 3.

Summary and future directions

In the present paper we have argued that there is sufficient evidence to consider insomnia and depression comorbid disorders, and that it is at least possible that insomnia and depression interact synergistically. The evidence supporting this includes:

- Each disorder may appear in the absence of the other disorder.

Figure 3. Etiology and pathophysiology of insomnia and depression. The box delineating the homeostatic and circadian factors is highlighted because the neurobiological control mechanisms are not detailed.



5-HT: serotonin; SL: sleep latency; TST: total sleep time; VLPO: ventrolateral preoptic area of the hypothalamus; WASO: wake after sleep onset.

- Insomnia remains a common residual symptom in remitted depression.
- Insomnia can be successfully targeted in the context of ongoing depression.
- Insomnia is a predisposing factor for depression (with preliminary evidence that it may also precipitate and/or perpetuate depression).

In addition, the two disorders present with different PSG findings, and to a less impressive degree, with different neurobiological profiles.

In order make a more compelling case for this theory, there are a variety of studies that need to be undertaken. These include:

- Large-scale longitudinal studies with multiple time point assessments (using validated insomnia instruments) to determine the time course between the onset of acute insomnia, the onset of chronic insomnia, and the development of new-onset depression. Such trials could also assay potential moderating/mediating factors as the ability to cope with interpersonal, social, and vocational stressors, the contribution of a sense of helplessness as opposed to control, and the level and type of neuroendocrine and neuroimmune abnormalities. These studies could also be designed to compare those individuals for whom insomnia appears to be only a symptom of depression that ameliorates with the depression, with those for whom insomnia persists.

Similarly, it would be useful to characterize and distinguish between depressed subjects who develop hypersomnia as opposed to insomnia.

- Intervention trials (both pharmacological and behavioral), which treat persistent insomnia in subjects with remitted depression or in subjects at risk of depression, would help assess whether this delays or aborts recurrent or first-onset episodes of depression.
- Studies that replicate the work by Fava and colleagues [91], which showed that adjuvant treatment for insomnia hastens recovery from depression.
- An inpatient intervention trial to assess the effects of treatment for insomnia in acute depression, where both pharmacological and behavioral anti-insomnia treatments are applied as monotherapies.
- An inpatient trial where subjects at risk for depression are exposed to a transient insomnia condition (such as those used by industry for Phase II trials) to determine whether insomnia can "trigger" new-onset episodes of depression. As noted earlier, this study (while a powerful demonstration) is likely to be too ethically challenging to conduct. The alternative would be to create an animal model of insomnia and use this to determine whether chronic insomnia predisposes, precipitates, or perpetuates an analogue form of depression in this context.

Disclosures

The authors have no relevant financial interests to disclose.

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