Insomnia ROUNDS

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Psychiatric Disorders and Insomnia: Managing the Vicious Cycle

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Sleep problems and psychiatric disorders are independent conditions that exacerbate each other, impair quality of life, and increase disability.[1] As most acute and many chronic psychiatric disorders are associated with delayed, disrupted, or nonrestorative sleep, normalizing sleep and its timing is essential to maximize recovery from severe and persistent mental illness. Utilizing the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision) diagnostic schema,[2] this issue of *Insomnia Rounds* focuses on the common psychiatric disorders – mood disorders, anxiety disorders, and schizophrenia – that are associated with prominent sleep complaints, describes the sleep disturbances associated with each disorder, and suggests diagnostic tools that can help confirm the diagnosis. In addition, an approach to management (both pharmacological and nonpharmacological) is discussed. The relationship between insomnia and substance use and abuse will be covered in a future edition of *Insomnia Rounds*.

What is the Relationship Between Disrupted Sleep and Psychiatric Illness?

Persistent childhood sleep problems are associated with the development of adult anxiety disorders.[3] In about 40% of adults with mood disorders, insomnia presents prior to the onset of other mood disorder symptoms.[4] Suicidal thoughts in adolescents are associated with both nonrestorative sleep and short sleep times.[5] In depressed adults, insomnia is linked to the intensity of suicidal thoughts, a link that appears to be mediated by nightmares and dysfunctional beliefs and attitudes about sleep.[6]

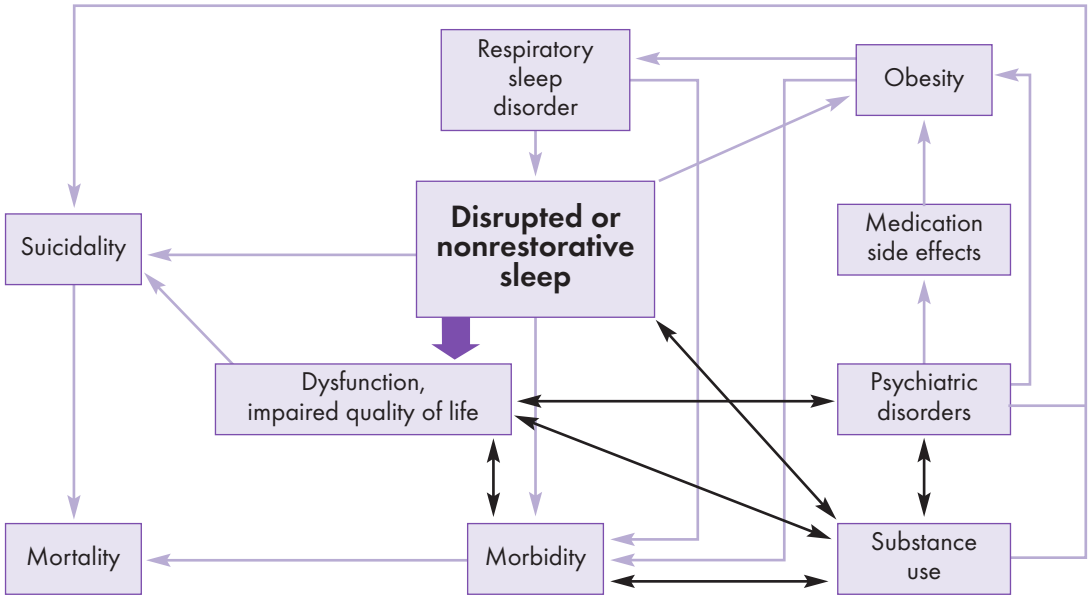
Community surveys and longitudinal studies confirm that chronically disturbed sleep both increases the risk of developing a psychiatric illness and hinders recovery from one. A study by Ford and Kamerow[7] reported that 40% of adults with insomnia met the criteria for various mental disorders, compared with only 16.4% of those without sleep complaints. In another study of 14 915 adults from 4 European countries, Ohayon and Roth[4] revealed that 28% of insomnia sufferers had a current diagnosis of a mental disorder and that 25.6% had a prior psychiatric history. Bidirectionality is also seen in the elderly. Alzheimer plaques disrupt sleep and, conversely, a lack of sleep promotes Alzheimer plaques. In one study, patients whose sleep efficiency was below 75% were >5 times more likely to have preclinical Alzheimer disease than good sleepers.[8]

The complexity of the interaction between insomnia and associated morbidities is illustrated in Figure 1. In primary care, the efficient evaluation of these complexities is facilitated by the use of a sleep diary (see *Insomnia Rounds* volume 1, issue 1)[9] and self-rating scales (Table 1).[9-13] Adding to these complexities is the fact that the majority of older patients complaining of inadequate or nonrestorative sleep also have comorbid insomnia. Previously known as secondary insomnia, comorbid insomnia requires the assessment of the primary medical or psychiatric illness or symptoms, as well as the need to maximize sleep performance through the use of medication and/or behavioural therapies.

Mood Disorders

Utilizing the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision; DSM-IV-TR) diagnostic criteria,[2] mood disorders are characterized by ≥1 episodes of depression or manic or hypomanic episodes. Cyclothymia and dysthymia are less severe

Figure 1. Interrelationship between disturbed sleep and dysfunction



The primary effect of acute insomnia is daytime dysfunction, but when it is chronic, it is associated with psychiatric disorders that have a bidirectional relationship (coloured arrows) with sleep disturbance, substance use, dysfunction and morbidity. Sleep deprivation, psychiatric disorders, and medication side effects can cause obesity that may cause or worsen a respiratory sleep disorder and directly or indirectly affect morbidity.

than major depressive disorder (MDD) and bipolar disorder, but are also associated with disturbed sleep and disability.

Patients with mood disorders complain of sleep disturbances before, during, and after remission of the mood episode, with 65%–75% of adults, adolescents, or children with depression complaining of insomnia or, more rarely, hypersomnia.[14,15] In addition to disrupted and nonrestorative sleep during the mood episode, patients are more likely to complain of increased awakenings, disturbing dreams, and decreased sleep time.

Manic or hypomanic periods are often associated with a feeling of being "full of energy." During these manic episodes, patients report both reductions in total sleep and a decreased need for sleep, whereas, during the depressed pole of their illness, they report insomnia or less frequently, hypersomnia.

Persistent insomnia after the resolution of other mood symptoms is a poor prognostic sign since it is predictive of increased severity and recurrence of major depression.[16] Insomnia is the most commonly reported residual symptom during remission of mood episodes in patients with major depression[17] or bipolar disorder.[18] Residual insomnia occurs in 20%–44% of patients with MDD despite standard antidepressant treatment. In addition to increasing the risk of recurrence, residual insomnia is also associated with concentration difficulties, decreased functioning, suicidal ideation, suicide attempts, and completed suicide.[19]

Unless the clinical history requires a sleep study to confirm or rule out other sleep disorders, subjective evaluation of a patient's sleep patterns through sleep diaries or actigraphy is sufficient to quantify and monitor the sleep complaint. However, in the search for possible biological markers for mood disorders, many systematically studied patients exhibit significant alterations from normal sleep during both depressive and manic episodes. Three differences have been noted and are described in Table 2. They include:

- disturbances in sleep continuity
- slow-wave (delta) sleep deficits
- Rapid eye movement (REM) sleep abnormalities (with REM sleep disinhibition in depression)

Table 1. Useful screening tools for assessing sleep and psychiatric conditions

- The Consensus Sleep Diary[9]
- The Pittsburgh Sleep Quality Index (PSQI)[10]
- The Patient Health Questionnaire (PHQ)-9[11]
- The Generalized Anxiety Disorder 7-item (GAD-7) Scale[12]
- Primary Care Posttraumatic Stress Disorder (PTSD) screen[13]

These tools are all in the public domain. You will be able to download the particular screening tool at the Internet address in the reference.

Table 2. Sleep changes in mood disorders[17]

Patient's complaint	*Sleep study (PSG) finding*
"I can't fall asleep"	Prolonged latency to stage 1 and 2 sleep
"I wake up through the night"	Increased arousals and awakenings through the night
"I wake up early"	Early awakening without return to consolidated sleep
"My sleep is too short"	Reduced total sleep time
"My sleep is shallow and unrefreshing"	Increased stage 1 Decreased stage 3 and 4
"My dreams are disturbing"	Awakening from REM sleep with difficulty returning to sleep Multiple REM sleep abnormalities, including increased REM sleep, increased eye movements in REM, etc.

REM = rapid eye movement

These sleep architecture findings reflect the complex neurobiological changes in brain and bodily functioning during and after a mood episode.[1,17]

Treatment

The treatment guidelines for MDD[20] and bipolar I and II disorders[21] emphasize pharmacological management and evidence-based psychotherapies such as cognitive behavioural therapy (CBT) and mindfulness-based CBT, and interpersonal and social rhythm therapy for bipolar disorder. Along with sleep hygiene strategies, these are the core components for the long-term comprehensive management of patients with these disorders.

Most of the currently available antidepressants (eg, amitriptyline, trazodone, and mirtazapine) have a beneficial effect on sleep. They vary in their adverse event profile and, when sedating, can be used as a single intervention given at night. However, adverse events such as morning hangover or weight gain may limit their use. Many of the second-generation antidepressants (eg, selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]) may contribute to or worsen insomnia in MDD;[22] therefore, they often require the use of a hypnotic at night. The preferred hypnotics are the short-acting benzodiazepines or nonbenzodiazepine receptor agonists such as zopiclone and zolpidem. These agents are well studied and safer than psychotropic agents such as trazodone and quetiapine,[23,24] which are often used to promote sleep in patients with mood disorders. Small studies suggest that use of benzodiazepines or nonbenzodiazepine agonists can enhance the effects of antidepressants, resulting in an earlier and more robust response.[25]

Anxiety Disorders

Although disturbed sleep can be seen with any of the DSM-IV-TR defined anxiety disorders listed in Table 3, only posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD) include sleep disturbance as one of the diagnostic criteria.

What is the effect of trauma on sleep?

Sleep is commonly disturbed after acute trauma. In one study, complaints of insomnia and excessive daytime sleepiness 1 month after a motor vehicle accident predicted the diagnosis of PTSD at 3 months.[26] Interestingly, in this study, sleep complaints were not supported objectively by actigraphy. This suggests that altered sleep perception – rather than sleep disturbance – may result in complaints of poor sleep in PTSD. Sleep study findings in chronic PTSD are variable, with normal or reduced sleep efficiency, normal or increased nocturnal awakenings, increased REM density, and increased phasic muscle activation during REM sleep all being reported.[1]

The core feature in PTSD is the experience of a significant, often life-threatening, trauma that causes marked anxiety. Three groups of symptoms make up the diagnostic criteria:

- reliving the trauma
- avoidance or emotional numbing
- physiological hyperarousal

Dreams and/or nightmares about the trauma and insomnia are the predominant sleep-related symptoms, so it is not surprising that >65% of PTSD patients report significant sleep difficulties.[27] Poor subjective sleep quality affects both the severity of PTSD symptoms and perceived mental health.[27] Interestingly, having fewer sleep-related symptoms is positively associated with psychological resilience and a decreased incidence of PTSD or other mental illnesses.[28]

A recent underpowered study utilizing polysomnography (PSG) and blood sampling in 13 veterans with PTSD revealed that a significant increase in awakenings correlated with adrenocorticotropic hormone levels during the night and the subjective perception of sleep depth. These findings refocus our attention on dysfunction within the hypothalamic-pituitary axis as a possible cause of disrupted sleep and daytime symptomatology in PTSD.[29]

Table 3. DSM-IV-TR list of conditions associated with anxiety disorders[39]

- Panic disorder with/without agoraphobia
- Agoraphobia without history of panic disorder
- Specific phobia
- Social phobia
- Obsessive compulsive disorder
- Posttraumatic stress disorder
- Acute stress disorder
- Generalized anxiety disorder
- Anxiety disorder due to general medical condition
- Substance-induced anxiety disorder
- Anxiety disorder not otherwise specified

DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision.

Treatment of PTSD

There are currently 7 guidelines for the management of PTSD.[30] All support the use of trauma-focused psychological treatment (TFPT) and recommend, to varying degrees, the use of SSRIs as first-line pharmacotherapy. Many psychiatrists and most general practitioners have little or no training in TFPT therapies such as eye movement desensitization and reprocessing, stress inoculation training, and trauma-focused CBT. Therefore, referral to a psychologist trained in these techniques is ideal.

Both psychological and pharmacological treatments are evidence-based interventions for traumatic nightmares that may persist after the core features of PTSD have resolved. The alpha1-adrenoceptor antagonist prazosin has shown robust clinical effects with minimal adverse events; however, there is less robust evidence for the use of low-dose risperidone and trazodone.[31] Nonpharmacological treatment interventions for post-traumatic nightmares include imagery rehearsal therapy (IRT) and exposure, relaxation, and rescripting therapy, as well as lucid dreaming therapy. Recently, a multi-component behavioural intervention combining IRT and CBT for insomnia improved sleep quality, insomnia severity, and reduced nightmare frequency in veterans.[32]

Generalized anxiety disorder (GAD)

GAD is a chronic anxiety disorder, characterized by excessive anxiety and intrusive worrying, restlessness, fatigability, muscle tension, irritability, and difficulty concentrating. Subjective insomnia – characterized by difficulty falling or staying asleep or by restless unsatisfying sleep – is common and supported by PSG with positive correlations between anxiety ratings and the number of awakenings, latency to stage 1 sleep, and percentage of stage 2 sleep.[33] Latency to REM sleep is often shortened in depression, but is normal in patients with GAD alone.[34] GAD is often comorbid with other psychiatric disorders such as major depression and adversely affects prognosis.[35]

Treatment of GAD

Current guidelines for the pharmacological management of GAD emphasize second-generation antidepressants. Drugs of choice that have passed regulatory approval for GAD include venlafaxine, duloxetine, paroxetine, and escitalopram;[36-39] however, the SSRIs can be activating and may cause or worsen insomnia.[40] In these cases, the temporary use of a hypnotic to stabilize sleep may be required. Interestingly, in a study of escitalopram (10 mg/day) in GAD, the addition of eszopiclone (3 mg) improved sleep and daytime performance.[41] There was a significant reduction in anxiety scores in subjects treated with escitalopram/eszopiclone (63%) compared with those receiving escitalopram/placebo (49%). Though not approved for this indication, pregabalin is widely used off-label for the management of GAD.

A variety of nonpharmacological interventions (eg, CBT, mindfulness, relaxation exercises) can help in managing GAD symptoms. These techniques can also be used in the nonpharmacological management of insomnia.[42] Patients with milder cases of GAD who have minimal impairment in functioning can also be successfully managed with behavioural or psychotherapeutic techniques in conjunction with behavioural approaches to improving sleep performance.

Panic disorder

Panic attacks are the core feature of panic disorder. They are characterized by discrete episodes of intense fear or discomfort, accompanied by physical symptoms (eg, palpitations, sweating, shortness of breath, chest pain, or feeling dizzy, unsteady, lightheaded, or faint) that develop rapidly over a period of about 10 minutes.[43] Initially, they are spontaneous, but they may become cued to certain situations.

It is also common for panic attacks to emerge spontaneously during sleep.[1] In addition to the general autonomic arousal seen in panic disorder, frequent nocturnal panic attacks may condition fear and apprehension about sleep and lead to secondary insomnia. Surveys reveal that insomnia is a common complaint of patients with panic disorder, a complaint confirmed by most PSG studies that show that sleep initiation is prolonged and frequent awakenings.[1,44] Panic attacks can suddenly awaken a sleeper with a start and evolve into the typical apprehension, fear, and somatic symptoms typically experienced in awake states. Between

33% and 71% of panic disorder patients report sleep-related panic attacks with as many as one-third of patients having more frequent episodes during sleep than when awake.[1] Studies indicate that patients with sleep-related panic may have a more serious variant of panic disorder that is characterized by earlier illness onset, higher symptom load, depression, and suicidal ideation.[44]

Treatment of panic disorder

Both pharmacological and nonpharmacological interventions are effective in reducing panic attack frequency and functional impairment.[45] The SSRIs and SNRIs are considered first-line treatments and, as in GAD, may require the use of a hypnotic to stabilize sleep and improve outcome.[46]

Schizophrenia

Acute psychotic states are frightening experiences associated with hypervigilance and hyperarousal that inevitably interfere with the ability to fall asleep and to stay asleep. As with mood disorders, disturbed sleep may precede the more florid symptoms of schizophrenia (hallucinations and delusions) by many months. Severe insomnia is one of the prodromal signs associated with impending psychotic exacerbation or relapse following the discontinuation of antipsychotic medication in chronic schizophrenia.[47]

In patients with chronic schizophrenia, particularly when it is associated with a loss of structured daytime activities, haphazard sleeping patterns (eg, protracted daytime sleeping) may add a circadian sleep disorder (eg, delayed sleep phase) to the burden of illness.[48]

How does sleep in patients with schizophrenia differ from healthy controls?

Sleep studies in patients with schizophrenia show that they take longer to fall asleep, have increased wake time during the night, decreased total sleep time, decreased latency to the onset of REM sleep, decreased amounts of slow-wave (delta or N3) sleep, and a decrease in the amplitude of electroencephalographic slow waves during non-REM sleep.[49]

A number of studies have identified inconsistent associations between PSG sleep indices and the positive symptoms (delusions, hallucinations, and disorganized thought), as well as the negative symptoms (affective flattening, avolition, alogia, attention problems) of schizophrenia.[19] The clinical significance and pathophysiological implications of these findings is unclear.

Treatment of schizophrenia

Although nonpharmacological interventions can be helpful in patients with schizophrenia, the cornerstone of treatment is antipsychotic medications. Both first- and second-generation antipsychotics vary in their sedative adverse events, but they can be given at night to promote sleep and minimize daytime sedation. This effect can be maximized by ensuring that the patient practices good sleep hygiene (*Insomnia Rounds,* volume 1, issues 2 and 3),[42,50] particularly with regard to rising at the same time every day, preferably with exposure to morning daylight.

Unfortunately, and to varying degrees, the new atypical antipsychotics, especially olanzapine and clozapine, are commonly associated with significant weight gain that may result in adding a respiratory sleep disorder to the many health problems associated with schizophrenia (Figure 1).[51]

Conclusion

Insomnia is no longer considered a trivial complaint. Not only is it associated with significant morbidities (ie, accidents and marked reductions in quality of life), chronic insomnia is also a risk factor for the subsequent development of mood, anxiety, and substance use disorders. Persistent residual insomnia after treatment of a primary psychiatric disorder worsens impairment, dysfunction, and prognosis. Preliminary research indicates that adding a hypnotic to standard SSRI treatment improves sleep performance in patients with depression and GAD and provides a more robust outcome. However, further research is required to confirm that awareness of insomnia and management in its early stages is an opportunity to prevent psychiatric illness.

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