Psychiatric Disorders and Sleep Issues

Eliza L. Sutton, MD

INTRODUCTION

Psychiatric disorders and sleep problems are both common, with an estimated prevalence in 12 months of about 30% for any of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) disorders and about 30% for insomnia experienced at least a few days a week for at least a month (as part of a greater but less well-determined prevalence for all types of sleep issues). Psychiatric and sleep problems overlap significantly and are related. Insomnia, for example, correlates with likelihood of having at least 1 psychiatric diagnosis with an odds ratio of 5.0 for severe insomnia, 2.6 for moderate insomnia, and 1.7 for mild insomnia.

In this review article, the neurobiology of the sleep/wake states and mental health and observed associations between selected psychiatric disorders and sleep issues

Disclosure: No financial relationships to disclose.
Department of Medicine, University of Washington, 4245 Roosevelt Way Northeast, Box 354765, Seattle, WA 98105, USA
E-mail address: esutton@uw.edu

KEYWORDS

- Anxiety
- Cognitive-behavioral therapy for insomnia
- Depression
- Insomnia
- Restless leg syndrome
- Circadian rhythm disorders
- Obstructive sleep apnea

KEY POINTS

- Sleep issues and psychiatric disorders commonly coexist and can influence each other (eg, insomnia and depression).
- Medications for psychiatric disorders can affect sleep and sleep disorders, particularly restless legs syndrome, positively or negatively.
- Medications for sleep disorders can cause or affect psychiatric symptoms (eg, dopamine agonists given for treatment of restless legs syndrome can cause gambling or other compulsive behaviors).
- Cognitive-behavioral therapy for insomnia in 4 to 8 sessions is the preferred treatment of chronic insomnia if acceptable to the patient and accessible.
- For depressed patients with insomnia, a sleep-promoting medication may be useful as adjunct therapy (zolpidem, eszopiclone, trazodone, or amitriptyline) or as monotherapy (mirtazapine, nefazodone, or trazodone).
Table 1) are described, and treatment considerations relevant to primary care (Tables 2 and 3) are presented.

NEUROBIOLOGY COMMON TO SLEEP, WAKEFULNESS, AND MENTAL HEALTH

Although the purposes and mechanisms of sleep are not truly known, sleep is clearly crucial to optimal functioning of the brain. Insufficient quantity or quality of sleep affects alertness, hormone regulation, memory formation, emotional regulation, executive function, and multiple facets of behavior. Multiple experiments subjecting small groups of healthy people to total sleep deprivation for a night or 2 have shown myriad specific impairments. In the area of emotional regulation, those findings include increase in symptoms of psychopathology (depression, anxiety, paranoia, and somatic complaints), reduction in the physical expression of emotion, and impairment in the ability to recognize emotion in others.

In observational studies, psychiatric conditions are associated with alterations in sleep architecture, although the direction of the effect and its importance are not known. However, there is increasing evidence that basic brain functions regulating sleep and wake play a role in psychiatric disorders. For example, alterations in the circadian pattern of release of the wake-promoting neurotransmitter orexin may contribute to hypersomnia and insomnia in depression. Narcolepsy, well known as the condition of orexin deficiency, is associated with a roughly 2.5-fold higher risk of psychiatric disorder, including major depressive disorder (MDD) and social anxiety disorder.

The association between sleep problems and affective disorders may be rooted at the genetic level. Circadian clock gene polymorphisms seem to be associated with mood regulation and affective disorders, with blunting of the normal circadian pattern of gene expression in certain areas of the brain, including the limbic system, in people with MDD. An orexin receptor antagonist is currently in phase 3 trials for treatment of insomnia, and other orexin receptor antagonists are being studied in animals for potential therapeutic effect in anxiety disorders and in compulsive behaviors, including eating and addiction.

For chronic insomnia not explained by another sleep disorder, cognitive-behavioral therapy for insomnia (CBTI) is considered to be the preferred treatment. CBTI has
<table>
<thead>
<tr>
<th>Observed associations between selected psychiatric disorders and sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insomnia or Nonspecific Disrupted Sleep</strong></td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Posttraumatic stress disorder</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Schizophrenia</strong></td>
</tr>
<tr>
<td><strong>Suicidality</strong></td>
</tr>
<tr>
<td><strong>Attention-deficit/hyperactivity disorder</strong></td>
</tr>
<tr>
<td><strong>Impulse control disorders</strong></td>
</tr>
</tbody>
</table>
Table 2
Treatment approaches for insomnia in depression

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect on Sleep</th>
<th>Other Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT for depression without</td>
<td>Improvement in sleep with improvement in depression, similar to pharmacologic</td>
<td>Beck Depression Index scores improve (with sleep item removed), including suicidality,</td>
</tr>
<tr>
<td>specific insomnia treatment</td>
<td>antidepressant therapy[39]</td>
<td>vs control[40]</td>
</tr>
<tr>
<td>CBTI without specific</td>
<td>Improvement in sleep is similar for people with high and low depression scores</td>
<td></td>
</tr>
<tr>
<td>depression treatment</td>
<td>[40]</td>
<td></td>
</tr>
<tr>
<td>CBTI + SSRI</td>
<td>On escitalopram, insomnia remitted in 50% with CBTI vs 8% with sleep hygiene</td>
<td>On escitalopram, depression remitted in 62% with CBTI vs 33% with sleep hygiene and</td>
</tr>
<tr>
<td></td>
<td>and other control therapy[41]</td>
<td>other control therapy[61]</td>
</tr>
<tr>
<td>Exercise + SSRI</td>
<td>Mixed results:</td>
<td>Depression improved more with exercise for those who had hypersonmia at baseline[42]</td>
</tr>
<tr>
<td></td>
<td>Sleep improved with exercise (16 kcal/kg/wk for 12 wk)[42]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep did not improve overall with exercise (45 min 3 times/wk × 16 wk, target</td>
<td></td>
</tr>
<tr>
<td></td>
<td>heart rate 70%–85% of maximum for 30 min/session). Subset showed trend toward</td>
<td></td>
</tr>
<tr>
<td></td>
<td>improvement early in study[43]</td>
<td></td>
</tr>
<tr>
<td>SSRI, SNRI</td>
<td>Insomnia occurs as an emergent symptom, can be moderately severe[44] is more</td>
<td></td>
</tr>
<tr>
<td></td>
<td>likely in those whose depression response is delayed beyond 6 wk[45]</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>More improvement in fatigue and hypersonmloence on bupropion than on SSRI or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>placebo (no comment on effect on sleep)[46]</td>
<td></td>
</tr>
<tr>
<td>SSRI + zolpidem</td>
<td>Improved sleep on SSRIs and zolpidem 10 mg.[47] Improved sleep and next-day</td>
<td>No difference in depression outcome up to 24 wk[48]; FDA has advised starting dose</td>
</tr>
<tr>
<td></td>
<td>functioning on escitalopram and zolpidem CR 12.5 mg[48]</td>
<td>should not exceed zolpidem 5 mg or zolpidem CR 6.25 mg for women and suggested</td>
</tr>
<tr>
<td></td>
<td></td>
<td>these doses for men[49]</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Description</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>SSRI + eszopiclone</td>
<td>Improved sleep on eszopiclone 3 mg initiated with fluoxetine, maintained over 8 wk. Improvement maintained over 2 wk after discontinuation of eszopiclone</td>
<td>On fluoxetine, depression scores improved faster and more with eszopiclone than placebo and did not relapse with discontinuation of eszopiclone after 2 wk; FDA has advised eszopiclone starting dose should not exceed 1 mg in women and men.</td>
</tr>
<tr>
<td>SSRI + quetiapine</td>
<td>Improvement in insomnia seen early on quetiapine</td>
<td>No difference in improvement in moods on quetiapine. Can cause metabolic syndrome.</td>
</tr>
<tr>
<td>St John’s wort + zolpidem</td>
<td>St John’s wort reduces zolpidem levels to a variable degree, combined use not advised.</td>
<td></td>
</tr>
<tr>
<td>Antidepressant + trazodone</td>
<td>Substantial improvement in antidepressant-associated insomnia at trazodone 25–100 mg</td>
<td></td>
</tr>
<tr>
<td>Trazodone monotherapy</td>
<td>Effective solo or as adjunct for depression</td>
<td>Once-daily extended-release form may improve tolerability.</td>
</tr>
<tr>
<td>Mirtazapine monotherapy</td>
<td>Improves sleep more than paroxetine or venlafaxine; sedation is similar to amitriptyline; sleep effects may be better at mirtazapine doses &lt;30 mg</td>
<td>Effect may be more rapid than SSRIs, and is greater than venlafaxine. Commonly causes weight gain.</td>
</tr>
<tr>
<td>Nefazodone monotherapy</td>
<td>Sleep improved early on nefazodone vs worsening on paroxetine and on fluoxetine; differences minimal by 8 wk</td>
<td>Can cause hepatotoxicity.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CBT, cognitive-behavioral therapy; CBTI, CBT for insomnia; FDA, US Food and Drug Administration; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, serotonin reuptake inhibitor.
been shown to be more effective after 4 to 8 once-weekly sessions than sleep medication and to have subjective benefit persisting well after the intervention. CBTI has similar efficacy for insomnia in people with low and high scores on the Beck Depression Inventory, although those who are more depressed may be less likely to follow some of the

### Table 3

<table>
<thead>
<tr>
<th>Effect of psychiatric medications on selected common sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RLS</strong></td>
</tr>
<tr>
<td>Antidepressant: Bupropion</td>
</tr>
<tr>
<td>Antidepressant: Mirtazapine</td>
</tr>
<tr>
<td>Antidepressants: SSRIs and SNRIs</td>
</tr>
<tr>
<td>Antidepressants: SSRIs and SNRIs</td>
</tr>
<tr>
<td>First-generation antipsychotics (neuroleptics)</td>
</tr>
<tr>
<td>Atypical antipsychotics: Aripiprazole</td>
</tr>
<tr>
<td>Atypical antipsychotics:</td>
</tr>
<tr>
<td>Atypical antipsychotics:</td>
</tr>
<tr>
<td>Atypical antipsychotics: Quetiapine</td>
</tr>
</tbody>
</table>

*Abbreviations:* OSA, obstructive sleep apnea; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, serotonin reuptake inhibitor.
behavioral steps. In people with insomnia, CBTI can improve the Beck Depression score, including the item on suicidal ideation, without antidepressant medication, and in 1 study, it significantly improved the response of MDD to escitalopram. CBTI may be effective for insomnia in depression in as few as 2 sessions.

CBTI cannot be provided on an individual basis to everyone who might benefit, and therefore the sleep medicine community is exploring stepped-care models, in which the first step would be accessed as general information or self-help by the patient (eg, via the tested approaches of a computer-based or printed resource). Individual therapy by psychologists would be reserved as the highest step, for the subset who need (or want) a more intensive or personalized approach.

Pharmacologic treatment of insomnia is also a reasonable approach and one used more commonly than CBTI, because of availability, familiarity, and patient or physician preference. Medication treatment of insomnia would ideally be reserved for relatively short-term use at the lowest dose effective for that patient, because medications pose potential risks, and the long-term efficacy and safety of hypnotic medications are not well known. Zolpidem and eszopiclone are the preferred medications for insomnia in the absence of a contraindication such as sleepwalking (a marker for increased risk of sleep-related activities on these medications, although other medications have also been linked with this effect [see Table 3]). Zolpidem and eszopiclone measurably improve sleep subjectively and objectively and are not associated with respiratory depression, dose escalation, or withdrawal. The US Food and Drug Administration (FDA) has warned that “all drugs taken for insomnia can impair driving and activities that require alertness the morning after use,” and it announced changes in labeling for zolpidem in 2013 and for eszopiclone in 2014, with changes in labeling for other medications potentially to follow. Based on findings that morning levels of these drugs may be increased and impair functions such as driving even if the person feels alert, the new labeling advises initial prescribing of the lowest strength for zolpidem, zolpidem CR, and eszopiclone, with allowance for consideration of higher doses of zolpidem in men, and of either medication in anyone who has had insufficient benefit on the lower dose. Treatment of insomnia beyond these considerations is discussed specifically in the section on depression and in Table 2.

INSOMNIA AND PSYCHIATRIC ILLNESS

Several epidemiologic studies have reported a strong association between insomnia and any psychiatric disorder. In a large multinational European study, 18% of the population reported insomnia of 6 months’ duration or longer, and of those, 26% had a past psychiatric disorder and 48% had a current psychiatric disorder using DSM-IV criteria. In contrast, only 8% of people without insomnia had any history of past psychiatric disorder. Current severe insomnia, chronic insomnia not explained by a medical or psychiatric condition, and insomnia related to a medical condition each had an odds ratio just less than 6 for having a past psychiatric history. Insomnia was severe in 45% of people with comorbid MDD and anxiety disorder, in 34% in people meeting criteria for a single psychiatric disorder, and in 21% for those meeting criteria for insomnia disorder (without another mental health disorder). Among a subset of people surveyed for the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area project, 40% of people with insomnia and 47% of those with excessive sleepiness were found to have a psychiatric disorder using DSM-III criteria, as opposed to 16% of those with no sleep issues.
Insomnia may be a residual symptom of psychiatric illness, but may also precede it. The evidence for a temporal relationship is discussed in the sections on depressive disorders and anxiety disorders.

Insomnia and other sleep problems may be associated not only with the presence of a psychiatric disorder but with its severity or manifestations. In patients admitted to a forensic psychiatry hospital, chronic insomnia and other sleep problems were associated with greater aggression, hostility, and impulsiveness and reduced tolerance for frustrations.38

Sleep difficulties, particularly insomnia, have been well correlated with suicidality, including in adolescents. Even in the absence of a known psychiatric disorder, disturbances in sleep are associated with a significant increase in completed suicide.31 In people with MDD and insomnia, the severity of insomnia correlates with severity of suicidal ideation.32 Patients with depression, posttraumatic stress disorder (PTSD), or panic disorder who experience difficulties with sleep are at roughly 3-fold higher risk for suicidal behavior than patients with those conditions whose sleep is not impaired; for people with schizophrenia, the risk may be even higher.33

DEPRESSIVE DISORDERS AND BIPOLAR DISORDER

Derangement of sleep or wakefulness is a cardinal symptom of, and diagnostic criterion of, MDD and bipolar disorder. However, sleep problems are not only symptoms or sequelae of depression; the associations are more complex. Several sleep problems have been associated with increased risk of depression.

Sleep Deprivation

Sleep deprivation increases the risk for subsequent depression, however, total sleep deprivation has also shown benefit as part of a therapeutic approach to depression in MDD and bipolar disorder. Regulation of rapid eye movement (REM) sleep may be particularly germane to the development and treatment of depression, although the role of the observed effect of REM suppression by many antidepressants is unclear.

Insomnia

The best characterized association between sleep problems and psychiatric disorders is between insomnia and both depression and anxiety; anxiety is discussed later. Insomnia is not only a common symptom of depression but also predisposes to (or at least precedes) depression, is a common emergent symptom with treatment, and may perpetuate depression.33

Insomnia has a well-described bidirectional association with depression. In the large multinational European study mentioned earlier, among those with insomnia and a mood disorder, the insomnia was present before the mood disorder 41% of the time, appeared with onset of the mood disorder 29% of the time, and appeared after onset of the mood disorder 29% of the time. Chronic insomnia predicted an at least 2-fold increase in risk for subsequent depression occurring a year or more later in a meta-analysis of 21 longitudinal studies, including 1 study that reported doubling of risk over the subsequent 3 to 4 decades.

Insomnia and sleep disturbances persist after initiation of treatment of depression in about 50% of people and can also emerge as a new symptom after initiation of antidepressant therapy. Sleep disturbance predicts relapse in depression and may contribute to treatment resistance. Insomnia commonly presages relapse or recurrence of depression.36,37

Sutton
There are limited data to suggest that insomnia treatment improves the outcome of the depression, but moderate to severe insomnia should be treated in depression to reduce the patient’s suffering.

Medications (FDA-approved hypnotics as well as sedating psychiatric medications used off-label for insomnia) are commonly prescribed to improve the sleep experience during treatment, particularly in the initial phase, and CBTI is also effective (see Table 2). Approaches for treating a patient with insomnia and depression include initiating:

- Antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) or bupropion without additional therapy for insomnia, anticipating that sleep will improve when the depression improves (a reasonable approach when insomnia is mild and tolerable)
- Antidepressant therapy with an SSRI or SNRI or bupropion, plus also a sleep-promoting hypnotic or adjunct antidepressant medication for use until depression and insomnia improve
- Antidepressant therapy with an SSRI, SNRI, or bupropion, plus also nonmedication treatment of insomnia as CBTI over 4 to 8 weeks
- Antidepressant monotherapy with a sleep-promoting agent (mirtazapine, trazodone, nefazodone, or a sedating tricyclic antidepressant)

The sleep-promoting antidepressants have an antagonistic effect at 5-HT₂ receptors or histamine receptors (trazodone, nefazodone, mirtazapine, amitriptyline, imipramine, and nortriptyline). These antidepressants can be effective for insomnia in depression, as can the benzodiazepine receptor agonists zolpidem and eszopiclone. Paroxetine, although sedating, results in more sleep disruption in the first 2 weeks of therapy than does nefazodone.62

Excessive daytime sedation is not uncommon as a side effect of any medium-acting to long-acting sedating medication taken at bedtime for sleep; besides being unpleasant for the patient, this sedation poses risk for injury. As discussed earlier, the FDA has warned that zolpidem levels can be sufficient to impair function such as driving the next morning even if the patient does not feel sleepy, particularly in women or at higher doses or with the extended-release form, and other medications taken for insomnia can also affect safe functioning of a motor vehicle.49

If acceptable to the patient and accessible, CBTI is the preferred approach for chronic insomnia, including insomnia associated with psychiatric disorders, given its relatively robust subjective effect after 4 to 8 sessions. CBTI has been shown to improve depression scores and even suicidal ideation in people with insomnia but should not be first line for the treatment of a mood disorder.

Circadian Rhythm Disorders

Advanced sleep phase syndrome (ASPS), a circadian rhythm disorder in which affected people fall asleep early and wake early compared with social norms and light cycles, can be readily mistaken for depression, because early morning awakening is inherent to ASPS, and an early bedtime can restrict opportunities for social engagement. ASPS occurs uncommonly as a familial condition and also occurs with aging.

Delayed sleep phase syndrome (DSPS), a circadian rhythm disorder in which affected people fall asleep later and wake later compared with social norms and light cycles, is more common than ASPS. It can be genetic, or the same delayed sleep/wake pattern can occur as a result of habit or, perhaps, as a result of a psychiatric disorder. Delayed sleep phase is more common in adolescents with bipolar disorder with depressed mood and in MDD than in control individuals.7
Bright light therapy is a fundamental treatment of seasonal affective disorder and may have some benefit in other depressive disorders, although mania or hypomania is a risk in people with bipolar disorder. Light therapy is also a cornerstone in the treatment of circadian rhythm disorders, for which the circadian timing of the exposure to light is key. Light exposure should be soon after awakening for DSPS and near the end of the day for ASPS.

**RLS**

RLS, experienced by 5% to 15% of the general population, also shows a bidirectional association with depression. Prospective evaluation of women in the Nurses Health Study found that those who reported physician-diagnosed RLS but no depressive symptoms at baseline were at 1.5-fold greater risk for being diagnosed with depression in the subsequent 6 years than those without a diagnosis of RLS. The same investigators performed a meta-analysis of all published studies of RLS and depression, calculating a pooled odds ratio of about 2.3 for the association.

RLS can be mistaken for agitation or for medication-induced akathisia, from which it can be distinguished by localization (most commonly experienced in the legs, rather than being described as a whole-body sensation or inner restlessness), its association with an urge to move and relief from movement, and its nocturnal timing. RLS can be mistaken for agitation or for medication-induced akathisia, from which it can be distinguished by localization (most commonly experienced in the legs, rather than being described as a whole-body sensation or inner restlessness), its association with an urge to move and relief from movement, and its nocturnal timing. Treatment of moderate to severe RLS with a dopamine agonist can improve depressive symptoms, and withdrawal of dopamine agonist therapy given for RLS has been reported to trigger major depression. Adding complexity to this interrelationship, RLS can also be a common side effect of pharmacologic therapy for depressive disorders and bipolar disorder (see Table 3).

**Obstructive Sleep Apnea**

Increased scores on depression inventories are a common finding among people presenting for initial diagnosis with obstructive sleep apnea (OSA). In those meeting criteria for MDD in a large cross-sectional survey using DSM-IV criteria, there was an odds ratio of 5.3 for also meeting criteria for OSA or related breathing disorder in sleep.

Among people with OSA, depression is associated with reduced adherence to continuous positive airway pressure (CPAP) therapy. Studies have found neutral to positive results from CPAP use in people with OSA and depression, with persistence of excessive daytime sleepiness correlating with persistence of depressed moods. Higher doses of hypnotic medications in people with depression are associated with higher risks of sleep apnea and of treatment-resistant depression, but the factors may be interacting in a complex manner.

**Sleepwalking**

MDD is associated with a 3.5-fold increased risk of sleepwalking 2 times or more per month compared with people without psychiatric or sleep disorders. SSRIs can also increase the risk (see Table 3). Although zolpidem can trigger complex sleep-related behaviors and thus should not be prescribed for someone already known to sleepwalk, published interventional studies of zolpidem for insomnia in people with MDD on SSRIs have not mentioned sleepwalking as an adverse effect.

**Narcolepsy**

MDD is common in people with narcolepsy. In a study of 320 people with narcolepsy, nearly 20% were found to have MDD, a 2.7-fold increase in risk over the general population; in more than 85% of those with MDD, the narcolepsy developed first.
In an observational study of 517 people with narcolepsy or idiopathic hypersomnolence, 80% of whom were treated with stimulants and 26% with medications for cataplexy, 55% had depression of some degree. In that study, the presence and severity of depression correlated with multiple measures of the severity of the sleep/wake disorder: lower cerebrospinal fluid orexin levels, more cataplexy, more REM sleep manifestations such as sleep paralysis and hypnogogic hallucinations, more daytime sleepiness, and lower health-related quality of life. The observed clinical correlation does not distinguish between (1) the 2 having a common neurochemical origin, and (2) narcolepsy causing functional impairment and subsequently causing depression.

**Isolated Sleep Paralysis**

Isolated sleep paralysis (ISP) (short episodes of paralysis with awareness occurring on awakening or falling asleep, sometimes accompanied by vivid hallucinations or fear) has been associated with bipolar disorders and to a lesser extent with depressive disorders. Almost 19% of people with frequent ISP meet DSM-IV criteria for bipolar disorders and just more than 6% meet DSM-IV criteria for MDD or dysthymia, compared with around 2.3% of people who had never experienced ISP.

**ANXIETY DISORDERS**

Sleep disturbances are common in anxiety, with almost 75% of primary care patients with anxiety disorders reporting insomnia or restless sleep, particularly those with generalized anxiety disorder (GAD), PTSD, or comorbid MDD.

Sleep disturbances including insomnia and short sleep time are common in obsessive-compulsive disorder (OCD); nocturnal rituals and coexisting depression may be contributing factors. Greater sleep difficulty correlates with increased OCD severity.

Nightmares and disturbed sleep are, respectively, symptoms of intrusion and hyperarousal that are included in the diagnostic criteria for PTSD. In a population study in the Toronto area, almost 76% of people with PTSD had at least 1 other psychiatric diagnosis and 70% of people with PTSD reported impaired sleep. In that study, those with PTSD were significantly more likely than those without PTSD to report sleep paralysis, talking during sleep, violent behavior during sleep, difficulty initiating sleep or early awakening, or hypnogogic or hypnopompic hallucinations. Nightmares and sleep disturbance before trauma seem to be a risk marker for future development of PTSD, suggesting that, as with depression, there may be a bidirectional relationship between sleep issues and this psychiatric disorder.

**Insomnia**

Anxiety disorders are more likely than depression to precede the development of insomnia, but anxiety and insomnia may each be manifestations of the same underlying process or trait. In the large multinational European study mentioned earlier, in people with an anxiety disorder and insomnia, the insomnia preceded the anxiety disorder in 18%, appeared around the same time in 38%, and appeared after the anxiety disorder in 44%. In the NIMH study mentioned earlier, people who reported insomnia at 2 interviews 1 year apart were 6 times more likely to have an anxiety disorder than those without insomnia. In a large Norwegian study of people initially without anxiety or depression, having insomnia at 2 survey points 11 years apart was associated with an almost 5-fold risk of having developed an anxiety disorder by the second survey, compared with not reporting insomnia in either survey. In
comparison, the risk was 3.4-fold higher when insomnia was present at the first survey but not the second and was 1.6-fold higher when insomnia was present at the second survey but not the first.²

People with insomnia commonly experience heightened arousal of the mind or body with attempts to sleep. Persistent insomnia is more likely to develop in people who worry about their sleep, and people with persistent insomnia are more likely than those who sleep normally to monitor and focus on their attempts to sleep.³ Such worry, heightened arousal, and focus on sleep (called psychophysiologic insomnia in prior nosologies) may be reported as anxiety at bedtime but can be differentiated from GAD by the absence of daytime worry.

For people with anxiety and insomnia, treatment with escitalopram has been studied in conjunction with extended-release zolpidem,⁴ which improved sleep but not GAD, and with eszopiclone,⁵ which improved sleep, daytime function, and GAD. CBTI has been less studied in GAD than in depression and PTSD, but cognitive-behavioral therapy for anxiety can improve sleep.⁶

**Circadian Rhythm Disorders**

Severe OCD has been associated with DSPS.⁷

**RLS**

RLS can mimic anxiety at bedtime, because feelings of restlessness and jitteriness prevent the patient from resting quietly in bed to fall asleep. The improvement of these symptoms with benzodiazepines can further mistakenly suggest anxiety. Other psychiatric medications used for anxiety can cause or worsen RLS (see Table 3).

**OSA**

People presenting for initial diagnosis with OSA have been reported to have increased scores on anxiety inventories as well as depression inventories.⁸ Uncontrolled studies suggest that CPAP for OSA in PTSD can reduce insomnia, nightmares, and PTSD symptoms⁹; however, adherence to CPAP is reduced in veterans with PTSD, particularly those reporting more frequent nightmares, with claustrophobia and air hunger being among the reasons given.¹⁰

**Sleepwalking**

People with OCD have a nearly 4-fold higher risk of sleepwalking, unrelated to medication use, compared with people without psychiatric or sleep disorders.¹¹

**Narcolepsy**

Based on the study of 320 people with narcolepsy mentioned earlier,¹² anxiety disorders occur commonly in narcolepsy, including social anxiety disorder in 21% overall, and panic disorder and PTSD in 11% to 13% of women. The timing of onset varied in this study, with OCD and social phobia appearing before narcolepsy in about half of cases; PTSD, GAD, and agoraphobia occurred after narcolepsy in more than 75% of cases; and panic disorder and simple phobia were both apparent after narcolepsy in all cases.

**ISP**

ISP has been associated with panic disorder, PTSD, and other anxiety disorders. A review of 35 studies of lifetime prevalence of ISP¹³ found that almost 32% of psychiatric patients, and 35% of psychiatric patients with panic disorder, reported experiencing sleep paralysis at least once in their lifetime, compared with less
than 8% of the general population, and that nonwhites are more likely to experience sleep paralysis at least once than are whites. Among African Americans with ISP, more than 15% met diagnostic criteria for panic disorder. Experiencing fear during paralysis episodes is more closely associated with PTSD than with other anxiety disorders. No association has been found with antidepressant medications, including specifically with SSRIs, but the findings with regard to anxiolytics are mixed.

**SCHIZOPHRENIA**

In a systematic review and meta-analysis, patients with schizophrenia with sleep disturbances of all types were 12.66-fold more likely to have suicidal ideation, suicide attempts, and completed suicide than those without sleep disturbances, although the 95% confidence interval was wide: 1.40 to 114.44.

**Insomnia and Circadian Rhythm Disorders**

Insomnia is common in schizophrenia, with circadian abnormalities (phase advance, phase delay, or non-24-hour cycles) occurring in about half of people, and irregular, fragmented, or prolonged sleep occurring even in those with normal circadian cycles. Physicians should be aware that worsening of insomnia can be the prodrome of a psychiatric exacerbation for a person with schizophrenia.

**OSA**

Atypical antipsychotic medications commonly cause weight gain but also increase the risk of severe OSA beyond that explained by weight. The prevalence, presentation, and treatment of OSA have not been studied in schizophrenia in as much detail as in other groups, although there are case reports of schizophrenia symptoms improving (and in 1 case becoming exacerbated) with CPAP therapy.

**Narcolepsy**

Narcolepsy can be confused for schizophrenia, because it can present with psychosis symptoms either from the narcolepsy itself or from stimulant use, and it can coexist with schizophrenia. The psychosis of narcolepsy may be more common than realized. In 1 recent study, 83% of people with narcolepsy reported having trouble distinguishing dreams from reality, and 95% reported experiencing such dream delusions at least once a month. When narcolepsy and schizophrenia are comorbid conditions, the schizophrenia may tend to present after the narcolepsy. A prospective study at the sole pediatric sleep clinic serving Taiwan found that 10% of school-aged children diagnosed with narcolepsy-cataplexy developed schizophrenia in a mean of 2.6 ± 1.8 years, whereas retrospective review of records in the associated pediatric psychiatry division over the previous 10 years showed no teenagers with both conditions who had been diagnosed first with schizophrenia.

**ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

Sleep in attention-deficit/hyperactivity disorder (ADHD) has been investigated to a greater degree in children than in adults.

**Insomnia**

Stimulant medications (amphetamines and methylphenidate) and the nonstimulant medication atomoxetine cause insomnia, particularly with long-acting or
twice-daily dosing and with higher doses. These medications can also improve sleep quality in adults with ADHD.

**Circadian Rhythm Disorders**

In adults more than children, ADHD has been associated with delayed sleep phase; this association may trace back to the genetic level.

**RLS**

In both children and adults, ADHD has been associated with RLS and periodic limb movements. Up to 44% of adults with ADHD have been found to have RLS, and up to 26% of those with RLS meet criteria for ADHD. In children, treatment of RLS with L-DOPA does not improve ADHD, and treatment of RLS has shown mixed results on ADHD.

**OSA**

In children, ADHD is associated with breathing disorders of sleep (OSA and similar conditions) and improves after adenotonsillectomy. However, in adults, this association has not been found.

**TREATMENT CONSIDERATIONS**

Effects of sleep disorder treatments on psychiatric conditions have been noted in the discussion of that psychiatric condition. Treatment approaches for insomnia in depression are listed in Table 2. Effects of psychiatric medications on selected common sleep disorders are listed in Table 3.

Additional considerations regarding sleep disorder treatments relevant to psychiatric conditions of note for primary care physicians include the following:

- To avoid causing or exacerbating RLS (and perhaps even to improve existing RLS), the antidepressant of choice is bupropion, and the atypical antipsychotic of choice seems to be aripiprazole.
- Atypical antipsychotic medications commonly cause weight gain (especially olanzapine), extrapyramidal symptoms, akathisia (especially aripiprazole), fatigue, and sedation as well as hyperlipidemia and hyperglycemia.
- Quetiapine is particularly sedating and is prescribed off-label for insomnia, despite its adverse effects, cost, and lack of studies directly comparing it with better studied hypnotic medications.
- The psychiatrically relevant side effect of impulse control disorders can develop in patients taking even low-dose dopamine agonists for RLS; in 1 study, 7.6% of the patients on dopamine agonists for RLS developed 1 or more impulse control and compulsive behaviors, including gambling, shopping, and sexual behavior, sometimes with severe social consequences.
- The wakefulness-promoting medications modafinil and armodafinil, currently FDA-approved only for narcolepsy, shift work sleep disorder, and residual excessive daytime sleepiness in OSA, have been studied off-label as treatments for psychiatric disorders and for side effects from psychiatric medications but have not shown significant benefits.
- In addition to its efficacy in chronic insomnia and insomnia associated with depression, CBTI is effective in insomnia in postpartum depression and during abstinent recovery from alcohol dependence. In conjunction with imagery rehearsal therapy to address nightmares, CBTI has been shown to improve subjective sleep and daytime functioning in people with PTSD.
SUMMARY/FUTURE CONSIDERATIONS

The associations described between psychiatric disorders and sleep issues include observations on the natural history of the overlap between sleep, wakefulness, and mental health. Awareness of these associations may help clinicians treating patients with psychiatric disorders or sleep disorders to recognize potential contributing factors from the other area, particularly when a treatment given for a psychiatric or sleep condition might be causing or exacerbating a problem in the other area. It is hoped that within the next few years, stepped care with CBTI will become a useful, accessible tool for the treatment of chronic insomnia, including that associated with psychiatric conditions. Sedating medications will continue to be part of our armamentarium as well as always requiring a balance between the desired promotion of sleepiness and the undesired side effects, including daytime sedation and functional impairment. Ongoing and future research to elucidate neurobiological mechanisms underlying both psychiatric disorders and sleep/wake disorders will likely provide a more solid basis for understanding the overlap areas as well as further means for diagnosis and effective treatment.

REFERENCES


49. US Food and Drug Administration. FDA Drug Safety Communication: risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien
89. Roberts RE, Duong HT. The prospective association between sleep deprivation and depression among adolescents. Sleep 2014;37(2):239–44.


