The bidirectional nature of sleep problems and psychopathology

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As sleep and psychiatric disorders are not only comorbid but also co-dependent, patients require individual and integrated attention. The benefits of treating sleep disorders in the context of psychopathology are likely to extend beyond improved sleep, with demonstrated improvements in mental health.

KEY POINTS

- Most patients with psychiatric disorders experience sleep disturbance.
- Patients with comorbid sleep problems have greater symptomatology and poorer treatment outcomes.
- Obstructive sleep apnoea (OSA) and insomnia are associated with higher rates of depression and anxiety than community prevalence rates.
- There is strong evidence indicating a bidirectional relation between sleep disorders and mental health.
- Treatment of sleep problems may have additional benefits on mental health for patients with comorbid psychiatric illness, and may prevent the onset of psychiatric conditions in 'at-risk' individuals.
- The night-to-night variability of sleep quality in both OSA and insomnia needs to be emphasised to help patients understand that good management is the key message along with the notion that 'a bad night is just a bad night!'

Severe psychiatric disorders are relatively common, with 2 to 3% of people in Australia receiving this diagnosis; 15 to 18% of people, however, experience psychiatric disorders of mild to moderate severity, which is of considerable concern.[1] Sleep problems are also prevalent, with 12% of the population having a clinical sleep disorder.[2] Sleep helps to maintain optimal emotional homeostasis, as shown in several psychiatric conditions, in particular depression, where there is a bidirectional relation between the condition and sleep quality.[3-5] Around 50 to 80% of psychiatric patients have disturbed sleep, and those with comorbid sleep disorders fare worse than those without sleep problems.[6] Sleep disorders require equal

MedicineToday 2016; 17(3): 23-28
Amended May 2016

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recognition and treatment in the context of psychopathologies, and without this approach there are likely to be relapses for both disorders.

This article discusses the relation between psychiatric conditions and sleep and the effects of treatment of each on the other, and provides guidelines for counselling patients. Nondrug approaches to treatment will be covered in greater detail in a future article in *Medicine Today*.

Sleep disturbances in psychiatric conditions

Major depressive disorder

Up to 90% of patients with major depressive disorder (MDD) experience insomnia, including difficulties initiating and maintaining sleep and feeling unrefreshed from sleep. A small percentage of patients will experience hypersomnia. Depressed patients often show a delayed sleep phase and diurnal mood variation, associated with increased depressive symptoms in the morning that improve across the course of the day.

One of the most common biomarkers of MDD on polysomnography is altered rapid eye movement (REM) sleep: REM sleep is reduced in latency, is greater proportionally (particularly in the first REM period) and shows increased density of eye movements. These changes in REM sleep are associated with an increased risk of depression, episode progression and treatment outcomes.[7]

Bipolar disorder

In patients with bipolar disorder, sleep varies with episodes of mania and depression. During a depressive episode, sleep is similar to that of patients with MDD, although generally less severely disturbed. During episodes of mania, however, a significant reduction in the perceived need for sleep is reported, with a substantially reduced sleep time yet feeling refreshed.[8] Sleep is also disturbed between episodes, with increased night-to-night variability and sleep fragmentation along with increased REM duration and density, and symptoms of insomnia.

Sleep disturbances escalate prior to a bipolar episode, and ongoing sleep disturbances may contribute to relapse.[9]

Schizophrenia

Many disruptions to sleep occur with schizophrenia, and acute sleep deterioration may precede a psychotic episode.[10] Patients experience insomnia, with particular difficulties with sleep onset, altered sleep cycles, delayed sleep phase, reversed day/night and sleep/wake patterns or polyphasic sleep cycles.[8] Many aspects of the sleep disturbance in schizophrenia are attributed to poor sleep hygiene, thus patients require targeted treatment for their sleep.[6]

REM sleep can also be altered in patients with schizophrenia, with decreased REM latency and normal or increased REM density (the frequency of rapid eye movements during REM sleep). This sleep disturbance varies with duration of illness, treatment and the current experience of symptoms.

Anxiety disorders

Patients with anxiety disorders often experience sleep-onset and maintenance insomnia along with being overwhelmingly concerned about their sleep and its unpredictability. Anxiety and stress are also common triggers for insomnia, and could potentially explain some of the nonrestorative and fragmentation aspects of this disorder at a subliminal level.[6] Anxiety is associated with heightened baseline arousal (hyperarousal), which often delays sleep onset and increases the frequency of arousals and wake after sleep onset. Sleep cycles observed on polysomnography are not necessarily abnormal, but are associated with an increased percentage of lighter stages of sleep with resultant reduced total sleep time and sleep efficiency.[6,11]

The clinical picture of insomnia and anxiety is an individual feeling trapped and frustrated but generally unable to 'down-regulate' arousal levels at bedtime for sleep onset to occur. Recent research further substantiates this premise, with night-time worry or persistent thinking negatively and significantly impacting on sleep, compared with similar daytime thinking patterns, in both children with anxiety and sleep-related problems and adults with sleep problems.[12,13]

When anxiety and insomnia are both present, treatment interventions need to focus on enabling individuals to manage uncomfortable feelings and still allow sleep onset to occur.

Post-traumatic stress disorder

Sleep disturbance and nightmares are core features of post-traumatic stress disorder (PTSD). Disrupted sleep may be a predisposing or propagating factor, or both, of the condition. Reduced slow wave sleep (SWS) and increased REM density are often seen.[14] Insomnia in patients with PTSD is associated with an increased likelihood of suicidal behaviour, depression and substance abuse as well as nonresponsiveness to treatment. Dreams of traumatic event(s) differ to usual nightmares, which are more abstract in content, and they may also be accompanied by movement and panicked awakenings. A range of organic sleep disorders is also prevalent in patients with PTSD, including obstructive sleep apnoea (OSA) and periodic limb movement (PLM) disorders.

Sleep disorders in patients with PTSD often require targeted treatment and do not simply resolve with treatment of PTSD.[15]

Mechanisms for mood changes

Sleep disturbance alters mood and emotional state. Individuals who experience poor sleep have heightened negative emotions (e.g. sadness, anger) and lowered positive emotions (e.g. happiness, joy) compared with good sleepers.[16] Sleep loss and poor sleep quality can also influence responses to emotional events or

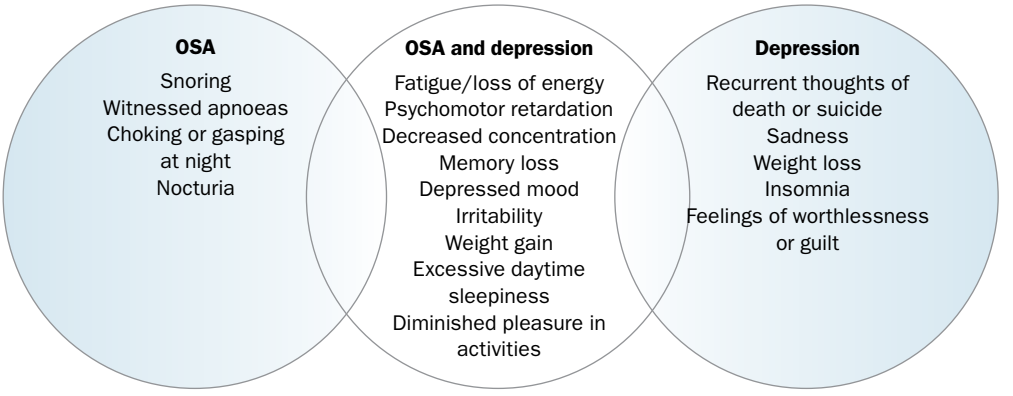

Figure. The overlapping diagnostic features of obstructive sleep apnoea (OSA) and depression.

information, amplifying negative affective responses to negative experiences and compressing the affective evaluation of positive experiences.[16]

In contrast, sleep deprivation may have an antidepressant effect in patients with MDD.[17] Between 40 and 60% of depressed patients experience improvements in mood after acute sleep deprivation, although relapse is observed in most patients after recovery sleep.[18] The mechanisms of the antidepressive effects of sleep deprivation are currently unclear but it has been suggested that the sleep disturbances observed in depressed patients (shorter REM latency, intermittent wakefulness and decreased SWS) may relate to the pathophysiology of depression, rather than just be symptoms of the disorder.

Until recently, the mechanisms for how sleep loss impacts on emotional state were largely unknown. A neuroimaging study found that participants deprived of sleep for one night have a 60% increase in amygdala activity relative to a sleep-control group when viewing aversive pictures.[19] In addition, there was a significant loss of functional connectivity between the amygdala and the medial prefrontal cortex – a region known to have inhibitory projections to the amygdala – in the sleep-deprived group compared with the group that slept. An impairment in top-down regulation of emotional control resulting from sleep loss may be one mechanism that produces this negative emotional state, which in turn affects mental health.

Altered sleep architecture, including changes to the amount and timing of REM sleep periods, appears to influence factors in the onset and maintenance of psychopathology.[20] Normally, REM sleep neurophysiology helps dampen reactivity to emotional information, possibly governing emotional homeostasis. It has been proposed that the reduction in aminergic neurochemistry and activation of the emotional brain regions during REM sleep create an ideal neurobiological environment for 'emotionally stripping' the brain, by depotentiating prior negative experiences and reducing emotional reactivity.[16] Shorter REM latency, greater proportional duration and greater density suggests an 'accumulated need' for emotional processing, or a greater quantity or intensity of emotions to be processed. This emotional processing may become dysfunctional in patients with psychopathology, where the quantity or intensity of disproportionately negative emotions is unable to be neutralised and processing retains or reinforces the negative affect bias.

Altered circadian profiles are also common in some psychiatric patients. Diurnal variations in mood, phase-advanced sleep timing and reduced amplitude of many rhythms are common features of MDD.[21] The profile of positive affect is in synchrony with diurnal changes in core body temperature, suggesting that positive mood may have a biological origin.[22] It is thought that internal desynchronisation may play a major role in mood state. One prime example of this is bipolar disorder, particularly in individuals who experience rapid cycling, in whom the affective state is strongly modulated by environment (light or dark) as well as behaviour (sleep or lack of sleep). The precise neurobiological underpinning of this remains unclear.

Psychopathology in patients with sleep disorders

Obstructive sleep apnoea

OSA is a common respiratory condition, affecting up to 25% of the adult population. It is associated with intermittent hypoxia and arousals from sleep. One of the most significant comorbidities of OSA is depression, with significantly higher rates of depressive symptoms identified in patients with OSA than in healthy controls.[23,24] Excessive daytime sleepiness and fatigue commonly occur in patients with OSA, and contribute to depressive symptoms (Figure).[24] Between 17 and 45% of patients with OSA have comorbid MDD, compared with prevalence rates for MDD in the general population of 3 to 4%.[25] Antidepressant use is prevalent (25 to 39%) among patients attending sleep laboratories for sleep assessments.[26]

OSA is also associated, although less commonly, with other psychopathologies, including anxiety, schizophrenia, substance abuse and bipolar disorder.[25] Psychiatric comorbidities can impact on the symptomatology, pathogenesis and treatment of

OSA, therefore assessment of these conditions in the clinical evaluation of patients is essential.

Insomnia

Cognitive and cortical hyperarousability during both wakefulness and sleep is a key factor in the pathophysiology of insomnia, and thus it is not surprising that insomnia is highly comorbid with anxiety disorder. The nature of these two conditions appears to be bidirectional, where sleep disturbance negatively impacts mood, and anxiety interrupts the initiation of sleep.[27]

Historically, insomnia has been viewed as a symptom of psychiatric conditions but this viewpoint has shifted in recent times and insomnia is now regarded as an independent comorbid condition.[20] This shift is reflected in the latest revisions of the *International Classification of Sleep Disorders* and the *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*.[28,29] The removal of implied cause and effect gives greater weight to the independent effects of insomnia in psychopathology, warranting treatment in its own right.

As well as co-occurring with psychiatric conditions, chronic insomnia may be prodromal, presenting many years before the onset of depression. A meta-analysis determined that people with insomnia who were not depressed were at a twofold increased risk of developing depression.[30] A recent longitudinal study showed that sleep disturbance may be a precipitating factor in the development of depression over time in young women.[31] A large prospective study of 11 years' duration found a bidirectional relation between insomnia and depression.[4]

Early diagnosis and treatment of insomnia may help prevent the development of psychiatric illness in individuals who are 'at-risk' of such conditions. This may be particularly important in adolescents, who are at a vulnerable stage both in terms of changes to their sleep and the onset of psychiatric disorders.

Treatment implications

As with the relation between psychopathology and sleep disorders, the effects of treatment of each are complex and potentially bidirectional. Patients with MDD and insomnia have poorer clinical outcomes and lower remission rates than patients without sleep issues. Residual sleep problems are common in many patients even after successful treatment of MDD, and these increase the risk of relapse. Psychiatric comorbidities may also impact on the treatment of sleep disorders. MDD reduces adherence to continuous positive airways pressure (CPAP) treatment in patients with OSA, and may also impact on patient-driven therapies such as behavioural therapies for insomnia.[32]

In people with psychiatric disorders, the use, abuse, tolerance of or withdrawal from medication and other substances can impact on sleep quality. Abuse of hypnotic and sedative medication also worsens sleep outcomes. Even prescribed medications for depression can impact on sleep, by either sedating or activating,

and timing of administration can assist with insomnia or hypersomnia, respectively. Most antidepressant therapies suppress REM sleep, however it is currently unclear why suppression of REM sleep has a therapeutic effect on these patients. Given that events are typically more severe in REM sleep, suppression of REM sleep in patients with OSA may reduce the severity of their OSA. Conversely, the variable effects of sedating antidepressants and antipsychotics on muscle tone may worsen OSA.[33]

Atypical antidepressant pharmacotherapies such as agomelatine were developed to act on the circadian pacemaker via the melatonergic system. The antidepressant effect of agomelatine may in part be due to sleep-regulating properties, without altering sleep architecture.[34]

Emerging evidence supports the notion that treatment of a sleep disorder may positively alter the course of a psychiatric condition. Cognitive behavioural therapy for insomnia (CBT-I) is an efficacious, multicomponent treatment that involves behavioural, cognitive and educational aspects. Recent data suggest that CBT-I not only significantly reduces insomnia severity but also has significant benefits on comorbid conditions, with the largest effects seen in comorbid psychiatric conditions.[35,36]

Similarly, there is mounting evidence that CPAP treatment for OSA reduces depressive symptoms.[37] To date, only limited studies have examined the efficacy of CPAP treatment in OSA patients with comorbid MDD. These studies have shown promising results, with around half of participants remitting from MDD at follow up, and some patients no longer requiring antidepressant medication. Depressive symptoms are reversible with treatment in some patients with OSA, suggesting that psychopathology in these patients is transient and possibly a consequence of the sleep disorder itself.

Guidelines for patient counselling

An important component of working with individuals with any psychiatric disorder is to acknowledge the level of distress they have been experiencing with their sleep difficulties and their vulnerability to increased negative mood responses.

There is considerable misinformation in the public arena and from the media surrounding sleep and mood. In relation to sleep, incorrect perceptions include statements such as 'good sleepers do not wake during the night', 'good sleepers have long periods of deep sleep' and 'dream sleep is deep sleep'. Being able to discuss these points objectively and highlight the benefits of so-called light sleep (non-REM stage N2 sleep) is important. This stage of sleep is often perceived as wake time by patients with insomnia due to the individual constantly monitoring the environment or self for a rational explanation of their wakefulness. If woken from N2 sleep and asked if they are awake or asleep, the individual will generally state they are awake. Treatment is about treating the 'wired and tired' and helping them to understand how these perceptions may have occurred. When these parameters are in place then explaining and working on behavioural interventions such as bed restriction, stimulus control therapy, paradoxical intention, constant waking and relaxation/mindfulness are the next important steps.

Sleep quality is variable across the week, and treating a sleep disorder effectively does not guarantee that a bad night will never return. It is about knowing how to manage it with the above listed interventions. Gaining confidence about sleep will also improve mood.

Special suggestions for rural GPs

The counselling steps described above can also be carried out by trained practice nurses who are often responsible for a large proportion of patient education in rural settings. A CBT intervention for insomnia is being trialled by the authors in a rural GP practice; if it is found to be effective then it is hoped it can be made available to other rural practices. Such a CBT program can also be used for individuals with a significant mood disorder and sleep problems as a baseline intervention, and will at least offer an alternative treatment option.

Conclusion

Sleep and psychiatric disorders are not only comorbid but also co-dependent, and therefore require individual and integrated attention. The benefits of treating sleep disorders in the context of psychopathology are likely to extend beyond improved sleep, with demonstrated improvements in mental health. Perhaps even more exciting is that the treatment of sleep disorders in otherwise healthy individuals may be a key strategy for preventing the onset of psychopathology. Clinical evidence suggests that treating sleep disorders could prevent the onset or reduce the severity of comorbid psychiatric conditions, allowing for the development of advanced models of care and new treatment approaches to psychiatric disorders. MT

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A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

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