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Sleep Disturbances in Depression

Michael Murphy, MD, PhD[a] and **Michael J. Peterson, MD, PhD**[b,*]

[a]Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, 6001 Research Park Boulevard, Madison, WI 53719, USA

[b]Assistant Professor; Director of Hospital Psychiatric Services. Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, B6/593 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA

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MAJOR DEPRESSIVE DISORDER

Epidemiology and Comorbidity

Major depressive disorder is one of the most common psychiatric illnesses in the United States, with an estimated lifetime prevalence of up to 17%.[1] Affected individuals are at high risk for comorbid medical and psychiatric illness and have worse medical outcomes than the general population.[2,3] Major depressive disorder is highly correlated with suicidality, and up to 3% of affected individuals ultimately complete suicide.[3] The societal cost of major depressive disorder is massive; according to some estimates it may be responsible for up to $44 billion a year in lost productivity in the United States alone.[4] Several pharmacologic agents have been developed to treat depression including multiple classes of antidepressant medications (Table 1). These drugs, even when combined with psychotherapy, will ultimately fail in approximately one-third of patients.[5] Furthermore, treatment for major depressive disorder typically takes at least several weeks to produce noticeable effects.[5]

Diagnosis

Major depressive episodes are defined by a history of a 2 weeks or longer of depressed mood or anhedonia (diminished enjoyment of normally pleasurable activities) with at least 3 of the following: significant weight change or change in appetite, psychomotor agitation or retardation, feelings of worthlessness or guilt, diminished ability to concentrate, recurrent thoughts of death (or suicidal ideation or suicide attempts), and insomnia or hypersomnia.[6] There are several subtypes and modifiers of depression, each defined by a distinctive set of clinical features and typically responsive to specific types of treatments. Atypical depression, characterized by mood reactivity, hyperphagia, hypersomnia, and hypersensitivity to interpersonal rejection, is described as responding well to monoamine

*Corresponding author. mpeterson2@wisc.edu.

oxidase inhibitors and poorly to tricyclic antidepressants.[6] Patients with melancholic depression show terminal insomnia, weight loss, and ruminate on negative thoughts and are more likely to respond positively to sleep deprivation (see later discussion). In addition, some depressed individuals can develop psychotic symptoms such as delusions and hallucinations and the recommended treatment includes antipsychotics in addition to antidepressant medication.[6] In major depressive disorder with a seasonal pattern (also known colloquially as seasonal affective disorder), there is a recurrent pattern of depressive episodes that reliably occur during the same time of year (usually winter) for at least 2 consecutive years. Seasonal affective disorder can be treated with light therapy in addition to medications and psychotherapy.[6]

Sleep and Depression

One of the most consistent symptoms associated with major depressive disorder is sleep disturbance.[7–9] These problems with sleep regulation are not secondary to the illness; rather, they often precede the depressive episodes and can persist during remission. Improving sleep in depressed patients is found to improve outcomes.[10,11] In addition, imposed sleep deprivation can precipitate depressive episodes in susceptible individuals and alleviate depressive symptoms in others.[7] These observations dictate that practitioners of sleep medicine are aware of patients with major depressive disorder and alert to the importance of addressing sleep complaints in this population.

BIOCHEMICAL PATHWAYS UNDERLYING MOOD AND SLEEP

Monoamines

Although the precise physiologic correlates of sleep and mood are only partially understood, a growing body of biochemical evidence suggests that the mechanisms that control sleep overlap with the mechanisms that regulate mood. The transition into rapid-eye-movement (REM) sleep is accompanied by a rapid decrease in monoaminergic (serotonin, norepinephrine, and dopamine) tone and a concomitant increase in cholinergic tone.[12] It is hypothesized that dysregulation of these same monoamine neurotransmitters is related to major depressive disorder and, therefore, may be responsible for the REM sleep abnormalities noted in patients with major depressive disorder.[7] In fact, most commonly prescribed antidepressant medications act to increase monoaminergic tone and reduce REM sleep. However, one caveat is that some of these drugs can improve mood symptoms while leaving REM sleep unchanged. Furthermore, other effective antidepressant medications do not increase monoaminergic tone (see Table 1).

Glutamate

Glutamate signaling also plays an important role in sleep, in particular, during the thalamocortical slow oscillations of non-REM (NREM) sleep. Glutamate deficiency is also linked to depression. It is argued that glutamate has a neuroprotective role that is mediated via brain-derived neural growth factor and that low levels of glutamate lead to cell death in areas of the brain responsible for mood regulation. Some antidepressant medications, in particular, selective serotonin reuptake inhibitors such as fluoxetine, have a positive

allosteric effect on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor subtype of glutamate receptor.[7]

Hypothalamic-pituitary-adrenal Axis

Proper functioning of the hypothalamic-pituitary-adrenal axis is required for appropriate sleep regulation.[13] Cortisol secretion is decreased during normal deep sleep, and administration of corticotrophin-releasing hormone produces increased arousals and poor sleep particularly in middle-age or older patients. Cortisol replacement is necessary for cortisol-deficient patients to have normal REM sleep. However, direct cortisol administration to non-cortisol-deficient patients seems to decrease REM sleep and increase slow wave sleep (SWS). Some evidence suggests that patients with primary insomnia have elevated levels of cortisol. Hypercortisolemia is also commonly observed in patients with depression. Treatment with selective-serotonin reuptake inhibitors is found to normalize salivary cortisol in depressed patients with hypercortisolemia, although the decrease in cortisol is only weakly associated with improvement in depressive symptoms.[14]

SLEEP DISTURBANCES IN MAJOR DEPRESSIVE DISORDER

A large and occasionally contradictory body of literature describes sleep findings associated with major depressive disorder. The most common subjective sleep complaints elicited from patients with major depressive disorder are insomnia (up to 88%) and hypersomnia (27%).[15] Insomnia, in particular terminal insomnia, is classically associated with major depressive disorder. The relationship between insomnia and mood symptoms is bidirectional in that poor sleep can precede an episode of major depressive disorder, and depressed mood can disrupt normal sleep patterns.[7] Furthermore, it is 3 times more likely that major depressive disorder will develop in individuals with insomnia than those without.[16] In addition, hypersomnia, fatigue, and sleepiness are closely correlated with depressive symptomology.[15] Complaints of nonrestorative sleep and excessive daytime sleepiness can be elicited from many subjects; however, these findings are not universal.[7] In addition, many patients with major depressive disorder have poor insight into their sleep quality, often misestimating their sleep latency, sleep time, and sleep duration.[17]

POLYSOMNOGRAPHY

Polysomnographic Findings in Major Depressive Disorder

Polysomnographic studies have found that major depressive disorder is associated with abnormal sleep architecture. Patients may have prolonged sleep onset latency and frequent nocturnal awakenings resulting in sleep fragmentation and poor sleep efficiency.[7] Depressed patients often have decreased REM sleep latency and prolonged REM sleep periods early in the night, leading to an overall increase in the proportion of REM sleep.[18] In addition, REM sleep in depressed patients is characterized by more frequent rapid eye movements than REM sleep in control patients.[7] The increased number of rapid eye movements normalizes when patients go into remission, whereas the decreased REM sleep latency persists.[19] In addition, decreased REM sleep latency has also been noted in unaffected first-degree relatives. This finding suggests a possible genetic link between REM sleep latency and

major depressive disorder. The relative excess of REM sleep seems to come at the expense of stage N3 sleep, also known as slow wave sleep. Not only is time spent in SWS decreased in depressed patients compared with controls, but the distribution of slow wave activity (SWA), a marker of SWS intensity, is abnormal. Control subjects have maximal SWA during the first sleep cycle, whereas depressed patients have peak SWA during subsequent cycles.[20] Unlike REM sleep findings, SWS findings in major depressive disorder are age dependent in that they often cannot be reliably found until patients reach the fifth decade of life.[20] Some research suggests that these findings may be linked to specific subtypes of major depressive disorder. In particular, decreased SWA in the first sleep cycle is more commonly seen in atypical depression than melancholic depression.[7] Although further research is needed, polysomnography may eventually be useful in guiding the choice of pharmacologic agent in depressed patients.

Polysomnography and Primary Sleep Disorders

Polysomnography is not routinely used in the evaluation of depressed or insomniac patients. However, polysomnography may be indicated in patients for whom there is a strong suspicion for a primary sleep disorder. Obstructive sleep apnea (OSA) can produce many of the symptoms of major depressive disorder, including fatigue, depressed mood, and difficulty concentrating.[21] In patients with depression, comorbid sleep apnea can aggravate mood symptoms and make them refractory to treatment. This is particularly relevant because patients with major depressive disorder may be at increased risk for OSA and vice versa.[21] Many patients experience weight gain while taking psychotropic medication, and increased body mass is correlated with increased rates of OSA. In patients with depression and OSA, sedating antidepressants, hypnotics, and benzodiazepines should be used sparingly or avoided entirely, because these drugs can worsen apneic symptoms. Polysomnography may also be considered in depressed patients who present with evidence of a new or worsened restless legs syndrome, periodic limb movement, or REM sleep behavior disorder, as antidepressant medication can induce or exacerbate these conditions.[22]

PHARMACOLOGIC STRATEGIES

Several studies have found better outcomes when major depressive disorder and associated sleep complaints are addressed in concert. Depressed patients with concomitant sleep disturbances are more likely to have suicidal ideation and more severe symptoms and be refractory to treatment.[7] Furthermore, even in individuals who do respond to antidepressant therapy, persistent insomnia in the absence of current mood symptoms is a strong predictor of future relapse.[23] This is especially concerning given that insomnia is among the most commonly reported residual symptoms during remission for major depressive disorder.[23] Similarly, residual hypersomnia is also commonly encountered and is also associated with an increased risk of relapse.[8]

Hypnotics and Sedating Agents

Insomnia is a common problem, even in individuals who do not have major depressive disorder, and many techniques have been used to address it. Behavioral techniques, such as improving sleep hygiene (see later discussion), are typically the first-line treatments, but

several different medications are frequently used as adjuncts. Although benzodiazepines have classically been used to treat insomnia, newer nonbenzodiazepine γ-aminobutyric acid agonists receptor potentiating agents such as zaleplon, zolpidem, and eszopiclone are increasingly popular.[24] Melatonin and melatonin-agonists (ramelteon) are also used and may be especially useful in patients for whom excess sedation is a concern. Many people with insomnia are prescribed sedating antidepressants, typically in doses that are much smaller than when used for mood symptoms. The tricyclic antidepressants, amitriptyline and doxepin, the tetracyclic antidepressant, mirtazapine, and the serotonin antagonist and reuptake inhibitor, trazodone, are the most commonly used drugs in this context.[24] Despite their widespread use, the appropriateness of using antidepressant medications to treat insomnia in nondepressed individuals remains controversial.[25] In contrast to patients with a primary sleep complaint of insomnia, patients complaining of isolated hypersomnia have been treated with stimulants or with modafinil.[7]

Antidepressant Therapy

Pharmacologic management of coincident depression and sleep complaints can be challenging. Most antidepressant medications have some effect on sleep regulation, either sedating or activating (see Table 1); therefore, effective treatment of mood symptoms may aggravate existing sleep disturbances or provoke new sleep problems. The situation is further complicated by the observation that each individual responds uniquely to a given medication; therefore, drugs that are typically activating can actually be sedating and vice versa.[7] As a first-line therapy, most clinicians try to determine the optimal dosing of a single agent to address both mood and sleep complaints. This dosing enhances adherence and eliminates the possibility of drug-drug interactions. In addition to their sedating quality, tricyclic antidepressants reverse many of the REM sleep changes observed in depressed patients.[26] However, because of the risk of intentional overdose, tricyclic antidepressants must be used cautiously in patients who have severe depression. Monoamine oxidase inhibitors (MAOIs) such as selegiline can suppress REM sleep. However, it is unclear whether the decreased REM sleep seen with MAOIs or tricyclics is associated with their effects on mood. Selective serotonin reuptake inhibitors, although effective in treating mood symptoms, are more likely to aggravate the polysomnographic abnormalities in depressed sleep and are unlikely to provide lasting sleep benefits.[26] Furthermore, selective serotonin reuptake inhibitors are frequently reported to cause insomnia.[7] Trazodone and mirtazapine are been successfully used as monotherapies to treat insomnia and depression in some patients.[27] Some investigators advocate that patients who have insomnia while taking selective serotonin reuptake inhibitors, bupropion, or venlafaxine should be switched to a sedating antidepressant like trazodone.[27]

Combination Therapy

Many patients have symptoms that cannot be adequately controlled by a single agent. For these patients, adjunct measures must be used. Psychotherapy has been used to treat insomnia accompanied by major depressive disorder. Combining escitalopram with cognitive-behavioral therapy specifically geared toward treating insomnia (see later discussion) provided greater remission from both sleep and mood symptoms than escitalopram alone.[11] Additional antidepressant medication is sometimes used to manage

sleep complaints that are resistant or secondary to treatment. The most common such scenario is when low-dose trazodone is added to patients who have insomnia secondary to use of a selective serotonin reuptake inhibitor.[27] Mirtazapine is also frequently used for this purpose. If the addition of a sedating antidepressant is inappropriate for a given patient, zaleplon, zolpidem, or eszopiclone may be used. A recent randomized, controlled trial found that the addition of eszopiclone to fluoxetine produced statistically significant improvements in subjective sleep quality and wakefulness after sleep onset, total sleep time, and sleep efficiency.[28] Finally, benzodiazepines may be used. However, these agents may be addictive and development of tolerance is also a concern.

NONPHARMACOLOGIC STRATEGIES

Psychotherapy and Sleep Hygiene for Insomnia

Cognitive behavioral therapy for insomnia (CBTI) can be a useful adjunct or alternative to pharmacologic therapy in patients with primary insomnia.[11,29] CBTI has several components, each of which plays a role in improving sleep. One component is stimulus control techniques, which are used to strengthen the connection between the bed and sleep. These include only using the bed for sleep and sex, only getting into bed when tired, leaving the bed if unable to fall asleep within 15 minutes, establishing a regular morning waking time, and avoiding napping.[30] CBTI can also include restrictions on the amount of time in bed.[30] In this case, baseline polysomnography or a sleep diary can be used to assess total sleep time. Initially, the patient is restricted to spending an amount of time in bed equal to their baseline total sleep time. Regular sleep studies or sleep diaries can be used to assess sleep efficiency. If sleep efficiency is greater than 85%, then the amountof time in bed is lengthened by 15 minutes, otherwise the amount of time in bed is decreased by 15 minutes. However, time in bed should be maintained at greater than 5 hours regardless of sleep efficiency. Cognitive therapies such as distraction techniques and cognitive restructuring can address negative and counterproductive beliefs about sleep.[30] Paradoxic intention, in which patients who fear insomnia intentionally stay awake, may be effective for some patients by reducing worry about the negative outcomes from an instance of poor sleep.[30] Several different relaxation therapies may also be used to address insomnia, although these are reported to be less effective than the other CBT techniques described above.[30] In progressive muscle relaxation, patients tense and then relax muscles, concentrating on the way the muscle relaxation feels. Patients may also be taught to breathe with their abdomen (diaphragmatic breathing) while in bed. This pattern of breathing is soothing and occurs naturally during sleep onset. Biofeedback techniques and guided imagery may also help some patients.[30] CBTI and stimulus control techniques and cognitive therapies are found to have an efficacy comparable to or greater than standard pharmacotherapy for insomnia.

Psychotherapy for Insomnia and Depression

Given its success in treating insomnia, researchers have attempted to use CBTI in patients with depression and concomitant insomnia. In a small study, patients with mild depression (Beck Depression Index >9) and insomnia received 6 weekly sessions of CBTI consisting of sleep hygiene education, stimulus control techniques, and progressive muscle relaxation. At a 3-month follow-up visit, all of the patients who had completed CBTI were no longer

experiencing clinically significant insomnia and 7 of 8 subjects were no longer in a depressive episode.[29] These benefits were preserved at a 3-month follow-up. A subsequent randomized, controlled trial found that CBTI had an additive effect when combined with escitalopram in the treatment of depression with insomnia.[11] Furthermore, this study found that the combination of escitalopram and CBTI was superior to the combination of escitalopram and a control therapy consisting of sleep hygiene education and a quasi-desensitization procedure for treating both depressed mood and insomnia.

Sleep Deprivation and Major Depressive Disorder

Several studies found positive effects of sleep deprivation on depression symptoms. Multiple studies have shown that a single night of total sleep deprivation (TSD) produces positive results in up to 50% of subjects.[31] This response rate is comparable to what can be achieved with antidepressant medications. Furthermore, TSD responders show benefits comparable with those observed with pharmacotherapy.[31] Patients with melancholic depression, characterized by terminal insomnia and diurnal variation of symptoms, are more likely to respond to TSD than patients with atypical or seasonal depression.[7] Imaging studies suggest that TSD responders have increased metabolism in the amygdala, orbital prefrontal gyrus, and inferior temporal and anterior cingulate cortices, which normalizes after sleep deprivation.[31] Intriguingly, the degree of hypermetabolism in these regions is correlated to the response to TSD. However, response to TSD is unpredictable in that prior positive responses do not predict future responses.[32] Furthermore, even in patients for whom it is effective, TSD is not a practical therapeutic intervention because the benefits dissipate after recovery sleep.[32] This has led researchers to study more sustainable ways of scheduling sleep to improve depression.

Partial sleep deprivation (PSD), including deprivation of REM sleep, deprivation of SWS, and disruption of individual slow waves have all demonstrated mild-to-moderate improvements in depression scores.[31,33] Because of the interrelated nature of these sleep parameters, it is difficult to say how much of the observed antidepressant effects in these studies are directly mediated by the parameters that were manipulated or which component of TSD is necessary. Additionally, the effects of PSD are not necessarily the same as the improvements after acute TSD.[31] In particular, several weeks of PSD produces a gradual improvement in mood symptoms, which persists longer than TSD although will eventually diminish when the therapy is discontinued.[34] Circadian phase shifting is found to improve depression symptoms.[35] Other studies have found benefits for combination therapies. Combining TSD with circadian rhythm interventions or light therapy can prolong the antidepressant effects of TSD. Both PSD and TSD potentiate the effects of selective serotonin reuptake inhibitors and tricyclics.[31] Although sleep scheduling techniques are promising avenues of research, they remain experimental and are not yet part of standard medical practice.

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KEY POINTS

- Major depressive disorder is frequently accompanied by subjective sleep disturbances and poly-somnographic abnormalities.
- Residual sleep disturbance after a major depressive episode is linked to future relapses.
- Sleep problems may be the first sign of the onset of a major depressive episode.
- Obstructive sleep apnea may mimic major depressive disorder and increase risk for depression.
- Pharmacotherapy or behavioral approaches are useful in depressed patients with sleep disturbances.

Table 1

Antidepressant effects on sleep.

Medication Class Examples	Dosage: Depression (Insomnia[a])	Pharmacologic Mechanism	Effects on Sleep
Tricyclic antidepressants			
Amitriptyline(Elavil)	75–150 mg (25–50 mg)	Inhibit serotonin and norepinephrine reuptake Anticholinergic and antihistaminergic effects	Sedation REM sleep suppression Increased stage 2 sleep
Nortriptyline (Pamelor)	50–150 mg (25–50 mg)		
Doxepin (Sinequan)	75–300 mg (6–50 mg)		
Clomipramine (Anafranil)	100–250 mg		
MAOis			
Phenelzine(Nardil)	45–90 mg	Inhibit monoamine oxidase, thus increasing norepinephrine, serotonin, and dopamine	Insomnia Potent REM suppression
Tranylcypromine(Parnate)	30–60 mg		
Serotonin reuptake inhibitors			
Fluoxetine (Prozac)	20–80 mg	Inhibit serotonin reuptake	Insomnia REM suppression Increased eye movements in NREM sleep
Sertraline (Zoloft)	50–200 mg		
Paroxetine (Paxil)	15–60 mg		
Citalopam (Celexa)	20–40 mg		
Escitalopram (Lexapro)	10–30 mg		
Serotonin-norepinephrine reuptake inhibitors			
Venlafaxine (Effexor)	150–450 mg	Inhibit serotonin and norepinephrine reuptake	Insomnia REM suppression Increased eye movements in NREM sleep
Duloxetine (Cymbalta)	20–120 mg		
Other antidepressants:			
Trazodone (Desyrel)	150–600 mg (25–75 mg)	Inhibit serotonin reuptake. Blocks alpha1 adrenoreceptors Serotonin-2 A receptor antagonist	Sedation
Bupropion (Wellbutrin)	100–450 mg	Inhibits norepinephrine and dopamine reuptake	Insomnia/activation
Mirtazapine (Remeron)	15–45 mg (7.5–15mg)	Alpha2 receptor antagonist. Serotonin-2 and -3 receptor antagonist. Antihistaminergic	Sedation, REM sleep suppression

[a] Use of these medications for treatment of insomnia is an off-label usage, not approved by the US Food and Drug Administration.