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Depression and sleep: pathophysiology and treatment
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Sleep is a critical aspect of the pathophysiology and treatment of depression at multiple levels. At the most superficial, descriptive level, a large majority of people with depressive disorders report disturbed or altered sleep and, as such, essentially all diagnostic criteria for depression include sleep disturbances as a key feature.[1] Insomnia in particular has been described in first-hand accounts of depression since antiquity.[2] Hypersomnia, although a less prevalent symptom than insomnia, is an important feature of the so-called atypical subtype of depression, as well as a not-uncommon feature of depression in younger people, particularly those with bipolar affective disorder.[3,4] Although vulnerability to mood disorders are not usually simply a consequence of sleep disturbances, longitudinal studies document that insomnia is a risk factor for onset

This review examines the relationship between sleep and depression. Most depressive disorders are characterized by subjective sleep disturbances, and the regulation of sleep is intricately linked to the same mechanisms that are implicated in the pathophysiology of depression. After briefly reviewing the physiology and topography of normal sleep, the disturbances revealed in studies of sleep in depression using polysomnographic recordings and neuroimaging assessments are discussed. Next, treatment implications of the disturbances are reviewed at both clinical and neurobiologic levels. Most antidepressant medications suppress rapid eye movement (REM) sleep, although this effect is neither necessary nor sufficient for clinical efficacy. Effects on patients' difficulties initiating and maintaining sleep are more specific to particular types of antidepressants. Ideally, an effective antidepressant will result in normalization of disturbed sleep in concert with resolution of the depressive syndrome, although few interventions actually restore decreased slow-wave sleep. Antidepressants that block central histamine 1 and serotonin 2 tend to have stronger effects on sleep maintenance, but are also prone to elicit complaints of daytime sedation. Adjunctive treatment with sedative hypnotic medications—primarily potent, shorter-acting benzodiazepine and γ-aminobutyric acid (GABA A)-selective compounds such as zolpidem—are often used to treat associated insomnia more rapidly. Cognitive behavioral therapy and other nonpharmacologic strategies are also helpful.

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of depressive disorder[5,6] and may herald relapses in patients with recurrent illness.[7] At the most basic level, the brain stem and thalamic nuclei that regulate sleep and the limbic mechanisms that modulate affective arousal are implicated in the pathophysiology of both sleep disturbances and depressive disorders.[8,9] To truly understand depression thus requires knowledge of sleep and its disorders and, conversely, physicians caring for patients complaining of insomnia must be cognizant of the relationship with depression.

The topography of normal sleep

Sleep regulation

As excellent detailed reviews are available elsewhere,[10,11] this section will only briefly summarize the basic aspects of the physiology of normal sleep. Sleep is regulated by three interrelated processes. First, there is the circadian sleep-wake cycle, which in human beings is entrained to both the solar photoperiod and the 24-hour clock. In addition to wakefulness and sleep, the activity of several hormone axes (ie, secretion of cortisol, growth hormone, and melatonin) and core body temperature follow this circadian rhythm. Normally, sleep is most likely to occur between sundown and sunrise, following the nocturnal rise of melatonin and coincident with reductions in core body temperature and cortisol secretion; increased, pulsatile release of growth hormone is typically greatest during the first hours following sleep onset. Several biological "clocks" or pacemakers regulate these rhythms, including one located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. Through this nucleus, the changes in light intensity that demarcate the transitions of day and night help to synchronize circadian rhythms. Whereas bright white light suppresses secretion of melatonin, the onset of darkness elicits hormonal release from the pineal gland, which serves to increase sleepiness.

The second process that regulates sleep is homeostatic, in that sleep has a restorative function that offsets the deleterious cognitive and physiological consequences of sustained wakefulness (see, for example, Borbely[12]). Specifically, a sufficient amount of sleep is necessary for optimal functioning, and sleep deprivation is now known to be associated with broad neurobehavioral deficits.[13] Although the specific neurochemistry has not yet been clarified, a sleep propensity factor (sometimes referred to as Process S) is presumed to accumulate during wakefulness and be used up during deep sleep.[12]

The third regulatory process involves the ultradian rhythm that consists of alternating periods of rapid eye movement (REM) and nonREM sleep. This characteristic was first identified more than 50 years ago, when electroencephalograms (EEGs) began to be used to record brain activity during sleep.[14] For the next four decades, as the methods were developed, what is now known as the polysomnogram—consisting of technically simple, simultaneous recordings of electroencephalogram (EEG), eye movements, and muscle activity—served as the best means to study the dynamic neurobiology of sleep.

Basic research has established that the reciprocal activities of thalamocortical and corticothalamic circuits mediate the regular alternation of nonREM and REM sleep.[10,11] Among the complex neurochemical mechanisms implicated in sleep, cholinergic projections for neurons in the dorsal tegmentum elicit the onset of REM sleep and serotoninergic neurons (originating from the dorsal raphe nucleus) and noradrenergic neurons (originating from the locus ceruleus) inhibit REM sleep.

Sleep architecture

Research using polysomnograms led to a reliable, five-stage "architecture" of sleep. As noted above, the first classification was based on the presence or absence of REM sleep. REM sleep is characterized by high-frequency, low-voltage EEG activity and bursts of rapid movements of the eye muscles, coupled with atonia of major skeletal muscles and penile erections or vaginal lubrication. Such a curious juxtaposition of characteristics led some early researchers to refer to REM sleep as paradoxical sleep.

A healthy younger person's normal night of sleep typically includes four to five distinct REM periods occurring at 90-minute intervals, accounting for about 20% of total time

spent asleep (TSA). REM periods typically grow longer and more intense across a normal night of sleep. Thus, if the accumulated homeostatic sleep "debt" is largely repaid by end of the second nonREM sleep period, there is a reciprocal, increasing "pressure" for REM sleep that builds progressively until the individual wakes up.

Originally called "dream sleep" because of the temporal association with most dreaming, REM sleep is still thought to serve an important role in consolidation of memory and processing of affectively charged cognitions. Parenthetically, an abnormally increased amount of REM sleep time or REM sleep intensity could be the result of a functional adaptation (ie, an increased need for affective processing), a relative increase in cholinergic neurotransmission, or decreased inhibitory input from serotoninergic or noradrenergic nuclei.

Most of the night is spent in nonREM sleep, which is further subdivided into four progressively deeper stages. Stage I sleep is the lightest stage of sleep, and functionally serves as the transition between drowsy wakefulness and deeper sleep stages. Ideally, less than 5% of the night is spent in stage I sleep. Stage II sleep is defined by the emergence of K-complexes and sleep spindles, and typically accounts for more than one half of a night's sleep. The deepest states of sleep, stage III and stage IV sleep, are characterized by undulating, desynchronized delta (or slow) waves. Such deep sleep is typically concentrated during the first two nonREM periods. The normal amount of deep sleep is highly age-dependent, and few individuals over age 50 spend more than 5% of the night in stage III and stage IV sleep.

For a healthy young person, the first progression through the four nonREM sleep stages (ie, stage I through stage IV) typically takes 70 to 100 minutes; the elapsed time from sleep onset until the beginning of the first REM period is called REM latency. With normal aging, REM latency characteristically grows shorter because of the loss of slow-wave sleep, and with advanced age the entire night may be spent in only three sleep stages (stage I, stage II, and REM).

Sleep architecture is somewhat sex-dependent and, as noted above, highly influenced by aging. Women tend to have a greater percentage of deep sleep than men, particularly prior to menopause. Across decades of aging, sleep typically becomes lighter, with more awakenings and awake time. There is also a progressive loss of slow-wave sleep with aging, which typically occurs in men at an earlier age than women. Sleep quality may be further adversely affected by age-dependent increases in sleep-disordered breathing.

Beyond the direct relationship between sleep deprivation and neurobehavioral function, recent research has linked disturbances of sleep to other important health risks. For example, insomnia is associated with an increase in the cascade of cytokines and other "markers" of inflammatory processes.[15] Disturbed sleep also is associated with alterations in glucose metabolism and may represent a risk factor for development of obesity[16] and adult-onset diabetes mellitus.[17] It is not surprising, then, that research has established that "healthy" sleep is a reliable correlate of subjective well-being, overall physical health, and successful aging.[18]

Neuroimaging and sleep

The availability of modern imaging methods has permitted a more functional characterization of selected aspects of the topography of sleep.[8,9,19,20] Although technological limitations in the measurement of cerebral blood flow or regional shifts in metabolic activity have necessitated focusing on key transition points, such as from waking to nonREM sleep or from nonREM to REM sleep, interesting findings are emerging. Consistent with the homeostatic function of sleep, blood flow and glucose metabolism globally decrease with the transition from waking to sleeping, with the greatest decline during deep sleep.[8,9,19,20] Conversely, individuals with primary insomnia have been found to have relatively greater cerebral metabolism during nonREM sleep.[21] The onset of REM sleep is associated with a sharp increase in blood flow and cerebral metabolism, including—but not limited to—limbic and pontine structures.[22]

Alterations of sleep neurophysiology in depression

Most depressed people show evidence of one or more alterations in sleep neurophysiology; multiple disturbances in polysomnographic recordings of sleep are evident in about 45% of depressed outpatients and 80% of more severely depressed inpatients.[1,23] About 10% of never-depressed people have "false-positive" sleep profiles.[23] With respect to "false-positive" profiles, less severely depressed patients—particularly younger depressed patients with atypical features such as hypersomnolence—are overrepresented. Although hypersomnolent depressed

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patients often have relatively normal sleep profiles, a significant minority do manifest increased REM sleep intensity.[24,25] It has been suggested that the tendency for long total sleep time may reflect a compensatory phenomenon that permits more slow-wave sleep across the night.

The most common disturbances documented in visually scored polysomnograms are: decreased sleep efficiency (a composite measure that takes into account difficulty falling asleep, nocturnal awakenings, and early-morning awakening), decreased slow-wave sleep (which reflects decreased stage III and stage IV sleep time), reduced REM latency, and increased REM intensity (which is typically expressed as increased REM density, a ratio of a measure of REM intensity divided by time spent in REM sleep).[1,23,24] Depressed men also have a decrease in nocturnal penile tumescence, which is paradoxical given the overall increase in REM sleep time.[25] Computer-scored abnormalities include a decrease in slow wave counts during the first nonREM period and an increase in REM counts during the first REM period.[25] None of these disturbances are truly specific to depression and are also observed in other psychopathologic states.[24] Increased REM sleep indices, for example, have been observed in eating disorders, some anxiety disorders, schizoaffective disorder, and borderline personality disorder. Reduced REM latency and increased REM density also characterize narcolepsy. Premature loss of slow-wave sleep and reduced REM latency are also common in chronic forms of schizophrenia, sleep apnea, alcoholism, and degenerative central nervous system disorders such as presenile dementia.[24]

Studies of depression utilizing neuroimaging methods document increased global cerebral metabolism during the first nonREM sleep period; there is also a relative decrease in cerebral blood flow and glucose metabolism during the transition from nonREM to REM sleep.[19,20] These abnormalities are thought to reflect nocturnal hyperarousal, which is particularly evident in frontal and prefrontal cortical structures.[20]

Longitudinal studies of sleep disturbance in depression indicate that some features do not fully normalize following recovery.[1] The most state-independent or persistently abnormal disturbances are decreased slow-wave sleep and reduced REM latency, which show some degree of heritability[26] and, as such, may represent vulnerability traits. Increased REM density and decreased sleep efficiency are more reversible and therefore are considered to be state-dependent. Consistent with this view, patients with increased REM density and poor sleep efficiency are more

likely to manifest various indices of hypercortisolism, another state-dependent correlate of severe depression.[27] In one longitudinal study, there was about a 50% chance that an abnormal sleep profile (on the basis of reduced REM latency, increased REM density, and decreased slow-wave sleep) would normalize following 16 weeks of cognitive behavior therapy.[28] As research by our group suggested that such sleep abnormalities predicted a poorer response to both cognitive behavior therapy[29] and interpersonal psychotherapy[30]—but not pharmacotherapy[30]—they may help to define a neurobiological profile that is more responsive to somatic antidepressant interventions.

Antidepressants and sleep neurophysiology

Although longitudinal studies of patients withdrawn from antidepressant medications suggest that pharmacotherapy, like psychotherapy, can result in a partial normalization of sleep disturbances,[1] antidepressant medications also have pronounced, direct effects on sleep neurophysiology that are also evident in studies of healthy individuals.[31] Most antidepressants directly suppress REM sleep, as evident by a marked (ie, >50%) reduction in REM time and prolongation (ie, >150%) of REM latency.[1,31] Suppression of REM sleep is evident within hours of beginning therapy with both selective serotonin reuptake inhibitors (SSRIs) and relatively selective norepinephrine reuptake inhibitors such as desipramine or maprotiline.[31] Pronounced REM suppression also is evident during treatment with nonselective monoamine oxidase inhibitors such as phenelzine[32] and tranylcypromine.[33] Mirtazapine, which enhances noradrenergic activity via blockade of inhibitory α_2 receptors, likewise suppresses REM sleep.[34] Thus, as antidepressants with diverse mechanisms of action suppress REM sleep, it is likely that potent modulation of either noradrenergic or serotoninergic neurotransmission underpins this effect.

Among currently available antidepressants, there are only a handful that do not suppress REM sleep—trazodone, bupropion, and nefazodone.[1,31] A fourth compound, trimipramine, which is a weaker REM suppressor than the rest of the tricyclics, does not exert much suppressant effect at lower doses.[35] The common link among these medications is that none of the three has potent, direct effects on norepinephrine or serotonin neurotransmission. In one small study, bupropion therapy actually resulted in an intensification of REM sleep in a subset of patients.[36] It is not clear

if this potentially unique pharmacologic effect is attributable to the proposed mechanism of action of bupropion (ie, potentiation of dopamine neurotransmission) or if it is simply an epiphenomenon of an enhancement of positive affectivity.[37]

Beyond improvements in sleep efficiency directly resulting from resolution of the depressive syndrome, some antidepressants also exert more rapid beneficial effects on initiation and/or maintenance of sleep.[1,31] As discussed below, these effects are largely attributable to blockade of histamine (H)$_1$ and/or serotonin (5-HT)$_2$ receptors. Whereas REM suppressant effects tend to predict subsequent antidepressant effects, at least in studies employing tricyclic antidepressants,[38] early improvements in sleep efficiency generally are not correlated with treatment response. In fact, effective therapy with potent and selective monoamine reuptake inhibitors can actually worsen some patients' ability to initiate or maintain sleep, which can slow or impair treatment response.[1,31]

In contrast to the reliable effects of antidepressants on REM sleep and, to a lesser extent, patients' ability to initiate and maintain sleep, antidepressant medications do not reliably increase hand-scored slow-wave sleep.[1,31] Given the importance of deep sleep as a neurobiologic marker of well-being, this is a target for future research. As discussed subsequently, some medications used to augment antidepressant effects, including lithium and the atypical antipsychotic olanzapine, have been shown to increase both hand- and computer-scored slow-wave sleep.[1]

Management of depressive insomnia

It would be an optimal solution if the same intervention that was used first-line to treat the depressive disorder also produced rapid and complete relief of the associated insomnia. This ideal is far from being realized, however, and in the following sections the relative merits and limitations of antidepressants, sedative-hypnotics, nonprescription sleep aids, and cognitive-behavior therapy are discussed.

Antidepressant pharmacotherapy

Despite the fact that there is compelling evidence that complaints of insomnia are reliably reduced by a wide range of antidepressants—when treatment is effective—there is also evidence that persistent insomnia is one of the more common residual symptoms of incompletely remitted depression.[39,40] This has potentially ominous implications because residual depressive symptoms are one of the best-validated predictors of subsequent relapse risk,[41,42] as well as persistent functional disability. Therefore, ensuring that patients taking antidepressants experience complete relief of associated insomnia is one of the best strategies to increase the likelihood that sustained remission and, subsequently, full recovery are realized.

The problem of persistent or incompletely remitted sleep disturbance may be greater today than in previous decades because of changes in the pharmacology of the most commonly used antidepressants. Specifically, whereas most of the tricyclic antidepressants (TCAs)—the mainstay of pharmacotherapy from the early 1960s until the late 1990s—had nonspecific sedative hypnotic properties, the SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) do not.[1,31] In fact, it is not common for increased complaints of insomnia to accompany the first few weeks of pharmacotherapy with SSRIs such as fluoxetine[43] or the SNRI venlafaxine.[44] Increased nocturnal arousal is presumed to be caused, at least in part, by stimulation of postsynaptic serotonin type 2 (5-HT$_2$) receptors.[1,31]

If the antidepressant-induced exacerbation of insomnia is not too marked, watchful waiting may be all that is necessary, as some degree of neuronal accommodation/desensitization often develops over several weeks of therapy. It is also true that, as the depressive syndrome lifts, patients are less likely to complain of insomnia, even in the absence of objective improvements in sleep neurophysiology. This is not always the case, however, and pharmacoepidemiologic surveys indicate that at least one third of patients taking modern reuptake inhibitors receive concomitant sedative hypnotic medications. Although controlled data are sparse, there is evidence that combining benzodiazepines (BZ)[45-47] or the selective γ-aminobutyric acid (GABA) type A receptor antagonist zolpidem[48] with antidepressants from the beginning of therapy will result in more reliable relief of the associated sleep disturbance and hasten improvement of the overall depressive syndrome. Although results of controlled studies with other GABA A selective agents such as zoplicone, eszoplicone, and zaleplon are not in the published literature, it is likely that these medications are also beneficial in combination with antidepressants.[49]

Two members of the now otherwise forgotten "second generation" of antidepressants, trazodone and mianserin

(which was never introduced in the United States), are still widely used as adjuncts to SSRIs and SNRIs to relieve insomnia.[1,50] Both medications are available in inexpensive generic formulations and—unlike conventional sedative-hypnotics—their longer-term use is not hampered by concerns about tolerance or potential for abuse. Moreover, there is ample clinical experience to support the use of low-dose therapy with trazodone or mianserin to manage insomnia that persists despite SSRI/SNRI therapy. Despite these strengths, neither medication has been extensively studied in combination with modern reuptake inhibitors nor—truth be told—do these compounds have the safety track record of the BZs.[1,50]

Among the modern antidepressants, only two reliably improve the insomnia associated with depression: nefazodone—a direct descendent of trazodone—and mirtazapine, a close "cousin" of mianserin.[1,31] Neither of these neurochemically distinct compounds have much inhibitory effect on monoamine uptake transporters, but both are potent antagonists of postsynaptic 5-HT$_2$ receptors. Mirtazapine also has early, nonspecific sedative effects via potent antagonism of H$_1$ receptors. The relatively favorable sleep effects of nefazodone were demonstrated versus fluoxetine in a large multicenter study that included pre-post polysomnograms.[43] Because the study was only 8 weeks long, however, questions persist about whether the advantage of nefazodone would have persisted across months of continuation phase therapy. Whether nefazodone would show comparable advantages versus SSRIs other than fluoxetine also remains an open question.[35] Mirtazapine was likewise shown to result in more rapid and favorable relief of insomnia symptoms in a pair of head-to-head studies versus venlafaxine,[51,52] as well as versus fluoxetine in a small study that included polysomnographic monitoring.[34]

Despite the ubiquity of sleep disturbances associated with depression and the empirically established advantage of these compounds for depressive insomnia, neither nefazodone nor mirtazapine were ever widely accepted as first-line antidepressants in most countries. Nefazodone was perceived to be more difficult to titrate and somewhat less effective than the reuptake inhibitors[1] and subsequent recognition of a rare but potentially catastrophic hepatic toxicity resulted in its withdrawal from the market in many countries (although it is still available in generic formulations in the US). Mirtazapine, while judged to be at least as effective as SSRIs,[53] was probably not more widely used because of the frequency of side effects mediated by H1

blockade, including increased appetite, weight gain, and excessive daytime sedation. Because of these side effects, the major advantage of mirtazapine therapy may well be limited to patients with more severe depressive episodes associated with marked insomnia, particularly in later life, where sleep disturbance and weight loss are more common problems.

Another novel antidepressant with favorable effects for sleep, agomelatine,[54] may soon be approved for use within the European Union. Agomelatine is thought to have a truly unique mechanism of action, namely agonism of melatonin type 1 (M$_1$) and type 2 (M$_2$) receptors. Agomelatine is also an antagonist of 5-HT$_2$ receptors. Early studies with this medication have yielded promising comparative results. Further research and, even more importantly, more extensive post-marketing experience will fully assess its relative merits and limitations.

Augmentation of antidepressants with sedating atypical antipsychotic medications such as olanzapine and quetiapine is also sometimes utilized. As reviewed elsewhere,[55] the members of this heterogeneous class of medications have diverse effects on sleep that undoubtedly include nonspecific benefits as well as more specific neuropharmacologic effects. Of note, in one small study olanzapine augmentation therapy resulted in a substantial increase in slow-wave sleep time.[56] The widespread use of atypical antipsychotics for management of insomnia is limited by cost (only the seldom-used clozapine is available in generic formulations) and the incidence of weight gain and other metabolic complications, as well as some lurking concerns about the eventual risk of tardive dyskinesia.

Concomitant therapy with sedative-hypnotic medications

Among the wide range of sedative-hypnotic medications still commercially available, only the BZs and the selective GABA A agonists warrant continued use.[10] The BZ class includes medications that were originally primarily developed for use as anxiolytics, as well as those marketed as hypnotics.[57] All can be used to reduce sleep latency and prolong total sleep time, although some members of the BZ class are clearly better suited for use as hypnotics on the basis of pharmacokinetic effects (ie, shorter elimination half-life, rapid absorption, absence of an active metabolite, and high lipophilicity, which ensures rapid passage through the blood-brain barrier). There is a small risk

that a patient who begins therapy with a BZ will develop dependence, and lethality in overdose does increase when BZs are ingested in combination with alcohol. Nevertheless, the reliable efficacy, low cost, and strong overall safety track record of this class is difficult to surpass, at least for short-term administration.[10,58]

The major shortcoming of this venerable class of medications is that, despite the fact that a subset of patients requires longer-term therapy, it is not at all clear from studies of primary insomnia that the BZs' benefits are sustained,[10,58] perhaps particularly for patients' longer-term antidepressant therapy.[59] In fact, in one of the fewer placebo-controlled, longer-term trials, the beneficial effects of clonazepam (a potent BZ with an intermediate half-life) on patients' sleep complaints were largely limited to only the first 3 weeks of therapy.[59] In fact, although it took slightly longer for the patients who were randomly assigned to receive placebo in combination with fluoxetine to experience relief of insomnia, the two groups had comparable outcomes after 12 weeks of therapy, on both depression and subjective sleep disturbance. It is unfortunate that this otherwise well-controlled study did not include polysomnographic recordings to ascertain if effects on objective measures of insomnia matched the subjective changes. Sadly, this study is not unique: despite nearly 20 years of routine clinical use, there does not appear to be a single controlled study utilizing serial polysomnograms to assess the effects of combination therapy with an SSRI or SNRI and BZ in the published literature.

As the BZs were hoped to be better alternatives to the barbiturates, the GABA A agonists were developed to improve upon the BZs' various shortcomings.[10,60] Specifically, these selective agents were developed to work quickly with minimal residual (ie, hangover) effects, little interaction with alcohol, and little risk of abuse. Although the debate is not fully resolved, these medications have arguably succeeded, at least for concomitant treatment of patients with milder insomnia.[10,60]

In addition to these more "mainstream" hypnotic medications, ramelteon—a novel selective agonist of MT_1 and MT_2 receptors—has recently been approved by the US Food and Drug Administration (FDA) for treatment of primary insomnia. Placebo-controlled trials have established that this medication reliably decreases time to sleep onset in adults with both transient insomnia as well as patients with more longstanding problems with primary insomnia.[61,62] When compared with the BZs and GABA A selective medications, ramelteon has the major advantage

of an apparent lack of abuse potential. In fact, it is the only currently available FDA-approved hypnotic that is not classified as a controlled substance. Experience with treating insomnia associated with depression and other mood disorders is, to date, quite limited and it would be premature to consider this promising medication a proven treatment for the sleep disturbances of patients taking antidepressants.

Patients with insomnia often self-medicate with over-the-counter medications and remedies, with range from various antihistaminergic compounds (such as diphenhydramine) to "natural" agents such as melatonin and valerian root. The utility (or, more accurately, the lack of efficacy) of these nonprescription medications has been reviewed elsewhere in more detail.[63-65] Suffice it to say that if a patient warrants treatment for relief of a significant persistent sleep disturbance, there are a number of more promising interventions that can be utilized.

Cognitive-behavioral management of insomnia

The past decade has witnessed increased interest in nonpharmacologic approaches to management of insomnia, particularly those emphasizing cognitive and behavioral methods.[65,66] Beyond explicit attention to sleep hygiene, cognitive behavior therapy (CBT) for insomnia utilizes stimulus control and arousal reduction techniques. There is evidence from studies of primary insomnia that comprehensive CBT results in short-term improvements that are—at the least—as effective as pharmacotherapy with sedative-hypnotics.[67] The potentially greatest advantage of CBT is evident over time, however, as effectiveness is more durable than pharmacotherapy and benefits persist after therapy is terminated.[68] Thus, although CBT may be a more costly approach than pharmacotherapy in the short run, it becomes a cost-effective approach across 6 months or longer. Given the positive experience as a treatment of primary insomnia, there is a clear need for studies on the utility of CBT—in combination with antidepressant therapy—for patients with major depressive disorder.[69]

It is noteworthy that other models of CBT directed more broadly at the overall depressive syndrome often fail to vigorously address insomnia. For example, in one large comparative study of patients with chronic forms of major depressive disorder, the antidepressant nefazodone had a substantial advantage over the cognitive behavior analysis system of psychotherapy for relief of both objective and

subjectively assessed depressive insomnia, even though the two therapies had comparable overall effects.[70,71] Given the relatively inconsistent performance of various models of psychotherapy for treatment of more severe depressive states[72] it would be prudent for therapists to consider adding a more specific CBT module to address insomnia.

Conclusions

Sleep disturbances are an integral aspect of depression, at phenomenologic, pathophysiologic, and therapeutic levels of inquiry. Improving the understanding of the relationship between sleep disturbances and mood disorders will only help to clarify the heterogeneity of depression. Persistent insomnia can reflect incomplete remission of the depressive episode and/or a side effect of pharmacotherapy; in either case it may be an ominous correlate of vulnerability to relapse. Although no universally effective strategy is yet available, there are a variety of effective strategies—both pharmacologic and cognitive-behavioral—that can be used to improve management of insomnia associated with depression. ❏

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Depresión y sueño: fisiopatología y terapéutica

Esta revisión examina la relación entre sueño y depresión. La mayoría de los trastornos depresivos se caracterizan por alteraciones subjetivas del sueño, y la regulación del sueño está vinculada de manera compleja con los mismos mecanismos que están implicados en la fisiopatología de la depresión. Después de revisar brevemente la fisiología y la topografía del sueño normal se discuten las alteraciones que han sido reveladas por los estudios de sueño en la depresión mediante el empleo de registros polisomnográficos y evaluaciones de neuroimágenes. A continuación se revisan los efectos de las alteraciones tanto a nivel clínico como neurobiológico. La mayoría de los fármacos antidepresivos suprime el sueño de movimientos oculares rápidos (REM), aunque este efecto no es necesario ni suficiente para la eficacia clínica. Los efectos sobre las dificultades de los pacientes para iniciar y mantener el sueño son más específicos de ciertos tipos de antidepresivos. Idealmente, un antidepresivo efectivo provocará una normalización del sueño alterado conjuntamente con la resolución del síndrome depresivo, aunque actualmente son pocas las intervenciones que restablecen la disminución del sueño de ondas lentas. Los antidepresivos que bloquean los receptores centrales de histamina1 y serotonina2 tienden a provocar mayores efectos en la mantención del sueño, pero también son más proclives a favorecer quejas de sedación diurna. El tratamiento conjunto con fármacos hipnótico sedantes benzodiazepinas primariamente potentes, de acción corta y compuestos selectivos sobre ácido gama amino butírico (GABA A) como el zolpidem– se utilizan a menudo para tratar más rápidamente el insomnio asociado. También resultan útiles la terapia cognitivo conductual y otras estrategias no farmacológicas.

Dépression et sommeil : physiopathologie et traitement

Cet article se penche sur les relations entre le sommeil et la dépression. La plupart des troubles dépressifs se caractérisent par des troubles subjectifs du sommeil, la régulation du sommeil étant étroitement liée aux mécanismes impliqués dans la physiopathologie de la dépression. Après un court rappel de la physiologie et de la topographie du sommeil normal, les troubles mis en évidence dans les études sur le sommeil au cours de la dépression grâce à des enregistrements polysomnographiques et à des évaluations de neuro-imagerie sont étudiés. Puis les implications thérapeutiques des troubles aux niveaux cliniques et neurobiologiques sont examinées. La plupart des antidépresseurs suppriment les mouvements oculaires rapides (MOR), bien que cet effet ne soit ni nécessaire ni suffisant pour une efficacité clinique. Les effets sur les difficultés du patient à s'endormir ou à prolonger son sommeil sont plus spécifiques de certains types d'antidépresseurs. Idéalement, un antidépresseur efficace permettra de normaliser les troubles du sommeil tout en traitant le syndrome dépressif, bien que, en réalité, il existe très peu de mécanismes restaurant le sommeil à onde lente diminué. Les antidépresseurs qui bloquent l'histamine 1 et la sérotonine 2 centrales ont un effet plus important sur le maintien du sommeil, mais sont aussi connus pour induire une sédation diurne. Un traitement supplémentaire avec des hypnotiques sédatifs – efficaces d'emblée, des benzodiazépines de plus courte durée d'action et des composés sélectifs de l'acide γ aminobutyrique (GABA A) comme le zolpidem- est souvent utilisé pour traiter l'insomnie associée plus rapidement. Un traitement cognitivocomportemental et d'autres stratégies non pharmacologiques sont également utilisés.

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