Depression, Sleep, and Antidepressants

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Sleep disturbances are an integral feature of depressive disorders. Like the disorders themselves, the sleep disturbances associated with depression are heterogeneous, ranging from hypersomnia to marked difficulties maintaining sleep. These difficulties are to some extent age dependent and reflect abnormalities of central nervous system arousal. Moreover, the sleep disturbances associated with depression have both reversible, or state-dependent, and more persistent trait-like characteristics. Polysomnographic recordings can be used to document sleep maintenance difficulties, and they often also reveal reduced slow wave sleep, an early onset of the first episode of rapid eye movement (REM) sleep, and increased phasic REM sleep. A deficit of serotonergic neurotransmission, a relative increase in pontine cholinergic activity, and, perhaps, an excess of noradrenergic and corticotropin-releasing hormone activity have been implicated in the pathogenesis of the sleep disturbances of more severe depressive disorders. Antidepressant medications have class- and compound-specific effects on polysomnographic profiles. Unlike other antidepressants, bupropion may increase or intensify REM sleep. While no single effect of antidepressants on sleep neurophysiology is necessary or sufficient for treatment efficacy, differences in drug effects may provide important clues to selection of specific medications for particular patients. *(J Clin Psychiatry 1998;59[suppl 4]:55–65)*

Difficulties with sleep are among the most common symptoms of mood disorders and have been described as characteristic of depression since antiquity. All contemporary sets of diagnostic criteria for depression include sleep disturbances, as do the major symptom-based rating scales. Moreover, the sleep disturbances associated with more severe depressive states appear to be the result of serotonergic, cholinergic, and noradrenergic abnormalities implicated in the pathogenesis of mood disorders. Most antidepressant medications have significant effects on both clinical and laboratory assessments of sleep. In this article, the relationship between depression, sleep, and antidepressants will be reviewed, including the effects of bupropion on sleep.

EPIDEMIOLOGY OF SLEEP DIFFICULTIES

We spend about one third of our lives asleep. Not surprisingly, the perceived quality of one's sleep is one of the principal indicators of subjective well-being. Sleep is an essential function, with well-recognized but poorly understood restorative effects. During times of emotional turmoil, insomnia is a common reaction to the stressor. It is likely that the mechanisms that cause such transient periods of insomnia are built into our "hard wiring" and have, or at one time had, survival value in terms of heightened vigilance and preparedness to respond to danger. However, chronic sleep deprivation is an aversive state with manifold adverse effects on mood, concentration and memory, and general health.

Approximately 16% of the adult population of the United States report "serious" difficulties initiating or maintaining sleep in any year.[1] The likelihood of developing insomnia increases with age and is more common among women than men.[1,2] Persistent insomnia is a harbinger of both anxiety and mood disorders. For example, people with persistent insomnia showed a markedly increased risk of developing a major depressive episode during a 1-year prospective follow-up study.[3]

Other people complain of sleeping too much, and about 8% of young adults report hypersomnia.[4] Beyond the upper limits of a normal need for sleep (i.e., 9 to 10 hr per night), hypersomnia is associated with an increased risk of depression.[4] Periodic hypersomnia also may be associated with menses, shift work, or chronic sleep deprivation.[1]

Nonaffective sleep disorders associated with hypersomnolence or excessive daytime sleepiness include sleep apnea, narcolepsy, toxic-metabolic states, and psychostimulant withdrawal states.[1] Disorders of sleep-related

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breathing are the most common cause of pathologically excessive daytime sleepiness and have been estimated to have a lifetime prevalence of 9% in men and 4% in women, with a marked increase in incidence after age 40.[5] Sleep apnea and narcolepsy, although less prevalent than insomnia in the general population, have relatively greater morbidity as well as increased mortality.[5]

About 5% to 10% of people evaluated in sleep laboratories meet criteria for a condition called primary hypersomnia.[1] This disorder is defined by either at least 1 month of hypersomnia or recurrent periods of hypersomnolence that last for at least 3 days' duration across at least 2 years. Primary hypersomnia is generally a diagnosis made by exclusion, i.e., after ruling out narcolepsy, the sleep apneas, toxic-metabolic states, and depressive disorders. Rare conditions such as Kleine-Levin syndrome and idiopathic recurring stupor also can cause an apparent primary hypersomnia.[1]

Some people, commonly referred to as "night owls," have a delayed sleep phase disorder.[6,7] Often, teens or younger adults do not sleep excessively; rather, they typically do not go to bed until 2 a.m. or later and do not wake up until 10 a.m. or later. Problems typically arise when a night owl tries to conform to responsibilities that necessitate awakening at "conventional" hours (e.g., 6 a.m. or 7 a.m.). Some people with delayed phase sleep disorder find adhering to a conventional schedule so unpleasant that they opt for careers that permit an alternate lifestyle.

SLEEP AND BIOLOGICAL RHYTHMS

The adaptation of humans to a diurnal lifestyle (i.e., awake during daylight and asleep during night) has resulted in a remarkable integration of circadian rhythms. Our sleep-wake cycle normally runs coincident, or in-phase, with a number of circadian rhythms that are maintained by an endogenous pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus.[7] The sleep-wake cycle is thus paired with the daily rhythms of body temperature and secretion of growth hormone, prolactin, melatonin, and cortisol. Various zeitgebers (e.g., sunrise, sunset, mealtimes, bedtimes, and good morning times) help to entrain circadian rhythms and the sleep-wake cycle within the 24-hour day. When people are removed from time cues, a free running sleep-wake cycle of about 25 hours' (± 0.5 hrs) duration emerges.[6]

Sleep propensity, a homeostatic process that builds over hours of sustained wakefulness, normally drives the onset of sleep after dusk. At sundown, melatonin is released from the pineal gland, further enhancing sleep propensity.[7] Sleep usually occurs at a time in which body temperature is low, which may reduce the probability of nocturnal awakenings. Pulsatile secretion of growth hormone and prolactin is typically highest during the first 90 minutes of sleep, although secretion of these hormones does not depend on sleep per se.[7] Cortisol secretion, by contrast, is typically low at sleep onset and begins to increase in the early morning hours, peaking after sunrise. When the sleep-wake cycle is artificially uncoupled from the circadian rhythms for body temperature and cortisol secretion, people often feel listless, "blue," or out of sorts.[7]

CLINICAL CHARACTERISTICS OF SLEEP IN DEPRESSION

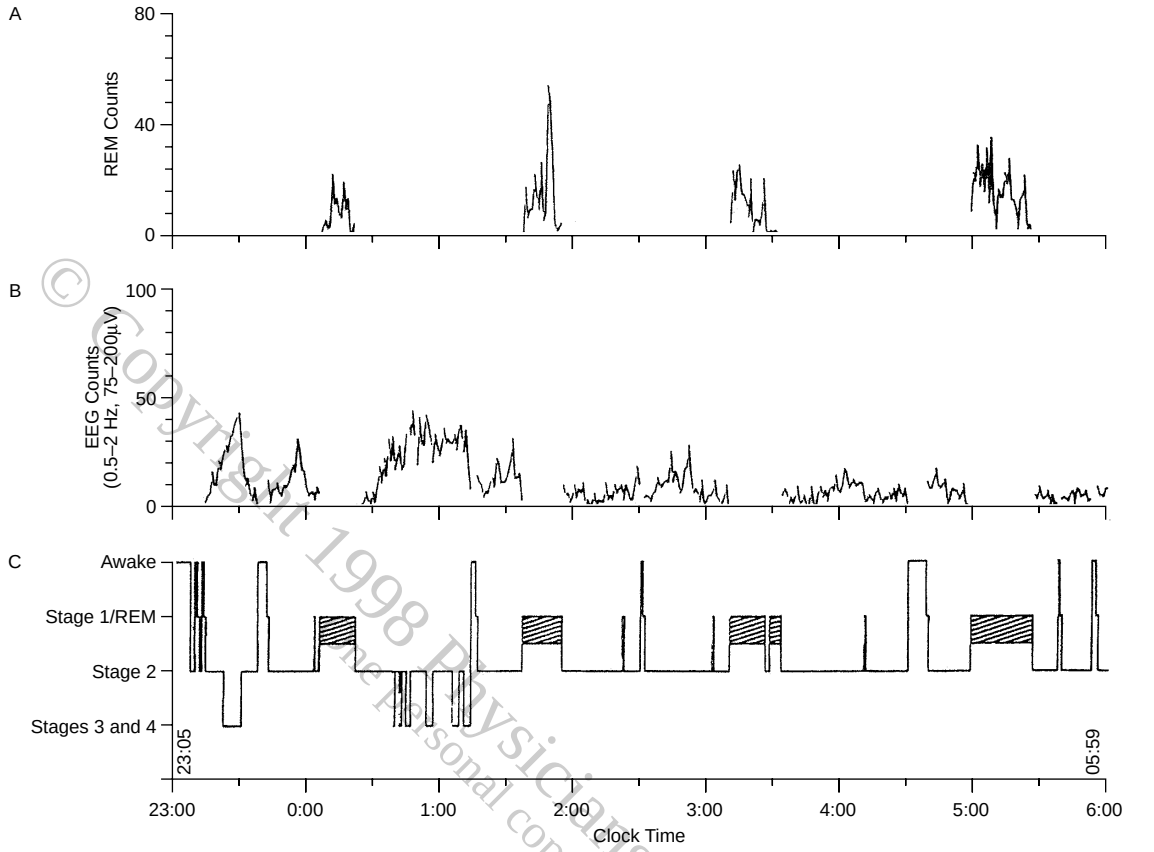
The subjective sleep disturbances of melancholia include difficulty maintaining sleep (sleep continuity disturbance) and early morning awakening.[8–11] There is also a tendency for mood to be worse in the morning upon awakening. This classic sleep profile is clearly age dependent, and it is most common among depressed people over age 50.[8–10] Early morning awakening and sleep continuity disturbance are linked to psychomotor disturbances and diminished appetite and weight loss.[8,12] Depressed people do not report consistent changes in dreaming, although their dreams may be more dysphoric or frightening in nature.[10]

As the onset of depression has become progressively earlier in life, the likelihood that a depressive episode will be characterized by the classical sleep disturbances of depression has probably decreased over the past 50 years. In fact, the Hamilton Rating Scale for Depression, which was developed in the late 1950s, does not even rate hypersomnia. Currently, many, if not a thin majority of early-onset depressions are characterized by oversleeping or increased time in bed.[13] Unlike narcolepsy and sleep apnea, however, the hypersomnia of depression is not associated with hypnagogic or hypnopompic hallucinations, cataplexy, or sleep-related breathing difficulties. Daytime nap studies document an intermediate level of daytime sleepiness when hypersomnic depressed patients are compared with healthy people and narcoleptic patients.[14]

Hypersomnia in depression is often associated with weight gain and increased appetite.[13] Once considered atypical, these reversed vegetative symptoms are commonly seen in depressed people in their 20s or 30s.[13] Our group prefers to use the term *anergic* depression to describe syndromes characterized by fatigue, psychomotor slowing, and hypersomnolence.[13] Episodes of depression among people with bipolar affective disorder[15] and seasonal affective disorder[16] are especially likely to have anergic features.

The association of aging with a higher probability of sleep continuity disturbance and early morning awakening suggests that depression may accelerate or exaggerate normal physiologic processes.[8,12,17] These symptoms, especially when coupled with weight loss and psychomotor agitation, suggest heightened central nervous system arousal. Further, sleep continuity disturbances are associated with other biologic correlates of heightened arousal, such as hypercortisolism and elevated sympathoadrenal activity.[18] Such increased arousal could be the result of an active pro-

Figure 1. One Night of Sleep in a Healthy Control Subject (37-Year-Old Woman)*



*Abbreviations: REM = rapid eye movement, EEG = electroencephalogram. EEG results show (A) automated REM detection, (B) automated delta analysis, and (C) visually scored sleep stages.

cess (i.e., increased activity of the limbic cortex or locus ceruleus), a deficit of counter-regulatory mechanisms (i.e., deficient "quieting"), or both.[18]

Hypersomnolence and overeating, by contrast, may be partially adaptive counterregulatory processes. Specifically, hypersomnolence permits more time spent in deep and dream sleep, maximizing the presumably restorative and cognitive processing effects. Likewise, increased consumption of palatable, high caloric foods can be viewed both as self-reinforcement (i.e., hedonic capacity is still functional) and as a means to increase central nervous system levels of serotonin and trace monoamines.

Longitudinal studies of recurrent depressive episodes across decades are necessary to determine if the characteristics of sleep and appetitive function during depressive episodes change or evolve as individuals grow older. Conversely, it is possible that different ages at onset reflect disorders that have different pathophysiologies. In any case, some people report periods of hypersomnolence and insomnia within the same depressive episode. Thus, it is best to view hypersomnia and insomnia as indicators of different types of depressive states rather than discrete subtypes of mood disorders.

POLYSOMNOGRAPHIC RECORDINGS

All-night electroencephalographic (EEG) recordings have been used to study sleep neurophysiology for more than 50 years.[1] A full-montage polysomnogram, typically consisting of an EEG, electromyograms of submentalis and tibialis muscle activity, respiration and pulse rates, capillary oxygenation, and electrooculograms (EOGs), remains an essential tool for clinical evaluation of narcolepsy and sleep apnea, as well as selected cases of insomnia.[1] Sleep EEG studies also provide a useful window through which researchers may observe changes in brain activity in a variety of neuropsychiatric illnesses and in response to various psychoactive medications.[8]

The EEG patterns of healthy sleep are well described (Figure 1).[1,19] Major characteristics of sleep architecture include the generalized slowing of EEG activity that characterizes the transition from drowsiness to light (stage 1) sleep, the emergence of sleep spindles and K-complex waves that accompany the onset of deeper (stage 2) sleep, and the loping, desynchronized slow (delta) waves that define sleep stages 3 and 4.[1,19] Sleep normally progresses to progressively deeper stages (i.e., stage 1 → stage

2 → stage 3 → stage 4), and each cycle of non–rapid eye movement (NREM) sleep ends with a discrete episode of rapid eye movement (REM) sleep. However, slow-wave sleep may not be visually scoreable after the first or second cycle. Thus, across the night, there is a general tendency for sleep to become lighter. Together, these four sleep stages are referred to as NREM sleep, which constitutes 75% to 85% of a normal night of sleep.

REM sleep is defined by faster EEG activity, rapid horizontal eye movements detected by the EOG, vital sign instability, and an apparently paradoxical occurrence of hypotonia of the skeletal musculature. About 90% of dreaming occurs during REM sleep. Hypotonia serves to prevent the vivid images of dreaming from being acted upon. The REM sleep behavior disorders probably result from a failure of this mechanism.[1]

The first REM period typically occurs after 60 to 110 minutes of sleep, although values as low as 40 to 50 minutes are commonly observed among the healthy elderly.[1] Longer REM latencies usually represent such marked nocturnal arousal that the individual cannot progress beyond sleep stages 1 or 2.[8] There are usually four or five REM periods across a normal night of sleep, separated by 90-minute intervals. REM sleep may be measured in regard to both its tonic (i.e., REM time or percentage and number of episodes) and phasic (i.e., activity or density of rapid eye movements) processes.

The 90-minute REM cycle continues even during wakefulness and is referred to as an ultradian (i.e., less than 24 hours) rhythm. REM propensity also follows a circadian cycle. Normally, REM propensity is greatest between 5 a.m. and about 9 a.m., and REM periods normally become longer and more intense as a night of sleep progresses. It is common to awaken out of a REM period in the morning. Among healthy men, REM sleep is typically accompanied by periods of penile tumescence and rigidity. Because this relationship occurs autonomously (i.e., independent of volition or dream content), nocturnal penile tumescence recordings have been used as a diagnostic test of erectile dysfunction.[1]

The association of REM sleep and dreaming has provoked fascinating speculations about the potentially adaptive and maladaptive interplay between dynamic psychology and sleep neurophysiology.[1] From a more traditional psychodynamic perspective, the dream (i.e., "the royal road to unconscious") represents a process by which conflictual issues are addressed, although the nature of the conflict is presumed to be disguised by symbolic representations. However, the discovery that REM sleep is driven by the firing of cholinergic cells in the pons led some to suggest that REM sleep has a simpler, physiologic basis.[20] This point is underscored by demonstration of REM sleep in dogs, cats, and rodents, creatures that are generally not presumed to have neurotic conflicts.[20] These perspectives are not mutually exclusive, however, and some evidence does indicate that REM sleep facilitates processing of both cognitive and affective waking experiences.[21,22]

NEUROCHEMICAL MEDIATION AND MODERATION OF SLEEP

The neurochemistry underlying the homeostatic processes that govern sleep onset remains somewhat of a mystery. In addition to melatonin, a sleep-inducing peptide or "process S" also may exist.[23] In any event, sleep propensity builds progressively during wakefulness. Most sedative-hypnotic agents work by diminishing central nervous system arousal via modulation of various aspects of the GABA system,[1,24] although antagonists of α_1-adrenergic and histamine receptors also facilitate sleep onset.[1,24]

Serotonergic neurons play a critical role in modulating the onset and maintenance of sleep.[1] The phylogenetically ancient serotonergic tracts emanating from the dorsal raphe nucleus mediate neurobehavioral response systems that are involved in both consummatory (appetitive) and inhibitory (quieting or calming) behaviors. The greatest density of slow waves during deep sleep is observed in serotonergically innervated areas of the prefrontal cortex.[25]

Serotonergic neurons projecting to the pons tonically inhibit the cholinergic neurons from firing. This effect may block, or inhibit, or delay the onset of REM sleep.[1] A deficit of serotonin (5-HT), either inherited or acquired, thus may cause both a disinhibition of REM sleep and a diminution of slow-wave sleep. Depressed people and those at high risk for depression (e.g., first-degree relatives of affected patients) also appear to have hypersensitivity or overreactivity to cholinergic agonists.[26,27]

Ascending noradrenergic and dopaminergic tracts, on the other hand, may drive arousal and disrupt or fractionate sleep.[1] Such disruption functionally inhibits REM sleep by preventing progression into the deeper sleep stages. Neuropeptides, such as the cytokines, thyrotropin-releasing hormone, and corticotropin-releasing hormone (CRH), also are likely to increase arousal and may disrupt both NREM and REM sleep.[1]

EEG SLEEP STUDIES IN DEPRESSION

The terms used to describe EEG sleep disturbances associated with depression are summarized in Table 1. Virtually all melancholic patients manifest at least several of the following EEG sleep disturbances: poor sleep efficiency, decreased slow-wave sleep, reduced REM latency, and increased REM activity, particularly in the first third of the night (Figure 2).[8–12,28,29] These features are not specific to depression, however, and they may occur as isolated false positive findings in healthy normals and in more characteristic constellations in schizophrenia, obsessive-compulsive disorder, alcoholism, and other "dysphorogenic" states.[30] In addition to such limited diagnostic

Table 1. Glossary of Terms Used to Describe Polysomnographic Disturbances Associated With Depressive Disorders*

Term	Definition
Delta sleep ratio	The ratio of computer-scored delta wave counts in the first and second NREM periods. Normally, values exceed 1.1. Lower values have been associated with an increased risk of recurrent depression.
Hypersomnia	Sleeping more than 1 hour longer each night than what is considered normal by the individual.
Phase delay disorder	A significant delay of the sleep-wake cycle in relation to the other circadian rhythms.
REM activity	The phasic activity of visually scored REM sleep (as measured minute by minute using a scale of 0 to 8).
REM density	The average phasic activity within each minute of visually scored REM sleep. Abnormal elevations are typically > 1.5 units.
REM latency	The number of minutes from the onset of stage 2 sleep to the onset of the first period of visually scored REM sleep. Reduced values are typically below 65 minutes in younger patients and 50 minutes among elders.
Sleep efficiency	The percentage of time spent asleep during the all-night recording period. Ideally, values should exceed 90% (older) to 95% (younger age groups).
Sleep latency	The number of minutes it takes from "lights out" to reach stage 2 sleep.
Sleep maintenance	Sleep efficiency recalculated after excluding sleep latency.
Slow-wave sleep	Visually scored sleep stages 3 and 4. Ideally, greater than 10% (younger) or 5% (older age groups).

*Adapted from references 1 and 8. Abbreviation: NREM = non–rapid eye movement.

specificity, EEG sleep studies are relatively expensive ($300–$600 per night) and inconvenient (e.g., typically, at least 2 weeks of medication-free status and consecutive overnight stays).

Our group has recently studied an EEG sleep profile based on three standard variables (sleep efficiency, REM latency, and REM density) that reliably distinguishes among depressed inpatients, depressed outpatients, and healthy controls (Figure 3).[28] This profile can be used as a composite measure of abnormality to identify depressed patients with greater and lesser degrees of neurophysiologic disturbance. Consistent with our prediction, outpatients with abnormal sleep profiles were older and less responsive to cognitive and interpersonal therapies than patients with more normal profiles.[28,31,32] A prospective, placebo-controlled study by our group using this classification to predict differential response to pharmacotherapy or psychotherapies is ongoing. We have not yet ascertained the specificity of this index score in groups of patients with other psychiatric disorders.

Many mildly depressed outpatients, including a majority of those with dysthymic disorder, have relatively normal EEG sleep profiles.[28,29] The depressive disorders, as currently diagnosed, are very heterogeneous conditions. Of course, visually scored sleep EEG recordings may not detect more subtle changes in brain physiology.[33]

Armitage[33] has proposed that microarchitectural disturbances in sleep patterns may yield more sensitive and/or more specific distinctions than visually scored profiles. This strategy utilizes computer scoring to identify and count individual REMs or slow waves within defined frequency ranges, to quantify the power of EEG frequency bans, and to compare differences in coherence between the left and right cerebral hemispheres. Depression has been associated with a reduction of overall EEG power during sleep, a reduction of delta wave counts, an increase in REM counts, and significantly reduced interhemispheric coherence when compared with healthy states.[33–35]

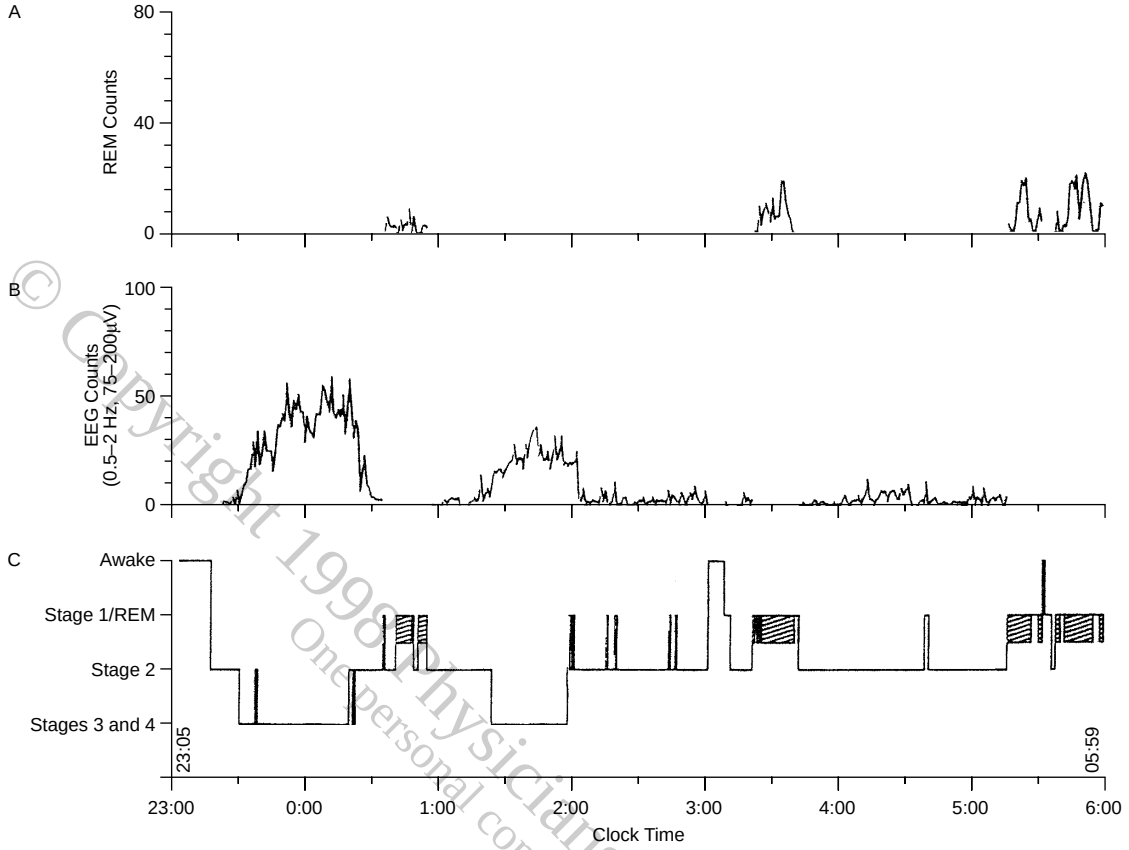
ARE THE EEG SLEEP DISTURBANCES OF DEPRESSION STATES OR TRAITS?

Most people report improvements in their sleep difficulties following recovery from a depressive episode. The subjective sleep symptoms of depression thus usually can be considered to be characteristics of depressive states, not of the people prone to develop depression. Moreover, persistent sleep problems after successful treatment usually can be identified as side effects of antidepressant treatment or the result of a preexisting primary sleep disorder.

Longitudinal studies of EEG sleep profiles in depression reveal both state-dependent and trait-like characteristics.[36] For example, the temporal association between insomnia and the subsequent onset of the full syndrome of depression probably reflects a forme früste relationship, as illustrated by the recent prospective study by Perlis et al.[37] in a small group of high-risk, unmedicated patients. Following treatment, sleep continuity disturbances and increased phasic REM sleep typically resolve or normalize even when the treatment is nonpharmacologic.[38,39] By contrast, a modest reduction of REM latency (e.g., 40 to 65 minutes) and decreased slow-wave sleep tend to persist despite clinical recovery. The trait-like nature of these latter abnormalities is also supported by family studies,[40] twin studies,[41] and research using other high risk paradigms.[42,43] Blunted growth hormone secretion, measured following sleep onset or after administration of a noradrenergic agonist, similarly shows trait-like characteristics in early onset and recurrent depressions.[44] As each of these more persistent abnormalities occurs during the first 90 minutes of sleep, it appears that the first and second NREM/REM cycles are important correlates of depressive vulnerability. Consistent with this notion, reduced REM latency[45] and a selective decrease of slow-wave activity during the first NREM period (referred to as a decreased delta ratio[46]) have been associated with higher rates of relapse/recurrence after recovery from a depressive episode.

Perhaps the most ominous state-dependent EEG sleep abnormality is a sleep-onset REM period (i.e., < 10 min-

Figure 2. One Night of Sleep in a Depressed Outpatient (31-Year-Old Woman)*



*EEG results show (A) automated REM detection, (B) automated delta analysis, and (C) visually scored sleep stages.

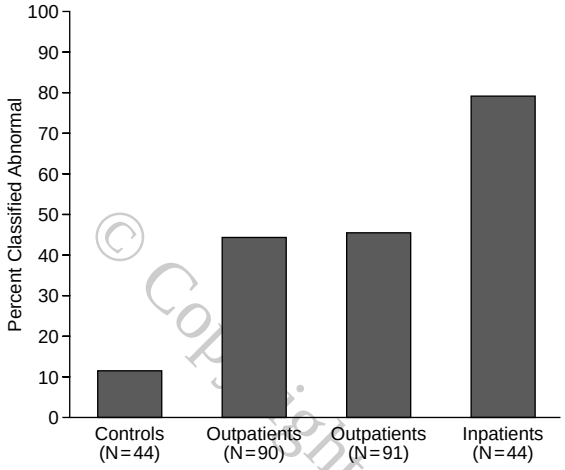
utes), which is associated with psychotic depression and severe melancholias.[47,48] Sleep-onset REM periods are almost always associated with increased REM density and/or poor sleep efficiency. The associations between these particular sleep abnormalities and both hypercortisolism and increased sympathomedullary activity further implicate the role of heightened central nervous system arousal in severe depression. There is some evidence that this prolonged and excessive stress response is either maintained or mediated by increased CRH and activation of the locus ceruleus.[49] Interactions between glucocorticoid and dopamine levels, and between CRH and locus ceruleus activity, constitute deleterious positive (i.e., additive) feedback relationships that may ultimately lead to hippocampal cell death and/or cortical atrophy.[49]

However, a sustained aberrant stress response does not fully explain the sleep profile of severe depression, nor is it relevant to anergic depressions. Studies that experimentally manipulate increased corticosteroid, norepinephrine, and dopamine levels in the brain tend to document fractionated or decreased REM sleep.[1,8] There are thus missing pieces to this puzzle that account for increased REM activity and prolonged sleeping in some depressive episodes. One might speculate that anergic depressions result from compensatory serotonergic (5-HT) mechanisms, whereas increased REM activity and deficient slow-wave sleep reflect failing 5-HT counterregulatory effects. Aging, which normally involves decreased integrity of feedback inhibitory systems, increases the likelihood of superimposed abnormalities of hypothalamic-pituitary-adrenocortical (HPA) and sympathomedullary activity.[18] Studies of nonpsychotic depression reveal a modest positive correlation between intensity of dysphoric affects and REM activity.[50] As discussed below, an abnormally activated prefrontal-limbic-thalamopontine circuit may drive both ruminative dysphoria during waking and increased pressure for phasic REM activity during sleep.[49,51]

NEUROIMAGING STUDIES

If some depressions are characterized by pathologically increased arousal, then evidence of areas of increased brain metabolic activity should be confirmed by positron emission tomography (PET). Few such studies have as of yet been completed because the technology is very expensive and labor-intensive and because it is difficult to sleep in a PET scanner. However, available evidence is fully consistent with the overarousal hypotheses. Specifically,

Figure 3. Comparison of the Proportion of Abnormal Sleep Studies in Healthy Controls, Two Groups of Depressed Outpatients, and Depressed Inpatients*



*From reference 28. The control group has a significantly lower proportion of abnormal profiles than either the outpatients ($\chi^2 = 40.5$, df = 1, $p < .0001$) or the inpatients ($\chi^2 = 41.3$, df = 1, $p < .0001$). The inpatients also have a significantly higher proportion of abnormal cases than the outpatients ($\chi^2 = 17.2$, df = 1, $p < .001$). The proportions of abnormality observed in the two outpatient groups were virtually identical ($\chi^2 = 0.01$, df = 1, $p = .934$).

depressed patients have increased global cerebral metabolism during NREM sleep as well as relatively greater right hemispheric metabolism during REM sleep.[51–53] Importantly, one research group has reported that increased glucose metabolism in the cingulate gyrus during sleep predicted a favorable mood response to 1 night of total sleep deprivation.[52] Prior research has suggested that an antidepressant response to total sleep deprivation is also associated with REM rebound on the subsequent recovery night, hypercortisolism, melancholic symptomatology, and subsequent response to antidepressant medication.[8]

EFFECTS OF ANTIDEPRESSANTS

Studies of the effects of various antidepressants on the sleep of healthy individuals demonstrate the relationships among pharmacologically induced neurochemical perturbations, clinical response, and changes in EEG sleep profiles.[8,54,55] Such studies also help to document the incidence of sleep disturbances that occur specifically as a result of the medication. Not surprisingly, different classes of antidepressants have distinctly different effects on sleep.[8,54,55] Moreover, the largest antidepressant class, the tricyclic antidepressants (TCAs), shows considerable variability of effects across individual compounds.

Perhaps the best-documented and most broadly applicable effect of antidepressants is suppression of tonic REM sleep, as measured by prolongation of REM latency and a reduction of REM time and percentage.[8,50,54,55] Phasic REM activity also is usually reduced initially, although some adaptation to this effect generally occurs within several weeks. As a result, the density of REM periods may actually increase during pharmacotherapy even though the total REM time is decreased. Redistribution of REM time into the later hours of the night, coupled with relatively higher phasic REM activity, also may explain why some people report increased dreaming or nightmares during antidepressant therapy.

The most widely prescribed antidepressants, including the TCAs, monoamine oxidase inhibitors (MAOIs), and serotonin selective reuptake inhibitors (SSRIs), suppress REM sleep,[8,50,54,55] with clomipramine and tranylcypromine having the most potent effects in standard antidepressant dosages.[8] Several studies in the 1970s and 1980s reported significant correlations between initial REM suppression, measured during the first 48 hours of tricyclic therapy, and subsequent antidepressant response.[55–57] These findings, coupled with the high prevalence of REM sleep disturbances in severe depression, suggested that REM sleep suppression was a critical factor in antidepressant action.[55] Further evidence of such a relationship was obtained by Vogel et al.[58] in an early study showing that nonpharmacologic REM deprivation (achieved by repeated awakenings during EEG-monitored sleep) had antidepressant efficacy. Of note, patients who did not respond to REM deprivation were not responsive to a subsequent trial of imipramine.[58]

REM suppression may be mediated by potentiation either of noradrenergic or serotonergic neurotransmission,[8,55] and direct agonism of 5-HT_{1A} receptors may prolong REM latency.[59] However, research has identified a number of effective antidepressants, including trazodone,[54] mianserin,[60] nefazodone,[61,62] and bupropion,[63] that do not suppress REM sleep. A key common feature of these medications is that they do not potently block the reuptake of serotonin.[54] It remains to be seen if REM-suppressing medications are better treatments for patients with more pronounced increases in REM sleep and, conversely, if the antidepressants that do not suppress REM sleep are better suited for the remainder of patients.

Antidepressants have quite variable effects on sleep maintenance.[8,54,55] A wide range of compounds are sedating, including several TCAs (e.g., amitriptyline, imipramine, doxepin, and trimipramine), trazodone, nefazodone, and mirtazapine. In fact, trazodone is probably now used more widely as a hypnotic than as an antidepressant.[64]

Other effective antidepressants may have disruptive effects on sleep maintenance.[8,54,55] These nonsedating agents include several TCAs (clomipramine, desipramine, and protriptyline),[8] the MAOIs (including moclobemide),[8,65] the SSRIs,[54,61,62] and bupropion. Two studies recently demonstrated these between-class differences in randomized clinical trials comparing fluoxetine and nefazodone.[61,62] Although equally effective on depressive symptoms, fluoxetine treatment was associated with a significant wors-

Table 2. Comparison of Sleep in Depressed Men Treated With Fluoxetine and Bupropion*

	Nondepressed Healthy Normals (N = 36)		Fluoxetine Responders (N = 11)				Bupropion Responders (N = 7)			
			Pre		Post		Pre		Post	
Measurement	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Time spent asleep, min[a]	90.6	5.3	87.8	8.5	89.8	4.1	83.7	15.6	90.2	3.5
Sleep efficiency, %[a]	396.7	34.5	406.7	56.4	408.4	44.7	364.4	61.4	395.0	52.3
Sleep latency, min[b]	14.6	12.6	29.8	39.3	16.3	8.6	16.0	9.2	18.9	7.8
REM latency, min[c]	79.8	37.2	76.3	24.9	113.3	39.6[f]	60.1	16.6	49.1	14.8[f]
REM time, %[a]	22.1	5.4	22.6	3.7	22.6	5.2	22.4	3.2	31.2	5.1[f]
REM activity, units[d]	114.6	64.1	165.5	82.9	187.3	77.5[f]	129.4	65.0	192.4	99.1[f]
Slow-wave sleep, %[e]	13.2	9.9	8.7	6.6	6.3	6.9[f]	4.8	5.5	1.9	2.9[f]
Delta sleep ratio[c]	1.5	0.5	1.4	0.4	1.9	0.8[f]	1.8	0.7	1.1	0.8[f]

*Adapted from Nofzinger et al.[63]
[a]Significant increase only in bupropion group.
[b]Significant decrease only in fluoxetine group.
[c]Significant drug × time interaction.
[d]Significant increase in both groups.
[e]Significant decrease in both groups.
[f]Differs significantly from controls at posttreatment.

ening of sleep maintenance, whereas nefazodone produced a modest but statistically significant improvement.

Antidepressant effects on sleep latency and sleep maintenance are not correlated reliably with antidepressant response.[8,54] Therefore, it is likely that these sedative effects are nonspecific qualities that are attributable to antihistaminergic effects or antagonism of α_1-adrenoceptors.[8,64] Nevertheless, the more sedating antidepressants usually are not well tolerated by hypersomnolent patients, and, conversely, early (albeit nonspecific) sedative effects are often appreciated by depressed patients with severe insomnia. The prevalence of insomnia during SSRI therapy probably accounts for the high prevalence of concomitant sedative-hypnotic prescription.[66]

None of the currently approved antidepressants increase visually scored slow-wave sleep.[8,54] Computer-scored measures of delta wave activity do, however, suggest some enhancement during pharmacotherapy with TCAs,[67] although decreased visually scored slow-wave sleep also has been reported following treatment with SSRIs.[54] Part of the problem here may be artifactual. An increase in slow-wave sleep would be expected and desirable only among patients with a significant deficit prior to treatment. Conversely, some hypersomnolent patients may actually have a state-dependent increase in slow-wave sleep that is decreased or normalized by effective treatment. Thus, the heterogeneity of sleep disturbances in depression may conceal important treatment-by-person interactions.

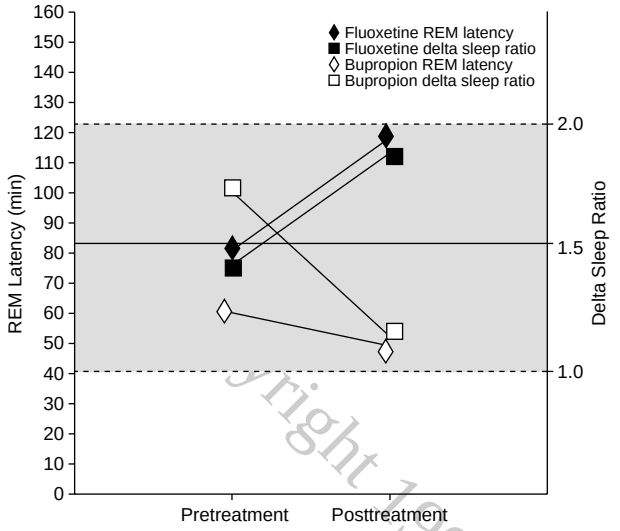
Recent research suggests that 5-$HT_{2A/2C}$ receptors are important mediators of drug effects on slow-wave sleep.[54,68,69] For example, ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, significantly increases slow-wave sleep in normal volunteers, insomniacs, and depressed patients.[54,68,69] By contrast, agonism of 5-HT_{2C} receptors by *m*-chlorophenylpiperazine (*m*CPP, a metabolite of both trazodone and nefazodone) decreases slow-wave sleep. Agonism of 5-HT_1 receptors also decreases slow-wave sleep.[70] The two clinically effective antidepressants that antagonize 5-$HT_{2A/2C}$ receptors potently, nefazodone and mirtazapine, do not reliably increase the slow-wave sleep of depressed patients. Could this be the result of competing effects via 5-HT_{1A} or noradrenergic receptors? One wonders if combining ritanserin with agents that have predominantly noradrenergic effects, such as desipramine, nortriptyline, or bupropion, might yield more selective results.

BUPROPION AND SLEEP

The novel aminoketone antidepressant bupropion has unique effects on sleep that may be attributable to (1) its weak inhibition of uptake of dopamine, (2) its weak inhibition of norepinephrine uptake, and/or (3) its virtual lack of direct effects on pre- and postsynaptic 5-HT mechanisms.[71] Nearly 10 years of postmarketing clinical experience has shown that most depressed patients experience bupropion as either a nonsedating or mildly alerting compound. Moreover, package insert data indicates that treatment-emergent insomnia is reported by approximately 5% more patients treated with either immediate release or sustained release formulations than placebo (reference 72 and package insert for Wellbutrin SR [bupropion SR]). These effects are fully consistent with bupropion's activating effect on waking EEG rhythms.[71]

To date, only one published study[63] has examined the effects of bupropion on all-night EEG sleep patterns. As summarized in Table 2, Nofzinger et al.[63] found that treatment of depressed men with bupropion (N = 7 responders) at an average dose of nearly 430 mg/day produced an unexpected improvement of sleep efficiency (i.e., a 6% increase, resulting in about 31 additional minutes of sleep per night), without altering sleep latency. Fluoxetine treat-

Figure 4. Differential Effects of Fluoxetine (N = 11) Treatment and Bupropion (N = 7) Treatment on REM Latency and Delta Sleep Ratio of Depressed Men*



*Adapted from Nofzinger et al.[63] The mean values (± standard deviation) of healthy men (N = 36) are represented by the area between the horizontal dashes.

ment (N = 11 responders), by contrast, resulted in improved sleep latency but no change in sleep efficiency. Bupropion treatment resulted in decreased slow-wave sleep, whereas fluoxetine increased the computer-scored delta sleep ratio, values that were decreased significantly with bupropion treatment. Similarly, fluoxetine prolonged REM latency, whereas bupropion treatment was associated with a significant reduction of REM latency and increased REM percent. Both antidepressants increased phasic REM activity. When compared with profiles in healthy normal control men, posttreatment sleep profiles of the antidepressant responders were strikingly divergent on two measures: REM latency and delta sleep ratio (Figure 4). If these variables are presumed to be state-independent markers of vulnerability to depressive hyperarousal, fluoxetine and bupropion might yield diametrically opposed results, with the former dampening responses and the latter activating responses.

Only men were studied by Nofzinger et al.[63] because the primary aim of that study was to evaluate differential effects of various treatments of depression on libido, waking sexual function, and nocturnal penile tumescence. Unlike imipramine and, to a lesser extent, fluoxetine, treatment with bupropion did not suppress nocturnal penile tumescence, nor did it affect the rigidity of nocturnal erections.[73] Bupropion did not enhance nocturnal penile tumescence, however, even among patients experiencing the largest increases in REM sleep. Bupropion treatment did have effects on patients' self-ratings of sexual satisfaction.[73] The central nervous system effects of bupropion that enhance tonic REM sleep, mood, and libido thus appear to be distinct from those that mediate nocturnal penile tumescence.

The effects of bupropion on sleep are unlike those of any other treatment studied in our sleep laboratory, including TCAs, SSRIs, MAOIs, ECT, sleep deprivation, and several depression-specific psychotherapies. We had expected that an agent that enhances central noradrenergic and dopaminergic neurotransmission would worsen sleep efficiency and suppress or fractionate REM sleep.[8] On the basis of prior studies of TCAs, MAOIs, and SSRIs, we had also expected a prolongation of the first NREM interval, instead of the nearly 20% reduction in REM latency and the large decrease in delta activity in the first, relative to the second, NREM period. Based on these effects, it is possible that bupropion possesses unique therapeutic effects for hypersomnolent patients, particularly those with more normal slow-wave sleep and REM profiles. REM sleep enhancement also may help to explain why some depressed patients with comorbid panic or posttraumatic stress disorder have difficulty tolerating bupropion. These interesting leads warrant further study in larger groups of depressed patients, particularly comparing response in relation to pretreatment sleep characteristics.

CONCLUSIONS

Sleep disturbances are an important feature of depression and help to characterize this heterogeneous group of disorders. The clinical sleep disturbances associated with depression have distinct electrophysiologic parallels, which are linked to alterations of neurochemistry and regional brain metabolism. Such dysregulated neurophysiology may be divided into trait-like and state-dependent abnormalities that point to either more persistent vulnerabilities (e.g., deficits of slow-wave sleep) or severity-linked, state-dependent processes (e.g., sleep continuity disturbance and increased phasic REM sleep). These types of biological dysfunction are most common in melancholia. Alternate mechanisms must be invoked to explain hypersomnolence, which is common in early-onset depressive disorders, including many cases of seasonal and bipolar depression.

Antidepressants exert both beneficial and, at times, detrimental effects on subjective and objective measures of sleep. Although most antidepressants suppress REM sleep, this effect is neither necessary nor sufficient for therapeutic response. Among the wide range of antidepressant compounds now available, the aminoketone compound bupropion may have a unique effect on sleep neurophysiology. Bupropion has modest, activating clinical effects, yet it improved patients' sleep efficiency. Bupropion also is the only antidepressant identified to date that enhances REM sleep. Moreover, bupropion has no effect on nocturnal penile tumescence, and it enhanced the waking sexual function of depressed men.[73] As a result of its

novel structure and unique effects on sleep neurophysiology, bupropion should not be overlooked as an alternative to the SSRIs, and it may prove to be a treatment of first choice for hypersomnolent depressed patients.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), clomipramine (Anafranil), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), imipramine (Tofranil), nefazodone (Serzone), nortriptyline (Pamelor and others), protriptyline (Vivactil), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil).

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