Sleep and Depression

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Background: Of all the psychiatric disorders associated with insomnia, depression is the most common. It has been estimated that 90% of patients with depression complain about sleep quality. Since the first reports of short rapid eye movement (REM) latency in depressed patients and of the effect of sleep deprivation on depression in the 1970s, numerous sleep studies have provided extensive observations and theoretical hypotheses concerning the etiology and pathophysiology of depression. The aim of this review is to summarize knowledge regarding the relationships between sleep and depression.

Data Sources and Selection: MEDLINE and PsycINFO searches of the literature published in English or French between 1964 and 2005 that examined the relationships between sleep disturbance and depression were conducted. Search terms used were *depression, depressive disorder, affective disorder, mood disorders, seasonal affective disorder, sleep, sleep disorders, insomnia, REM, polysomnography, sleep deprivation, electroencephalography, PET, SPECT*, and *fMRI*.

Data Synthesis: Two hundred five papers were identified and selected and then integrated into the following categories: sleep architecture, antidepressive therapies, age- and gender-associated differences, functional imaging results, and sleep-related hypotheses explaining the pathophysiology of depression.

Conclusion: Numerous studies provide findings indicating the remarkable relationship between sleep alterations and depression. Although the existing hypotheses are not likely to explain all aspects of the sleep alterations in depression, each may be worth being maintained for refinements of pathophysiologic models of depression as new data accumulate. Further research taking into account the heterogeneity of depressive disorder and linking the different areas of research is needed to develop more comprehensive theoretical models and new therapies for depression.

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Sleep disturbances are a neurologic feature of many psychiatric disorders. However, both clinical and theoretical research has focused on the relationship between sleep disturbance and depression first due to their high rates of co-occurrence, and more recently because studies of sleep disorder have contributed to our knowledge of the underlying physiology of depressive disorders. With regard to comorbidity, epidemiologic studies estimate that complaints of poor sleep quality are observed in between 50% and 90% of subjects with diagnosed depression.[1–4] Furthermore, about 20% of subjects complaining of insomnia screened in general population studies have been classified as depressed, and of all cases of psychiatric disorder with insomnia, depression is consistently the most frequent disorder.[5–7]

The lifetime prevalence of depression has been estimated at around 16% with recurrence rates after 1, 2, and 3 prior episodes of depression of 50%, 70%, and 90%, respectively.[8,9] Recurrent episodes of depression tend to become more severe, with shorter remission between each new episode. Moreover, each new depressive episode may increase risks of chronicity or treatment resistance.[8,10,11] The prediction and prevention of new episodes or relapses of depression are thus of considerable clinical importance.[12,13] In spite of methodological differences, several studies have consistently demonstrated that sleep disturbance is one of the most important predictors of a new or remitting depressive episode.[4,14–16] It is also known that a stable sleep-wake rhythm and adequate sleep hygiene are essential in the prevention of relapse in remitted depressed patients.[17,18]

In the absence of reliable and specific biological markers, the clinical diagnosis of depression is essentially based on symptom counts, with corresponding symptomatic treatment. In the early 1970s, abnormalities of rapid

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eye movement (REM) sleep were first proposed as a potential biological marker of depression. Although subsequent research did not confirm this assumption, the biological relationship between sleep disturbance and depression has attracted considerable interest as a means of elucidating the underlying pathophysiology of depression. For example, although patients with depression generally complain of insomnia, a single night of sleep deprivation induces rapid and dramatic improvement of mood in about 60% of all depressed patients, independent of diagnostic subgroup.[19] Pharmacologic research continues to produce increasingly effective antidepressive drugs; however, sleep deprivation is still the only intervention in depression that shows antidepressant effect within 24 hours.[20,21] Pathophysiologic models of the etiology of depression are currently principally based on pharmacologic findings, while the mechanism of action of the antidepressant effect of sleep deprivation is still poorly understood. Sleep indicators, along with neuroendocrine and neurochemical measures, are now becoming of increasing interest in the search for biological markers for all affective disorders. This review examines the present knowledge of sleep changes in depression, discusses the contribution of this information to our understanding of the etiology of depression, and finally considers the current potential of sleep indicators as potential markers for the screening and clinical monitoring of depression.

DATA SOURCES AND SELECTION

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CHANGES IN SLEEP ARCHITECTURE AND DEPRESSION

Differential Diagnostic Value of Sleep Measures for Depression

Since the early (late 1960s and early 1970s) work of Kupfer and colleagues[1,22] formalizing polysomnographic procedures for research in depression, the sleep electroencephalogram (EEG) has provided important information about depression. Polysomnographic sleep research has shown in particular that alterations of sleep architecture in depression are characterized by an impaired sleep efficiency, a reduction of slow-wave sleep, and a disinhibition of REM sleep, manifested by a shortening of REM sleep latency, a prolongation of the first REM period, and an increased number of eye movements during REM periods (increased REM density)[1,22] (Table 1).

Table 1. Alterations of Sleep Architecture in Depression

Impaired sleep continuity and duration
Decreased deep sleep (sleep stages 3 and 4)
Reduction of slow-wave sleep
Decreased REM sleep latency
Shortening of the interval between sleep onset and the occurrence of the first REM period, to 20–30 minutes of 90 minutes in normal subjects (ie, short REM sleep latency)
Increase in the proportion of REM sleep in the early part of the night
Increased amount of REM sleep
Prolongation of the first REM period
Increased number of eye movements during REM period (REM density)

Abbreviation: REM = rapid eye movement.

The most significant alteration in sleep during depressive episodes is the shortening of the time from sleep onset to the beginning of the first REM period, i.e., short REM latency. Initially, short REM latency was postulated to be a psychobiological marker for "primary" depression,[23] as primary depression (that is, depressive episodes that are not secondary to other psychiatric or physical disorders) showed significantly shorter REM latency than "secondary" depression (mean = 39 vs. 71 minutes). Numerous studies have subsequently tried to confirm the differential diagnostic value of short REM latency for depression and other mood disorders, but it currently seems unlikely that a short REM latency is specific to a subtype of depression. A reanalysis of the original data by the same group[24] did not confirm the original assumption, REM latency for secondary depression (mean = 46.6 minutes) being found to be well within the range seen in samples with primary depression (mean = 46.8 minutes). The authors suggested that the discrepancy in their studies might be attributable to the clinical heterogeneity of secondary depression. Table 2 summarizes studies comparing sleep in patients with primary/endogenous depression and patients with secondary/nonendogenous depression. Other studies have reported that short REM latency is also observed in patients with other psychiatric disorders.[25–27]

A reduction in slow-wave sleep has also been described in anxiety disorders,[205] schizophrenia,[26,28] and PTSD.[27] On the other hand, Lauer et al.[29] reported that depressed patients showed lower amounts of slow-wave sleep compared to patients with panic disorder. The application of computerized analysis to sleep research in depression in the 1980s has enabled the quantification of sleep measures, especially of stages 2, 3, and 4 slow-wave activity, which is difficult to detect visually.[30–32] Studies using computerized techniques for quantifying EEG results

Table 2. Comparison Between Primary/Endogenous Depression (PD) and Secondary/Nonendogenous Depression (SD): Overview of the Literature

Study	Sample Characteristics	Subject Number		Slow-Wave Sleep	REM Sleep	
		PD	SD		REM Latency	REM Density
Kupfer, 1976[23]	PD consisted of unipolar and bipolar type; 3 SDs with drug-abuse states	18	11	No difference	Shortened in PD	No data
Kupfer et al, 1978[194]	17 PDs with psychotic features; 18 SDs with concurrent medical disease; 66 inpatients and 29 outpatients	47	48	No data	Shortened in PD	Increased in PD
Akiskal et al, 1982[195]	Outpatients diagnosed by Modified Feighner (St Louis) diagnoses	49	19	No data	Shortened in PD	No data
Berger et al, 1982[196]	Hospitalized patients	20	19	No difference	No difference	No data
Rush et al, 1982[197]	Unipolar type according to Research Diagnostic Criteria; age matched	32	38	No difference	Shortened in PD	No difference
Thase et al, 1984[24]	Unipolar type according to Research Diagnostic Criteria; hospitalized patients	23	23	No difference	No difference	No difference
Giles et al, 1986[198]	Unipolar type according to Research Diagnostic Criteria; age matched	49	19	No data	Shortened in PD	No data
Giles et al, 1987[199]	Unipolar type according to Research Diagnostic Criteria; age matched	88	15	No data	Shortened in PD	No difference
Kerkhofs et al, 1988[200]	Hospitalized patients; age matched	127	26	Decreased in PD	Shortened in PD	No data
Riemann et al, 1994[201]	Patients with major depressive disorder diagnosed by DSM-III	113	65	No difference	No difference	No difference
Hubain et al, 1996[202]	Depression diagnosed by Research Diagnostic Criteria; endogenous or nonendogenous defined by Newcastle Endogenous Depression Diagnostic Index	155	155	No difference	No difference	No data

Abbreviation: REM = rapid eye movement.

have suggested that a reduction of delta wave production (0.5–4 Hz), particularly during the first period of non-REM sleep, is commonly observed in depression and that slow-wave activity is strongly associated with severity of depressive symptoms.[4,32,33]

Moreover, recent work based on computer analysis of sleep EEG frequencies and the relationship among sleep EEG rhythms has indicated that measures of all-night delta EEG activity have consistently shown an abnormal distribution of delta activity in non-REM sleep in those with depression.[34,35] Armitage et al.[36,37] investigated 90-minute sleep EEG rhythms between the 2 hemispheres (interhemispheric coherence) and between frequency bands within a hemisphere (intrahemispheric coherence). Their studies showed significantly lower interhemispheric and intrahemispheric coherence in patients with major depressive disorder, primarily in women. On the other hand, depressed men are more likely to show reduced slow-wave or delta activity, particularly in the first non-REM sleep period[38] (see also the section "Age, Gender, and Sleep Parameters in Depression").

Short REM sleep latency and reduced slow-wave sleep appear to be insufficient as single and specific sleep measures of depression; however, the combination of sleep measure abnormalities might have greater predictive validity. A meta-analysis[39] of 177 studies with data from over 7000 patients and controls has concluded that most psychiatric patient groups show significantly reduced sleep efficiency and total sleep time, accounted for by decrements in non-REM sleep. Reduction in REM sleep latency was seen in affective disorders but occurred in other categories as well. Although no single sleep variable appeared to have absolute specificity for any particular psychiatric disorder, patterns of sleep disturbances associated with categories of psychiatric illnesses were observed. The authors concluded that findings of overall sleep patterns for patients with affective disorders differed most frequently and significantly from those for normal controls.

Sleep Abnormalities as "State-Dependent" or "Vulnerability" Markers of Depression

A central question is whether sleep abnormalities of patients with depression are "state-dependent" or "trait" markers. State-dependent abnormalities reflect transient neurobiological processes underlying an acute episode, whereas trait or vulnerability markers suggest increased risk for occurrence or relapse linked to genetic transmission of the disorder. Some researchers have described a tendency for REM sleep abnormalities to normalize with remission after successful treatment.[40,41] These polysomnographic studies have, however, mostly included patients treated with pharmacotherapy that independently affects polysomnographic recordings. Some researchers have overcome this problem by using nonpharmacologic treatment such as cognitive-behavioral therapy. Nofzinger et al.[42] reported the intensity of daytime affect in depressed patients receiving cognitive-behavioral therapy correlated significantly and positively with phasic REM sleep measures at both pretreatment and posttreatment. Thase et al.[43] indicated that reduced REM sleep latency, decreased delta

sleep ratio (the ratio of first non-REM sleep period to second in delta wave intensity), and decreased slow-wave sleep were stable across time whereas sleep efficiency and REM density improved significantly with remission, although a minority of patients in remission had persistent abnormalities. These results suggest that patients with a low risk of relapse after a depressive episode normalize their sleep, whereas patients more prone to relapse continuously exhibit sleep abnormalities.

Several studies[44–46] have shown that the "depression-like" polysomnographic changes are not state-dependent and persist during remission. Giles and colleagues[47] found the persistence of shortened REM latencies during remission to be associated with an increased risk for relapse, and longitudinal studies[45,48] have shown REM sleep latency to be stable within individuals over time. Kupfer et al.[49] reported that depressive patients with lower amounts of delta sleep showed more rapid and more frequent recurrences compared to those with higher delta ratios. Although the follow-up periods in these studies may be too short (6–24 months), these findings suggest a "trait" or "vulnerability" characteristic of at least some of the polysomnographic alterations in patients with depression.

Sleep Abnormalities and Family History of Depression

REM disinhibition and slow-wave sleep reduction may represent familial risk factors for depression. Lauer and coworkers,[50] investigating 54 high-risk probands by polysomnography, found that the polysomnographic patterns of subjects without a personal history but with a strong family history of depression showed reduced slow-wave sleep and increased REM density in the first sleep cycle compared with those of control subjects with no personal history or family history of psychiatric disorders. Giles et al.[51] reported that lifetime risk of depression was almost twice as high in relatives of depressed probands with short REM latency as in relatives of depressed probands with normal REM latency. In a more recent study, Modell et al.[52] have further suggested that decreased slow-wave sleep during the first sleep cycle and increased REM density index of the first REM period may constitute potent vulnerability markers.

Among patients with depression, about 30% to 50% of outpatients and 50% to 80% of hospitalized patients exhibit short REM latency, compared with rates of around 20% in healthy adults.[51,53] Since not all depressed patients have short REM latency, and many healthy people do, the trait cannot be used to diagnose depression. However, in families in which depression has been identified, it might constitute an indicator of vulnerability in other family members.

Hypersomnia and Depression

Hypersomnia in depression. About 16% to 20% of patients with depression exhibit hypersomnia.[14,54,55] However, there are few studies that document polysomnographic findings in depressive patients with hypersomnia. Three studies objectively investigated sleep throughout 24 hours. Shimizu et al.,[56] using 24-hour polysomnographic recordings, reported that 6 depressed patients with hypersomnia showed shorter sleep latency and longer total sleep time compared with the control subjects. In contrast, Nofzinger et al.,[57] performing a multiple sleep latency test (MSLT) to evaluate hypersomnia, reported that no abnormalities were noted for depressed patients with hypersomnia. They suggested that hypersomnia in depressive patients, unlike hypersomnia in patients with narcolepsy or other organic forms of hypersomnia, is a subjective complaint more than an objective finding. MSLT provides an assessment of the degree of sleepiness at a given moment and ultimately an evaluation of circadian variations in sleepiness. However, these tests are not suitable for investigating certain disorders in which the main symptom is the lengthening of nocturnal sleep time, such as idiopathic hypersomnia. Billiard et al.[58] used MSLT and 24-hour polysomnography in an investigation of 36 mood disorder patients suffering from hypersomnia. In comparison with patients with idiopathic hypersomnia, mean sleep latency was significantly longer and total sleep time was significantly shorter in patients with mood disorder.

Several possibilities may explain the inconsistency of these findings. Idiopathic hypersomnia no doubt represents a pure form of hypersomnia, while hypersomnia in depression is difficult to quantify and to evaluate with the appropriate equipment necessary to rule out other causes of hypersomnia associated with the complaint. For example, complaints of hypersomnia in depressive patients often involve excessive daytime sleepiness. Many assessment tools for daytime sleepiness have been developed; however, they show little agreement, because tools for assessing sleepiness are often operationalizations reflecting the theoretical framework the investigator has on sleepiness. Another possible reason for the inconsistency of the findings may be the heterogeneity of subjects among these studies. Depressive patients in the above-mentioned 3 studies had several subtypes of mood disorder. Patients in Nofzinger's study[57] all had bipolar disorders. However, in Billiard's study,[58] 31 patients with dysthymia and 1 with manic state were included in the evaluation, and in Shimizu's study,[56] 2 patients with bipolar and 4 with unipolar depression were included.

Hypersomnia in seasonal affective disorder. A complaint of hypersomnia is not typical for depression and is probably principally related to subtypes of depression such as seasonal affective disorder (SAD) or atypical depression.[59,60] Several clinical studies[61–63] showed that patients with SAD reported more hypersomnia than patients with nonseasonal mood disorders. On the other hand, some polysomnographic studies[64,65] demonstrated that the

lengths of sleep times seen in patients with SAD do not differ greatly from those in the general population. It has been reported that SAD was not associated with the typical sleep patterns of major depressive disorder and that patients with SAD had significantly longer non-REM episodes and greater slow-wave activity during non-REM sleep compared with healthy controls.[64–67]

In SAD, there is sufficient research evidence to support the efficacy of bright light therapy.[68] Most studies show bright light to be more effective when administered in the morning than in the evening.[69,70] This finding supports the hypothesis that SAD sufferers have circadian phase delay, with bright morning light effecting a phase advance that is thought to be the key to the efficacy of light therapy.[71] Melatonin has been used as a marker for the phase and period of the endogenous circadian pacemaker. On the basis of the observation that light can suppress nocturnal pineal melatonin secretion, melatonin has also been investigated as a treatment for SAD. However, research findings of the validity of melatonin treatment are conflicting. Wirz-Justice et al.[72] reported that a 5-mg dose of melatonin given in the morning or the evening was not effective against SAD. In contrast, preliminary studies by Lewy et al.[73] indicated that smaller and more physiologic doses of melatonin, when appropriately timed to achieve a circadian phase advance, had therapeutic effects in SAD.

SAD and atypical depression, which include hypersomnia as a characteristic symptom, are listed as specifiers of major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV).[74] However, the current definition and modeling of SAD and atypical depression appear problematic.[55,75] The *International Classification of Diseases,* Tenth Revision (ICD-10)[76] gives only provisional diagnostic criteria for SAD on the grounds that its status is uncertain. Further research is needed on homogeneous clinical groups to elucidate the relationship between hypersomnia and depression.

ANTIDEPRESSIVE THERAPIES AND SLEEP

Sleep Deprivation

One of the most striking links between depression and sleep regulation has been the observation that depressive symptoms are acutely alleviated by 1 night of sleep deprivation and that the initial symptoms reoccur after 1 night of recovery sleep.[77] Total sleep deprivation for a whole night improves the symptoms of approximately 50% to 60% of all depressive patients and is the only known intervention in depression that has proven antidepressant benefits within 24 hours.[20,21] Furthermore, gender, age, number of hospitalizations, earlier treatments, duration of the episode, and severity of depression do not appear consistently related to responsiveness to sleep deprivation.[19]

Variants of total sleep deprivation have been developed for therapeutic intervention on the basis of observed characteristic sleep disturbances in depression. Because of the changing direction in circadian rhythm of several bodily functions, Schilgen et al.[78] assumed that staying awake in the early morning should be the central target for maximizing the therapeutic efficacy of total sleep deprivation and that it should therefore be sufficient to restrict therapeutic sleep deprivation to this time. They reported that late partial sleep deprivation was as effective as total sleep deprivation. However, a more recent study did not support this finding and concluded that total sleep deprivation was indeed more effective than partial sleep deprivation.[79]

Almost all antidepressant compounds inhibit REM sleep.[80] On the basis of the observation of REM sleep suppression by antidepressants, a few studies[19,81,82] have attempted to confirm whether this pharmacologic effect is a sine qua non or the underlying mechanism of antidepressant action by using selective deprivation of REM sleep. Vogel[83] reported that selective REM sleep deprivation showed an antidepressant treatment response comparable to that of imipramine, and Grozinger et al.[84] subsequently attempted to reproduce this observation with a more sophisticated research design. In the latter study, both selective REM sleep deprivation and non-REM sleep deprivation groups responded to the treatment. However, it was observed that non-REM sleep deprivation exhibited a significantly stronger antidepressant effect.[84] In that study, while the REM sleep awakenings shortened the sleep cycle considerably, the non-REM intervention paradigm lengthened the ultradian alternations. The authors speculated that both effects might be interpreted as a challenge imposed on the non-REM–REM alternating mechanism possibly responsible for the antidepressive impact. Moreover, it has been found that not all antidepressants are associated with REM sleep suppression[4,80,95,96] (see also the section "The Effect of Antidepressants on Sleep").

Taken together, these results cast doubt on the equivalence of selective REM sleep deprivation and partial/total sleep deprivation. There is a growing body of evidence which now suggests that the amount of sleep is probably more important than the kind of sleep in terms of therapeutic effect and that REM and non-REM sleep are partially interchangeable.[85] It is important to note, however, that this type of transient relapse characteristic of treatment with sleep therapies does not usually occur in pharmacologic antidepressant treatment. The acute and transient therapeutic response to sleep deprivation would thus appear to be mediated by mechanisms other than those involved in the more gradual improvement obtained with antidepressants.

Several techniques have been used to try to prevent the high-rate, short-term symptomatologic relapse in the first days after sleep deprivation. Although antidepressant

medication has little influence on rate of response to a single night of sleep deprivation, it may increase the susceptibility to multiple nights of sleep deprivation.[86] Smeraldi et al.[87] investigated 40 bipolar depressed patients who were randomly assigned to receive the 5-HT_{1A}–β-blocker pindolol or placebo in combination with 3 consecutive total sleep deprivation cycles. Coadministration of pindolol and sleep deprivation resulted in a complete response, which could be sustained for 6 months with lithium salts alone in 65% of cases.[87] Early studies[88,89] of sleep deprivation and light therapy also indicated that bright light therapy during sleep deprivation could lead to a more prolonged improvement in responders. Colombo et al.[90] showed that, in bipolar depressed inpatients, a half-hour exposure to a 2500-lux light during sleep deprivation and in the morning after a recovery night was shown to enhance and sustain mood improvement caused by sleep deprivation. The same group[91] recently showed that a functional polymorphism within the promoter of the serotonin transporter gene that is associated with a better response to fluvoxamine and paroxetine was also associated with a differential effect of combined sleep deprivation and light treatment on bipolar depressed patients. The authors suggest that the mechanism of action of combined sleep deprivation and light therapy may involve an enhancement of serotonergic function as a mechanism of antidepressant action.

Some studies[21,92] using functional imaging techniques such as single photon emission computed tomography or positron emission tomography (PET) have consistently shown a hyperperfusion or enhanced glucose metabolism in limbic areas of the brain at baseline in responders, but not in nonresponders, to sleep deprivation. In addition, these neuroimaging studies have found that the hyperactivity in the limbic areas prior to sleep deprivation is normalized after sleep deprivation in depressive patients who respond to treatment.

Effect of Antidepressants on Sleep

Almost all antidepressants have been shown to be associated with modifications in sleep architecture,[80] notably delayed onset of REM sleep, reduced amount of REM sleep, and increased slow-wave sleep.[93] Suppression of REM sleep with antidepressant medication has been consistently observed. Vogel et al.[94] reported a significant correlation between the improvement of depressive symptoms and REM sleep suppression in a study using selective REM sleep deprivation (see also the section "Sleep Deprivation"). These studies supported the hypothesis that suppression of REM sleep was necessary if an antidepressant effect were to be obtained. The suppression of REM sleep appears, however, to be specific to classical tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine), the tetracyclic substance mianserin, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, and the monoamine oxidase inhibitor (MAOI) phenelzine.[4] However, some studies[4,80,95,96] have suggested that not all antidepressants show REM sleep suppression (trimipramine, trazodone) and that even atypical antidepressants such as nefazodone or moclobemide may increase REM sleep. A study[97] has also reported that antidepressant response to phenelzine does not depend on elimination of REM sleep. A temporal discordance between suppression of REM sleep and clinical response to antidepressants has also been observed. Clomipramine produces immediate suppression of REM sleep, whereas the clinical improvement is only seen about 10 days later.[203] On the other hand, although suppression of REM sleep by MAOIs takes much more time than that by clomipramine (about 10 days), it coincides temporally with clinical improvement.[203,204]

Almost all antidepressants (excluding those cited above) appear to influence REM latency consistently, whereas the influence of antidepressants on non-REM sleep is less evident and less consistent.[98] For example, some antidepressants are observed to increase slow-wave sleep (e.g., tricyclic antidepressants such as amitriptyline and trimipramine), while others decrease it (e.g., SSRIs such as fluoxetine and paroxetine).[95] There are very few reports of the therapeutic significance of changes in non-REM sleep, and most medication trials have been 6 to 8 weeks, not long enough for most patients to achieve remission. One study has examined the long-term effects of imipramine on polysomnography in 27 subjects who completed 3 years of maintenance treatment with imipramine without experiencing a recurrence.[99] In this study, a rapid redistribution of slow-wave sleep in the first part of the night was observed without an increase in the total amount of slow-wave sleep throughout the night. The application of spectral analysis confirmed that the sleep changes following drug administration remained stable throughout all phases of drug treatment. Another recent study[100] suggests that the power spectrum in the higher sigma frequency range (14–16 Hz) of non-REM sleep decreased significantly in males who responded to treatment, but not in male nonresponders or female patients, independently of the type of medication. The authors emphasize the importance of taking gender into account in the study of the biological effects of drugs.

In research examining the effect of drugs on polysomnography, several factors complicate evaluation of the scoring of non-REM–REM sleep cycles. Some antidepressants cause a "dissociation" among the characteristics that define a sleep stage.[101,102] *Dissociation* refers to the simultaneous occurrence of apparently incompatible features. In spite of REM sleep suppression by antidepressants, REM periods episodically recur at the end of the night. During these periods, the muscle tone remained, and the EEG activities and electrooculogram findings were those of REM sleep.[101,102] These periods

occur at the end of the night from 4 to 6 hours after the onset of sleep and can be organized in cycles of various number and duration; this type of sleep is known as dissociated REM sleep. The duration and eye movement density observed in this particular sleep stage are lower than those observed in REM sleep at baseline.[102] The REM dissociation makes it difficult to score REM sleep. In other words, it is almost impossible to evaluate the quantitative scoring of REM sleep in subjects prescribed antidepressants. Moreover, fluoxetine enhances both eye movements and muscle tone during sleep.[103] Clinically significant periodic limb movement disorder is also often observed in fluoxetine-treated depressed patients.[104] Most antidepressants, including SSRIs, as mentioned above, may interfere with the occurrence of sleep stage and therefore may affect the scoring of that particular stage. These drug effects may explain the discordance of findings concerning antidepressant effects between medications and sleep deprivation.

In summary, because the majority of antidepressants, irrespective of their chemical classes, suppress REM sleep, it has been hypothesized that REM sleep suppression is a key mechanism underlying treatment response.[82,83] However, as the above-mentioned studies demonstrate, no clear relationship between clinical change and REM sleep characteristics has been demonstrated. Antidepressant effects are not restricted to REM sleep and also include alterations in sleep architecture that may be relevant to both clinical response and the need for concomitant or augmentative treatment. It appears that the mechanism of action of antidepressants does not necessarily depend on REM sleep suppression.

AGE, GENDER, AND SLEEP PARAMETERS IN DEPRESSION

Age-related changes in sleep in healthy humans are well documented. These changes include a reduction of sleep continuity and slow-wave sleep, early morning awakening, and a shortening of REM sleep latency.[105,106] Aging effects on sleep patterns in depression have consistently been evidenced by some studies.[107–110] These studies conclude that REM sleep latency becomes progressively shorter and that both sleep efficiency and slow-wave sleep decrease progressively with aging. However, the significant differences in these parameters between depressive patients and age-matched controls in childhood or adolescence and old age are somewhat ambiguous.[4,13,111] Well-controlled studies of adolescent cohorts with depression have shown relatively few polysomnographic changes.[112] Lauer et al.[110] have shown that there is no difference in REM sleep latency between depressed patients and controls until the middle of the fourth decade of life. Similarly, elderly patients with depression do not tend to show significant differences in their sleep patterns as compared with age-matched controls.[106] One possibility is that, due to the age-related decline in sleep variables such as slow-wave sleep, elderly patients have less to lose. It is also possible that depression in the very young and the very old has a different etiopathogenesis than in midlife. For example, Giles et al.[113] have suggested that family history of affective disorder may play a decisive role, especially in young patients with depression, and that only depressed children and adolescents with an affective family "loading" display the typical features of sleep disturbance associated with depression.

More recently, a number of studies have indicated that the influence of age on sleep varies as a function of gender.[38,100] Gender differences exist in the polysomnography of depressed patients under baseline conditions as a higher incidence of delta activity, more delta and beta activity of a higher amplitude, and power of the delta- and sigma-frequency ranges in women.[114,115] These findings provide further evidence that the pathophysiology of depression differs between men and women and suggest that sleep studies should evaluate gender differences statistically in their samples.

FUNCTIONAL IMAGING STUDIES

In the past decade, functional imaging methods have emerged as powerful tools for neuroanatomical investigations in humans. The functional neuroanatomy of sleep has been recently explored with PET. Examination of the regional cerebral blood flow distribution as an index of neuronal activity revealed that the intense and widespread cortical activation observed during sleep was not uniform.[116–121] In healthy subjects, the functional neuroanatomy of slow-wave sleep is characterized by low cerebral blood flow in central core structures (brain stem, thalamus, basal forebrain), in basal ganglia and cerebellum, and in some cortical areas (frontal, parietal, mesiotemporal).[116–118] During REM sleep in normal subjects, significant activations were found in the pontine tegmentum, thalamic nuclei, limbic areas (amygdaloid complexes, hippocampal formation, anterior cingulate cortex), and posterior cortices (temporo-occipital areas). In contrast, the dorsolateral prefrontal cortex and parietal cortex, as well as the posterior cingulate cortex and precuneus, were seen to be the least active brain regions.[119–121] Ho et al.[122] examined the non-REM period using PET in 10 patients with depression and 12 controls. They found that, on relative measures of cerebral glucose metabolism, depressed patients exhibited hypometabolism compared with controls in the medial orbital prefrontal cortex, anterior cingulate, and basal ganglia. They concluded that these findings of a hypofrontality pattern support a hyperarousal hypothesis of depression.

Nofzinger et al.[123] have more recently shown that, while both healthy and depressed groups show activation in the

anterior paralimbic structures from waking to REM sleep, the spatial extent of this activation is greater in depressed patients. Additionally, depressed patients showed relatively greater activation in bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, as well as in the midbrain reticular formation. The authors suggest that altered function of limbic/anterior paralimbic and prefrontal circuits in depression is accentuated during the REM sleep state and that the characteristic sleep disturbance of depression may reflect this dysregulation. Nofzinger's group[124] also investigated the functional neuroanatomical correlates between REM and cerebral metabolic rate during REM sleep in depressed subjects. REM density positively correlated with relative regional cerebral metabolic rate bilaterally in the striate cortex, the posterior parietal cortices, and the medial and ventrolateral prefrontal cortices. REM density was negatively correlated with relative regional cerebral metabolic rate in areas corresponding bilaterally to the lateral occipital cortex, cuneus, temporal cortices, and parahippocampal gyri. The authors assumed that, since temporal and occipital cortices showed hypermetabolism during REM sleep in depressed patients compared with healthy controls, REM density might be an indirect correlate of metabolic activity in these areas. They suggested that the observed pattern might be a marker of hypofrontality during REM sleep in depression.

Taken together, these findings indicate that the neuronal processes underlying sleep differ between brain regions and share some similarities compared with previously reported findings in healthy subjects using regional cerebral blood flow indicators. A hypofrontality pattern of cortical activation has also been observed in healthy subjects during REM sleep[121] and in schizophrenia patients.[125] The hyperarousal hypothesis has in fact often been evoked in relation to other psychiatric disorders such as PTSD[126] and schizophrenia.[127] Comparisons between the sleep of patients with depression and patients with other psychiatric disorders are crucial for determining the extent to which the activation of the brain region observed is specific to depression or characteristic of psychiatric disorder in general. It would also be valuable to include in future research relevant findings from functional neuroimaging studies that have explored effects related to sleep deprivation, cognition, pharmacology, and particular sleep disturbances such as primary insomnia and hypersomnia.

PATHOPHYSIOLOGY OF SLEEP DISTURBANCE IN DEPRESSION

Several hypotheses have been advanced to explain the underlying pathophysiology of depression, taking into account the numerous observations of sleep changes in depression.

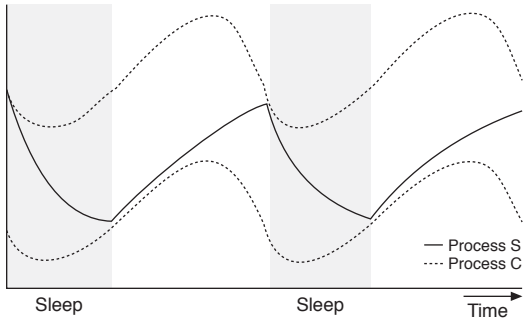
Neuroendocrine Abnormalities

Elevated levels of cortisol and adrenocorticotropic hormone (ACTH) in around half of all depressive patients have been consistently observed for over a quarter of a century.[128] Most sleep-endocrine studies have reported elevated cortisol and ACTH levels in depressive patients throughout the night or 24-hour cycle.[129,130] The findings of dexamethasone suppression and corticotropin-releasing hormone (CRH) challenge testing, although insufficient as diagnostic tools, have indicated the possible role of an adrenocortex hypersensitivity in depression resulting from persistent exposure to high levels of ACTH.[131,132] These findings have been interpreted as indicating an overactivity of the hypothalamic-pituitary-adrenocortical (HPA) system.

This raises the interesting question of whether abnormal endocrine functioning and sleep abnormalities are related or even causally linked to each other. Slow-wave sleep onset is a powerful physiologic stimulus for growth hormone (GH) secretion.[133] Much of the disturbance in the polysomnography of depressed patients occurs within the first half of the night, the time when GH is usually secreted, and some researchers have suggested blunted sleep-related GH release in patients with depression.[46,134] Ehlers and Kupfer[135] assumed a deficient release of sleep-promoting growth hormone–releasing hormone (GHRH) and an increased output of sleep-impairing CRH in accordance with the assumption that an "overdrive" of CRH plays a key role in depression. They have also suggested that the GHRH/CRH ratio may be an indicator of the strength of the process "S."[135] Steiger et al.[46] conducted a sleep-endocrine evaluation study among unmedicated patients with depression during their depressive episode and following full clinical remission and drug withdrawal. This study concluded that while abnormally high values for cortisol secretory activity normalized after remission, low GH release and polysomnographic abnormalities remained unchanged.[46] Other studies also reported the persistence of most polysomnographic changes,[136] and GH changes after recovery have been confirmed over a period of 3 years.[134] Cortisol levels normalized independently from changes in sleep architecture.[128] These findings suggest that elevated cortisol levels, resulting from HPA overactivity, are state markers in patients with depression, whereas blunted GH release is a trait marker that persists after remission.[128]

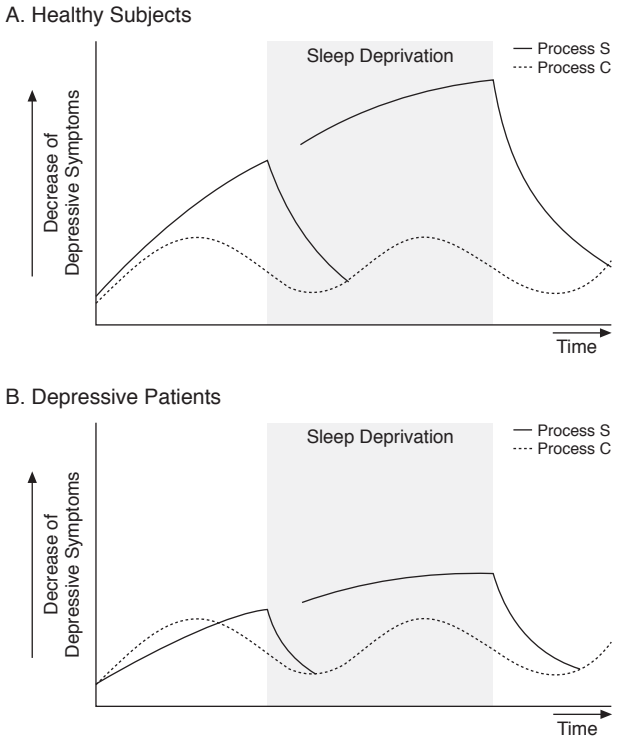
Several studies examining the influence of sleep deprivation on the HPA axis in healthy subjects have shown that cortisol secretion is either not at all or minimally affected by sleep following prolonged wakefulness.[137,138] Two more recent studies have reported somewhat antithetical results, with one study[139] showing that cortisol secretion is elevated on the evening following sleep deprivation and the other study[140] showing a significant decrease of plasma cortisol levels the next day and on the recovery

Figure 1. Two-Process Model of Sleep: Interaction of Homeostatic Process S and Circadian Process C Leads to the Timing of Sleep and Waking[a]



[a]Based on Borbély.[143] Process S, which depends on sleep and waking, increases during waking and declines during sleep. Process C modulates the threshold of awakening. When S declines to the level of C, sleep is terminated.

Figure 2. Course of Processes S and C in Normal Conditions and After Sleep Deprivation in Healthy Subjects (A) and Depressive Patients (B)[a]



[a]Based on Borbély and Wirz-Justice.[148] This model assumes that, in depressed patients, deficiency of process S results in more superficial sleep and reduced sleep duration. Sleep deprivation, by prolonging wakefulness, increases process S and improves depressed mood.

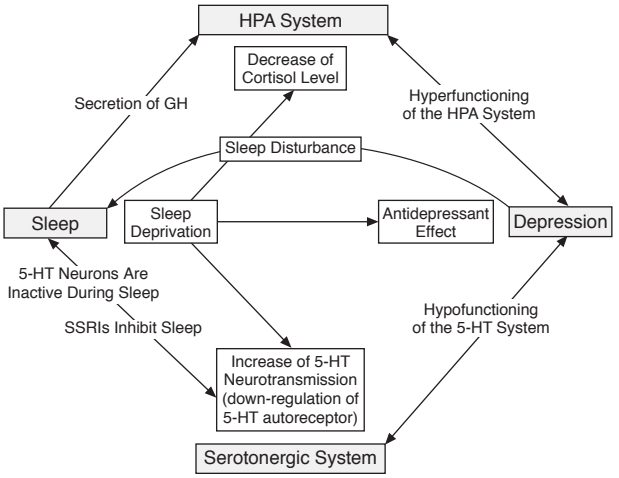
night. The latter study indicated that this inhibition of the HPA axis activity was associated with an enhanced activity of the GH axis. Further to these inconsistent results from studies of total sleep deprivation, partial sleep loss has been reported to be associated with evening cortisol elevation, while a modest restriction of sleep to 6 hours per night for 1 week was associated with a significant decrease of peak cortisol secretion.[141,142] Methodological differences, primarily relating to the way subjects were managed during deprivation, may explain these opposing findings. The finding that sleep deprivation leads to lower cortisol levels post-deprivation suggests that lowering the level of HPA activity may be one of the mechanisms through which sleep deprivation improves depressive symptoms temporarily.

Two-Process Model of Sleep Regulation

Borbély[143] has proposed a model based on the theoretical assumption that sleep is dependent on 2 processes: a homeostatic, sleep-inducing process (process "S") and a circadian process (process "C") (Figure 1). According to this model, the interaction between a homeostatic process and a circadian process determines sleep propensity. The homeostatic process, process S, increases gradually during waking, resulting in an elevated initial level of slow-wave activity (lower band of the EEG activity between 0.5 and 4.75 Hz), which decreases exponentially during sleep.[144] The circadian process, process C, modulates the threshold of awakening and that of falling asleep (circadian process). When S declines to the level of C, sleep is terminated. In accordance with the 2-process model of sleep, the time course of slow-wave activity has been shown to be a monotonic function of prior wakefulness in various experimental situations.[145,147] Moreover, slow-wave activity is not influenced by the circadian phase of sleep, nor is its time course correlated to that of core body temperature.[146]

This model attempts to explain the effects of sleep deprivation on depression, REM sleep disinhibition, and reduced slow-wave sleep in patients with depression. Borbély and Wirz-Justice[148] assumed that process S was deficient in patients with depression, reflected in a reduction of slow-wave activity in depression (Figure 2). Process S in patients with depression thus does not reach the level observed in normal subjects. The authors theorized that as a consequence of reduced slow-wave sleep, particularly during the first phase of non-REM sleep, REM sleep latency shortens in patients with depression. Sleep deprivation, by prolonging wakefulness, increases process S and slow-wave activity and improves depressed mood. However, several studies showed no significant differences in total time of slow-wave sleep or the relative power of slow-wave activity in the first to the second non-REM periods between patients with depression and healthy controls.[109,149] These findings call into question the assumption of a 2-process model of reduced slow-wave sleep in depression.

Figure 3. The Relationship Between Sleep, Depression, the Hypothalamic-Pituitary-Adrenocortical (HPA) Axis, and the Serotonergic System[a]



[a]Based on Steiger[128] and Adrien.[168]
Abbreviations: GH = growth hormone, SSRI = selective serotonin reuptake inhibitor, 5-HT = serotonin.

It has been said that the pathophysiology of SAD is especially associated with an abnormal interaction of circadian and sleep-wake cycle–dependent processes.[68] Some studies also, however, suggest that homeostatic processes are not involved in the disturbance of sleep in SAD.[65,150] For example, Koorengevel et al.[150] polysomnographically investigated 7 SAD patients and matched controls subjected to a forced desynchrony protocol that discriminated the influences of the circadian pacemaker from those of the sleep-wake cycle. Between SAD patients and controls, no significant differences were observed in homeostatic parameters: sleep stage variables, relative power spectra, and time courses of power in various frequency bands across the first 3 non-REM–REM cycles showed no differences.[150] In addition, the same group[151,152] suggested that a disturbance of the circadian pacemaker is not likely to be involved in the pathogenesis of SAD.

Circadian Rhythm Abnormalities

The periodic nature of depression is strongly suggestive of the implication of an endogenous biological clock. Depression is a fluctuating disorder with a tendency for both relapse and remission; such regular periodicity is not seen in other psychiatric disorders.[153] Recent progress in molecular genetics has pointed to some "clock" genes implicated in the regulation of circadian and seasonal rhythms in humans.[154–157] In addition, mutations in clock genes have been related to delayed circadian cycles.[158,159] A subgroup of depressed patients has shown circadian abnormalities in mood, sleep, temperature, and neuroendocrine secretion. Recent studies have tried to relate these clock genes to the circadian abnormalities in depression.[160–163] Abnormalities in clock gene function are speculated to be associated with depression characterized as having circadian-related abnormalities including disturbances in sleep, hormones, and behavior.[163]

Monoamine Hypothesis

The original theory of high cholinergic and low monoaminergic neurotransmission in depression was elucidated over 3 decades ago.[164] This monoamine hypothesis was originally based on the antidepressant action of MAOIs and the depressive effect of reserpine. Recent studies have emphasized that serotonin (5-hydroxytryptamine, 5-HT) and catecholamine play key roles in the monoamine hypothesis.[165] It is interesting to note that the regulation of REM sleep also depends on a balance between the cholinergic and aminergic systems.[166] The secretion of 5-HT, for example, is closely related to sleep-wakefulness states, being highest during waking, reduced during slow-wave sleep, and further reduced during REM sleep.[167] The therapeutic action of widely prescribed antidepressants such as the SSRIs is directly linked to enhancement of central serotonergic neurotransmission.

Figure 3 shows interactions among sleep, depression, the HPA axis, and the serotonergic system. Adrien[168] recently hypothesized that blockade and desensitization of 5-HT somatodendritic autoreceptors at the beginning of SSRI use, in the presence of sleep deprivation, are indicative of a shared neurobiological basis for antidepressant effect. Adrien suggests that sleep loss could represent an endogenous or compensatory therapeutic process enabling 5-HT receptor down-regulation, enhancement of available 5-HT in the synaptic clef, and thus improvement of mood. This hypothesis is consistent with observations that chronic insomnia predisposes to the development of depression[169,170] and that REM sleep disinhibition in earlier clinical episodes is more evident than in later episodes.[171,172] However, some studies reported that REM sleep latency and REM sleep time and percentage appear to be stable over time.[33,48] These findings thus do not support the hypothesis that REM sleep abnormalities emerge as serotonergic deficits worsen. In addition, Adrien's hypothesis does not take into account reduced slow-wave sleep in depression, which is strongly correlated with illness severity.[33] While the hypothesis is intriguing, it would have to take into account not only the serotonergic links between sleep and depression, but also the role of other systems such as the HPA axis.

FUTURE DIRECTIONS

Whether sleep disturbance is a prodromal symptom or in itself a trigger or risk factor for depression is uncertain. It is well known that sleep disturbance is a significant risk factor for subsequent clinical depression.[173] Some studies

have emphasized the importance of stable sleep-wake cycles and proper sleep hygiene in preventing relapses in remitted depressed patients.[17,18] On the other hand, it has been suggested that the experience of disturbed sleep, which includes unsuccessful efforts to initiate sleep, may in itself lead to "learned helplessness," which is considered to be a valid model for the induction of depression.[4,6] Several epidemiologic studies have indicated that chronic primary insomnia can even act as an independent predictor for developing depression decades later.[174,175] To clarify this issue, further epidemiologic longitudinal research is needed to show that insomnia is an independent predictor for later depression and not simply a subclinical or subsyndromal prodrome of depression.

Another possible approach would be to evaluate the differences in terms of pathophysiology between primary insomnia and secondary insomnia due to depression. Numerous studies have demonstrated that beta frequency activity on polysomnography is elevated at sleep onset and during sleep in patients with primary insomnia.[176–180] Elevated beta activity findings are consistent with neurocognitive research suggesting that patients with primary insomnia may suffer from hyperarousal and/or excessive rumination at sleep onset and during sleep.[181] It is well known that patients with primary insomnia underestimate their total sleep time and overestimate their sleep onset latency; that is, objective measurements of sleep by polysomnography are not consistent with subjective complaints in patients with primary insomnia.[182,183] Hyperarousal is interpreted in terms of a neuronal group theory, with the neurocognitive model of sleep providing a possible explanation for the paradoxical discrepancies observed between subjective impressions and objective measures of sleep in patients with primary insomnia.[178,181] It is hypothesized that elevated beta activity in primary insomnia represents an abnormally high level of brain activity that occurs when neuronal populations do not progress normally and/or uniformly from high to low frequency modes around sleep onset and during sleep and that this high level of brain activity results in the occurrence of sensory and cognitive processes that interfere with sleep initiation and sleep maintenance and also alter the perception of sleep quantity and quality.[181]

However, depressed patients do not exhibit increased high-frequency activity in the beta range during sleep compared to patients with primary insomnia.[176–180] As mentioned above in the section on functional imaging studies, hyperarousal theories have often been referred to as an underlying pathophysiologic model of sleep disturbance in depression,[122,124] in contrast to functional imaging findings that indicate specific patterns of hyperperfusion or hypermetabolism in anterior limbic/paralimbic structures and prefrontal circuits,[124,184] with patients with primary insomnia showing globally a pattern of hypoperfusion in various brain regions during non-REM sleep compared with good sleepers.[185] Two recent studies[184,186] demonstrated that, relative to healthy subjects, both depressed patients and patients with primary insomnia show less decrease in relative regional cerebral glucose metabolism from waking to non-REM sleep states. According to these studies, it is likely that patterns of relative regional cerebral glucose metabolism changes from waking to non-REM sleep differ in depressed patients and patients with primary insomnia. It has also been suggested that depression may be associated mainly with somatic hyperarousal, as measured by, for example, increased levels of plasma and urinary cortisol and by elevated nocturnal core body temperature.[183,187–189]

These findings suggest that the distributions of brain neural activity during sleep are different in patients with primary insomnia compared with depressed patients. This difference, as opposed to a simple quantitative distinction based on levels of arousal, may reflect the distinction in terms of an underlying pathophysiologic mechanism between primary insomnia and sleep disturbances in depression. If increased beta activity represents a pathologic neurocognitive process, primary insomnia may be a more subjective disorder of perception, whereas sleep disturbances in depression may represent other pathologic processes indicated by more objective indices such as short REM latency or increased REM density.

CONCLUSION

This review of the considerable body of research findings relating to sleep and depression suggests the existence of powerful indices for exploring the pathophysiology of depression. The diagnostic value of these indicators is, however, limited due to overlap with normal functioning and low specificity for depression as opposed to other psychiatric disorders. This problem is undoubtedly due, at least in part, to the clinical heterogeneity of depression, which remains a disorder grouping various profiles of symptoms and for which etiology and pathogenesis are poorly understood. The classification of depressive disorders is highly controversial, with differences persisting between the DSM-IV and the ICD-10. In the absence of an objective index that reflects the etiology and prognosis of depression, treatment algorithms are often subjective, reflecting the attitudes of individual clinicians and their patients. This undoubtedly is in part a response to the fact that although clinicians have access to a wide variety of interventions such as pharmacotherapies and behavioral therapies, 30% to 40% of patients with depression fail to respond to first-line treatment, 60% to 70% fail to achieve complete remission, and up to 20% do not recover even after 2 years of treatment.[190–192]

Although a clear causal relationship between sleep disturbance and depression has not yet been established, further research on sleep in depression may play an im-

portant role in optimizing prevention and treatment.[13] Research on sleep in depression has, however, provided an enormous database and a number of interesting theoretical models of the etiology and pathophysiology of depression. Further studies linking the different areas of research are now needed to validate such theories. A fundamental problem of systemic pharmacologic probes in human subjects, even with very specific receptor-selective drugs, is that it cannot be directly determined whether a drug's action is mediated by presynaptic receptors, postsynaptic receptors, or heteroreceptors or by a combination of them.[193] Research taking into account sleep regulation as a model of the neurophysiology and neuroanatomy of depression may provide new insight into the roles of neuroendocrine and monoamine systems in the pathophysiology of depression. If sleep alterations in depressive patients are related to a vulnerability marker for depression, genetic research in combination with research on sleep abnormalities could subsequently provide an interesting way forward in our understanding of depression.

Drug names: clomipramine (Anafranil and others), desipramine (Norpramin and others), dexamethasone (Mymethasone, Hexadrol, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), pindolol (Visken and others), reserpine (Serpalan and others), trazodone (Desyrel and others), trimipramine (Surmontil).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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