Sleep Pathologies in Depression and the Clinical Utility of Polysomnography

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Abnormal sleep accompanies many psychiatric conditions, but has long been recognized as a particularly conspicuous feature of affective disorders. More than a mere epiphenomenon, the powerful link between sleep and mood regulation is most dramatically demonstrated by the high efficacy of sleep deprivation in alleviating depression. Indeed, the sleep abnormalities that accompany depression may be due to the same neuropathologies that are responsible for its mood and cognitive symptoms. This powerful link between sleep and mood regulation makes polysomnography (PSG) a useful window into the underlying pathophysiology of depression, yet it is underused, particularly in clinical diagnosis. Recent depression research has emphasized the importance of establishing biologically relevant subtypes of depression with treatment specificity and prognostic value. PSG measures, among other biological markers, may be of importance in establishing these subtypes. Two subtypes of depression that appear to have robust biological differences, the melancholic and atypical subtypes, have recently been shown to have different sleep profiles that can aid in differential diagnosis. Further, routine use of PSG in the workup of a depressed patient would minimize the chances of misdiagnosis in those suffering from primary sleep disorders such as sleep apnea, which can present secondary mood symptoms resembling depression. Increased use of PSG in clinical psychiatric practice would enlarge the body of data available for defining new depressive subtypes in the future. It would also serve an immediate purpose in the separation of atypical, compared with melancholic, depression, and the differential diagnosis of depression from primary sleep disorders.

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Clinical Implications

- PSG measures are gaining increasing importance in the differential diagnosis of depressive subtypes, particularly atypical, compared with melancholic, depression.
- PSG measures obtained in the clinic need to be modernized and standardized to increase their sensitivity to neurobiological changes.
- Depression is highly comorbid with primary sleep disorders; PSG should be routinely employed to prevent misdiagnosis.

Limitations

- Research investigating the relations between depressive subtypes and sleep abnormalities using modern measures is at an early stage.
- There has been a general lack of standardization in PSG measures, which reduces the ability to compare results between different laboratories and (or) clinics.
- Sleep laboratory-based PSG assessments introduce scheduling and compliance issues with patients, and may delay (but improve) diagnosis.

Key Words: *major depression, sleep, polysomnography, REM density, differential diagnosis, atypical depression, melancholic depression, subtypes*

In a companion paper, Dr Lee and Dr Douglass[1] review the sleep abnormalities that accompany various psychiatric conditions. Pathological sleep seems to accompany most psychiatric disorders, but appears to be most closely tied to affective illness.[2] So typical are sleep disturbances in depression that by the early 1980s, hundreds of PSG studies had been reported on patients with affective illness.[3] More than 90% of depressive patients report sleep problems that can be confirmed by PSG.[4] Some of these sleep abnormalities may be trait markers, that is, characteristics that predate development of the disorder and indicate vulnerability to it. Others may be state markers—features that are only present during depressive episodes, or so-called scars that have developed as a consequence of the disorder.[5]

Most antidepressant drugs alter sleep architecture, usually increasing RL and (or) reducing the amount of REM sleep in the night.[6] Thus most drugs that alleviate depression also affect sleep. The reverse is also true: manipulations of sleep affect depression. Under no circumstance is this bidirectional relation more striking than in total sleep deprivation. Unlike pharmacological interventions, which typically require 2 to 3 weeks of treatment before antidepressant effects are seen, sleep deprivation provides immediate and pronounced relief from depressive symptoms. Recovery sleep reverses these effects just as quickly, sometimes after as little as a 15-minute nap.[7] Total and partial sleep deprivation both show treatment efficacy in about 60% of patients,[8] with the efficacy of total sleep deprivation climbing to 90% following 3 sessions at 1-week intervals.[9]

Abbreviations used in this article

5-HT	serotonin
ACh	acetylcholine
BDNF	brain-derived neurotrophic factor
cAMP	cyclic adenosine monophosphate
CREB	cyclic-AMP response element binding protein
CRH	corticotropin releasing hormone
DLPFC	dorsolateral prefrontal cortex
DST	dexamethasone suppression test
ECT	electroconvulsive therapy
EEG	electroencephalogram
HPA	hypothalamic–pituitary–adrenal
IRI	inter-*rem*-interval
LDT–PPT	lateral dorsal tegmental–pedunculopontine tegmental nuclei
MAOI	monoamine oxidase inhibitor
NA	norepinephrine
NREM	nonrapid eye movement
PFC	prefrontal cortex
PSG	polysomnography
PSM	polysomnogram
RA	REM activity
RD	REM density
REM	rapid eye movement
rem	individual rapid eye movement in REM sleep
RL	REM latency
RT	REM time
SSRI	selective serotonin reuptake inhibitor
SWS	slow-wave sleep
TCA	tricyclic
TST	total sleep time

A major impediment to all depression research, including investigations of its sleep features, is the heterogeneity of the condition. Patients vary widely in age of onset, course of illness, and symptom profile.[10] Classically, the clinical subtyping of affective disorders has included designations such as unipolar and bipolar, or melancholic and psychotic depression. These subtypes are highly interrelated, and are neither relevant to personality traits predating the disorder, nor do they have much treatment specificity.[11] Recently, numerous researchers have stressed the importance of defining biologically relevant subtypes of depression.[11–14] Some have even gone so far as to state that depression can exist, "as a disease, a disorder, a syndrome, and/or be a normal or abnormal reaction to salient stressors."[11, p 471]

On what basis, then, should major depression be subdivided? Antonijevic[15] asserts that sleep features may be useful markers for the division of major depression into biologically relevant subtypes. Indeed, the cognitive, affective, and sleep symptoms of depression all appear to depend on similar pathophysiological states; as such, sleep measures may be a useful tool for understanding the functional imbalances underlying depression. The past 3 decades of research have yielded several theories of depression and sleep that are both overlapping and divergent in their description of the underlying neurobiology.[5,16] In general, this research points to 3 major areas of dysfunction: monoamine–cholinergic imbalance, HPA imbalance, and neurotrophin deficiency.

The Monoamine Hypothesis of Depression

The first antidepressant drugs, TCAs and MAOIs, were discovered in the 1950s and 1960s. Their mechanisms of action, which typically increased the availability of NA and dopamine, seemed to point to an obvious cause of depression—a deficit of catecholamines,[17] hence the so-called catecholamine hypothesis of depression. This was later expanded to include 5-HT and became the monoamine theory of depression.

Most antidepressants increase monoaminergic transmission, and do so in one of several ways: blockade of reuptake, inhibition of metabolism, alteration of receptors that influence signal transduction, increase of neuronal firing rate, or increased neurotransmitter release.[18] Despite this, investigations of the major NA metabolite (3-methoxy, 4-hydroxy

phenyl glycol) in urine, blood, and cerebrospinal fluid have failed to show consistent pretreatment differences between people with depression and control subjects.[19] Monoamine depletion also typically fails to either induce depression in control subjects,[20,21] or exacerbate symptoms during a depressive episode.[20] Clearly, depression is more than a simple monoamine deficiency.

More recently, the receptor sensitivity hypothesis suggests that the key action of antidepressants is to change the sensitivity of pre- and postsynaptic receptors, thus affecting monoamine release and postsynaptic neuronal sensitivity to the monoamines. The alpha-2 adrenoceptor is a presynaptic autoreceptor whose excitation inhibits NA release.[19] Enhanced alpha-2 adrenoceptor sensitivity and density could be responsible for reduced NA levels in depression. Several types of treatment, including antidepressant drugs and ECT, decrease alpha-2 adrenoceptor density and affinity in blood platelets.[22] Effective antidepressant treatments also affect 5-HT receptors. Rat studies show that the desensitization of inhibitory 5-HT_{1A} autoreceptors is crucial to the action of both SSRI and MAOI antidepressants, and the time-course of this adjustment matches the human antidepressant response lag.[9] Unlike MAOIs and SSRIs, TCAs may increase postsynaptic 5-HT receptor sensitivity.[20] Thus monoaminergic transmission may be altered in depression, not as a result of deficiency but rather owing to dysfunction of the associated receptors.

Dysfunctions in monoamine receptor sensitivity have important implications for neuronal circuits in which the monoamines modulate the action of other neurotransmitters. In 1972, Janowsky et al[23] proposed that depression was caused by an imbalance between ACh and NA. Monoamine–ACh balance is also critical to REM sleep regulation, and in 1982, quite independently of Janowsky et al,[23] McCarley[24] advanced an aminergic–cholinergic imbalance theory of sleep in depression.

People suffering from depression exhibit numerous REM sleep abnormalities, including increased RA and RD, reduced RL, and reduced SWS. These observations could be consistent with increased so-called REM sleep pressure, decreased REM suppression, or a lowered REM threshold.[2,25] The regulation of REM sleep relies heavily on the balance between REM-off inhibitory influences (from NA cells located in the locus coeruleus and 5-HT cells located in the dorsal raphe nucleus), and REM-on cholinergic neurons (in the pontine tegmentum LDT–PPT).[26]

Manipulations of neurotransmitter levels have confirmed that monoaminergic function has a profound impact on sleep. Prevention of NA synthesis in control subjects produces hypersomnia and reduced RL; in one study, this also produced depressed mood.[3] The 5-HT depletion produces some REM disturbances in healthy volunteers with no family history of depression, but fails to produce depressed mood.[21] Cholinergic agonists, such as arecoline and agents that increase ACh levels, such as physostigmine, both shorten RL and increase RD. This effect is particularly notable in depressed patients.[27,28] Control subjects with a high familial risk for depression are also more easily induced into a depressionlike sleep pattern with cholinergic challenge than control subjects without familial risk.[29] As such, cholinergic supersensitivity may be a trait marker for depression. However, control subjects forced into ACh supersensitivity exhibit depressionlike sleep, but not depressed mood.[30]

Almost all antidepressant drugs suppress REM, either by increasing RL and (or) reducing RT. This REM suppressive effect is thought to be caused by facilitation of monoaminergic function and (or) blockade of muscarinic cholinergic receptors.[6] Remitted depressed patients treated for several years with imipramine and interpersonal therapy demonstrate normalized tonic REM features such as RL and REM percent; however, phasic measures like RD are only temporarily suppressed before returning to pretreatment levels.[4,31]

Antidepressant treatment by sleep deprivation also influences monoamine–ACh balance. As reviewed by Adrien,[9] the 5-HT system is strongly implicated in the antidepressant action of sleep deprivation, which may rapidly desensitize 5-HT_{1A} autoreceptors, allowing 5-HT levels to increase. Such desensitization is also thought to underlie the effects of MAOIs and SSRIs, but in sleep deprivation it occurs much more rapidly. Antidepressant drugs can prevent relapse after sleep deprivation and enhance its effectiveness, which supports the idea that they share a common action. Adrien[9] further hypothesized that the insomnia that often accompanies depressive episodes acts as a protective mechanism that increases 5-HT levels. By this hypothesis, depression occurs when this compensatory mechanism can no longer sufficiently combat the depressive process.

Reduced RL has been associated with depressive symptoms such as early morning awakening, anhedonia, unreactive mood, and appetite loss.[4] Healthy relatives of depressed patients also tend to exhibit reduced RL and SWS, particularly if their depressed relatives also display a short RL.[32] However, a technical problem in comparing RL across studies has been the wide variation in definitions[33] of this measure owing to differences in the definition of sleep onset, onset of the first REM period, and whether awake time in the first NREM period should be included or excluded (RL, compared with RL minus awake time). In a longitudinal study, Lauer et al[34] found that RL shortened with age in all subjects, but depressed patients did not differ from control subjects until the fourth decade of life. This suggests that age should always be used as a covariate in the analysis of RL, which was not done in many of the early papers.

Lauer et al[34] found that, unlike RL, the increased RD observed in depressed patients differentiated them from control subjects in all adult age groups. Further, RD differentiates healthy relatives of depressed patients from control subjects, while RT and RL do not.[35] Another German study[36] also concluded that RD is a better marker for depression than

RL or RT. Nevertheless, as with RL, there are inconsistencies in the definition of RD across laboratories.

The most straightforward method of determining RD is to visually count each eye movement (*rem*) in a REM period, then divide the total by RT; however, visual counting is difficult because there can be hundreds or even thousands of *rems* per night. This method also discards valuable information about the time intervals between *rems.* To facilitate the process of manual REM detection, the Pittsburgh group designed a method to score RD in a semi-quantitative manner (Dan Buysse, 3 October 2005, personal communication) that has been described as "an integrative approximate measure of the frequency of rapid eye movements during sleep."[37, p 45] In this method, each minute of REM sleep is scored between 0 and 8 based on how many eighths of the minute were taken up by eye movements visible on the PSM. This measure is summed over the whole REM period to produce an overall score of RA. In this method, RD is defined as RA divided by RT. Other methods used multiple time windows of various lengths within the REM period that were then scored as either zero for no *rems*, or one if some *rems* were observed. The length of this time window varied widely from laboratory to laboratory—from seconds to minutes.[36,38,39]

REM eye movements are highly nonrandom in their time distribution and are not normally distributed—closely spaced *rems* (bursts) are separated from each other by long periods of rarely occurring eye movements (isolated). Therefore, averaging eye movements across the REM period by calculating crude RD may mask important information. Modern digital acquisition systems permit the automatic detection of individual *rems*[40,41] and also provide the exact time interval between *rems* (or IRI). The statistical distribution of IRIs preserves information about the phasic, nonrandom nature of *rems.* Phasic RA is the only REM disturbance that appears to distinguish patients with primary depression from secondary depression, according to Foster et al,[42] who concluded that phasic RA and RD could be considered as objective indicators of central nervous system impairment, to indicate the organicity of depression. However, it should be acknowledged that other authors[43] have noted increased RD in schizophrenia and questioned the specificity of elevated RD for depression.

Another method for quantifying the phasic nature of *rems* is Markovian mathematical analysis, which determines the probability of transitioning from one state to another (that is, burst state to isolated state). When such analyses are applied to REM phasic activity, they reveal that the increased RD observed in depression results from a tendency of bursts to be prolonged, whereas isolated *rems* do not differ from control subjects. This could be due to abnormal ACh receptor-mediated activity in the parabrachial pons (LDT–PPT) causing an imbalance between 5-HT and ACh.[44] Alternatively, it could reflect overactivation of the LDT–PPT by an excitatory neurotransmitter such as glutamate. Abnormal patterns of brain activity in the REM sleep of depressed patients as measured by positron emission tomography are consistent with a monoamine–ACh imbalance.[45]

The HPA Axis Theory of Depression

Dysregulation of the HPA axis, the system that mediates the neuroendocrine stress response, is one of the most consistently reported biological correlates of depression.[8] The earliest marker of HPA dysfunction to be reported in depression was an abnormal response on the DST.[10] Administration of the synthetic steroid dexamethasone should suppress cortisol production in a healthy HPA system via negative feedback. Excessive activity of the HPA axis, including increased cortisol secretion (hypercortisolemia), elevated levels of CRH, and (or) an abnormal response on the DST occurs in about 50% of people with depression.[46] The observed pattern of HPA dysfunction suggests that hypercortisolemia in depression stems from either a resistance to glucocorticoid negative feedback or a hyperactive HPA axis whose drive overcomes negative feedback.[14]

The HPA system influences monoamine function. The release of NA is stimulated by cortisol and CRH; conversely, NA stimulates CRH production by the hypothalamus—thus there exists an NA–CRH positive feedback loop. Further, the sensitivity of some β-adrenoceptor-linked intracellular second messenger systems is altered by glucocorticoids.[47] Studies using continuous cerebrospinal fluid monitoring have confirmed that depressed patients with hypercortisolemia also demonstrate high NA levels.[48] CRH projections also interact with the midline raphe nuclei, the principal source of 5-HT.[49] Corticosteroid administration causes 5-HT_{1A} receptor downregulation in rats.[50] Serotonin also has an indirect modulatory role in HPA activity via its influence on NA production.[51] Glucocorticoid and mineralocorticoid receptors can also influence gene transcription, including the transcription of genes critical to monoamine production.[52] Thus the HPA system has strong reciprocal connections with the monoamines—HPA overactivity is linked to elevated NA levels and reduced sensitivity to 5-HT, while HPA underactivity is linked to reduced 5-HT levels.

CRH acts not only as a hormone but also as a neurotransmitter.[8] CRH receptors are widely distributed in the brain, notably the amygdala, cerebral cortex, hippocampus, septum, bed nucleus of the stria terminalis, cerebellum, and brain stem nuclei,[53] including those controlling REM sleep. Gold and Chrousos[14] note that there is a strong similarity between the neurobiology of the stress response and that of depression. When a threatening stimulus triggers fear, the amygdala activates HPA and locus coeruleus activity. The NA and cortisol produced by this response enhance the transfer of affectively negative memories from the amygdala to other sites in the brain, notably the PFC. In depression, it is thought that the stress response sets up a feed-forward system that increases the encoding of aversive memories, and inhibits the PFC, leading to altered cognition in which the worst outcome is always predicted and fear is prolonged.

Hypersecretion of CRH in depression has been shown to normalize with treatment by several antidepressants.[14] Perhaps even more convincing is the effectiveness of some CRH_1 receptor antagonists, steroid receptor blockers, and glucocorticoid biosynthesis inhibitors as antidepressants.[52] Nevertheless, unusual HPA activity is not limited to depression. Dexamethasone nonsuppression is often found in normal people,[54] thus it is inadequate as a sole diagnostic marker for depression.[10]

The HPA axis also plays a critical role in sleep regulation.[55] HPA overactivity is linked to hyperarousal of the nervous system, resulting in reduced SWS and TST. Pulsatile administration of CRH or the adrenocorticotropic hormone analogue ebiratide in control subjects reduces SWS, producing shallower sleep overall.[56] Conversely, the CRH_1 receptor antagonist, NBI 30775, normalizes sleep in depressed patients by increasing SWS and improving sleep efficiency.[57] Higher cortisol levels on the DST are also correlated with lower sleep efficiency, less Stage 2 NREM sleep, and less SWS.[58] The concept of hyperarousal during sleep in depression is also supported by imaging studies. In the wake–NREM sleep transition, depressed patients demonstrate higher activity, compared with control subjects, in numerous cortical and subcortical structures, especially the frontal cortex.[59,60] In most areas, this is a consequence of a waking hypermetabolism that persists into NREM sleep.

As mentioned, the HPA system has numerous influences on monoaminergic function. Among these, reduced expression of $5\text{-}HT_{1A}$ receptors could have a powerful influence on REM control. Interactions between the HPA system and 5-HT activity may therefore result in REM disinhibition. There appears to be no correlation between cortisol levels on the DST and RL,[58] but NBI 30775 normalizes RD in depressed patients.[57]

Some effects on the HPA axis are also observed during sleep deprivation. Total sleep deprivation has been shown to reduce cortisol secretion in the following 24-hour period, particularly during recovery sleep.[61] In summary, hyperactivity of the HPA system can result in hyperarousal that decreases sleep efficiency and the drive for SWS, as well as causing destabilizing effects on the monoamine–ACh balance that regulates REM. HPA hyperactivity may also support a pathological feed-forward system in limbic and cortical structures associated with the cognitive and affective features of depression.

The Neurotrophin Hypothesis of Depression

Another system that is implicated in the pathophysiology of depression is the neurotrophin system. Neurotrophins are agents that promote neuronal regeneration in the central nervous system. Critical to the neurotrophin hypothesis of depression is CREB, a transcription factor that regulates the transcription of numerous genes, including the gene for BDNF—a neurotrophin that powerfully influences neuronal development, survival, maintenance, and plasticity.[62]

Serum levels of BDNF are lower in people with depression than in control subjects, with the severity of depression correlating negatively with BDNF concentration.[63] Consistent with a general reduction in BDNF levels, depression is associated with global volumetric loss in the cerebral cortex, which correlates significantly with the total lifetime duration of depressive episodes.[64] Reductions in frontal activity, particularly in the DLPFC, are consistently observed in depression,[65] and reduced hippocampal volume is also very common.[8] The PFC and hippocampus likely suffer cumulative neurotoxic damage owing to activation of the HPA axis during depressive episodes.[66] The PFC and hippocampus are also heavily reciprocally connected,[66] and decreased rostromedial prefrontal and hippocampal activation is associated with impaired positive affect.[67]

Recent evidence suggests that chronic antidepressant administration results in an increase in hippocampal BDNF that is at least partly mediated by CREB.[46] Increased CREB-mediated gene expression is also seen in the mouse amygdala, cerebral cortex, thalamus, and hypothalamus after chronic antidepressant treatment, with the exact pattern of changes depending on the antidepressant used.[68] Even nonpharmaceutical antidepressant treatments such as ECT affect this system. In fact, ECT influences neurotrophin expression even more than antidepressants, corresponding to its higher efficacy as a treatment for depression.[19]

The exact mechanisms by which antidepressants influence BDNF expression are difficult to discern, because CREB is influenced by more than one intracellular signalling cascade.[62] Owing to this complexity, novel antidepressants are being developed that are aimed specifically at the cAMP pathway, a major intracellular cascade that controls CREB. One such substance is rolipram, an inhibitor of the cAMP degrading enzyme phosphodiesterase, but humans show poor tolerance for this drug.[46]

Despite the abundance of indirect evidence, low BDNF levels alone do not appear to cause depression. Knockout of the BDNF gene in mice produces obesity and anxious behaviour, but not depression.[46] Further, abnormal BDNF function is implicated in several other disorders, including amyotrophic lateral sclerosis, Alzheimer disease, and schizophrenia.[63] However, direct BDNF infusion near monoaminergic nuclei in the rat brain stem does show antidepressantlike effects.[69] As neurotrophin disruption alone does not appear to play a causative role in depression, and is not limited to depression, it is possible that BDNF reductions are a consequence of dysregulation in one or more systems that control its production. Both the monoamines and the stress hormones of the HPA axis strongly influence BDNF levels.[70]

Another compound that may influence the expression of neurotrophic factors is adenosine, a purine nucleoside that results from the breakdown of adenosine triphosphate, the intracellular energy storage molecule. Adenosine receptors are strongly implicated in the neuroprotective and neurotrophic actions of glial cells, which are important for

neuronal resilience to excitotoxicity.[71] Significant reductions in glial cells are noted in the subgenual PFC, DLPFC, and orbitofrontal regions of depressed people, with these losses most pronounced in familial depression.[72] Glial loss can ultimately result in neuronal atrophy. People with depression show marked reductions of the large neurons in cortical layers II, III, and VI in the DLPFC, and also in layers II, III, and IV of the rostral orbitofrontal cortex.[73] Layer II is also affected in the anterior cingulate cortex.[66] Depressed patients also demonstrate a blunted platelet adenosine A_{2A} receptor response.[74] Therefore, reduced responsiveness to adenosine is another candidate mechanism for reduced neurotrophin levels in depression.

In 1982, Borbély and Wirz-Justice[7] proposed a 2-process model of sleep in depression that described the interactions between 2 key factors: Process S, a sleep need that builds up during the waking hours and dissipates during sleep, and Process C, a circadian rhythm for (largely REM) sleep propensity. During sleep, the dissipation of Process S is reflected by the amount of SWS observed, as well as TST. Borbély and Wirz-Justice[7] proposed that people with depression may have a Process S deficiency, causing sleep need not to accumulate properly during the day. Indeed, people with depression show less SWS than control subjects across all age groups.[3] The advent of computerized detection methods that count individual delta waves in the EEG led to the development of the delta sleep ratio, in which the amount of delta EEG activity in the first NREM period is compared with that in the second NREM period.[4] This ratio is consistently reduced in people with depression, while a higher ratio is associated with reduced tendency to relapse.[75] Reduced Process S accumulation could account for the increased SL, shallower sleep, earlier wake times, and shortened RL observed in depressed patients.[7] In support of this concept, sleep deprivation that results in alleviation of depressed mood is associated with reduced sleep latency, increased sleep efficiency, and improved SWS during recovery sleep, all of which are consistent with increased Process S accumulation during the sleep deprivation period.[4]

There is currently general agreement that the physiological substrate of sleep need is adenosine.[76] In rats, sleep deprivation has been shown to increase levels of extracellular adenosine, as well as levels of adenosine A_1 receptor messenger RNA in the basal forebrain.[76] Taishi et al[77] found that 8 hours of sleep deprivation in rats produces significant increases in several plasticity-related factors, including BDNF. All of these factors returned to baseline levels following 2 hours of recovery sleep. Thus the effects of sleep deprivation on adenosine function and neurotrophin expression closely match the pattern of depression remission and relapse in response to total sleep deprivation. ECT also increases adenosine levels in the brain, and the therapeutic response both to ECT and to sleep deprivation is accompanied by changes in SWS, cerebral metabolic rate, and cerebral blood flow that are at least partly regulated by A_1 and A_2 receptors.[71] Thus altered responsiveness to adenosine is a good candidate for some of the neurodegenerative and SWS effects of depression, and accounts well for the antidepressant effects of sleep deprivation and ECT. However, owing to their unwanted side effects, there are few data on adenosine receptor agonists as antidepressants.

Depressive Subtypes and Sleep Disturbances

The sleep abnormalities observed in depression appear to result from the same biological imbalances that underlie its cognitive and affective symptoms, and as such they may provide useful noninvasive windows into its functional neurochemistry. As reviewed by Riemann et al,[16] the idea that sleep measures may delineate subtypes of depression is not a new one. Several subtypes of depression have been examined for PSG specificity. Sleep features were not found to distinguish primary from secondary depression, or unipolar from bipolar depression. Other methods of subtyping, such as endogenous, compared with nonendogenous, and psychotic, compared with nonpsychotic, depression remain equivocal in their sleep profiles. However, note that subtypes such as these have proven to be tightly interrelated.[5] Thus the failure to demonstrate sleep differences may have resulted from the use of clinical subtypes that are not biologically distinct. Further, inconsistencies between laboratories in the definitions of RL and RD, as well as underuse of more sophisticated measures such as Markovian REM analysis and delta sleep ratio may have impaired the strength of previous research.

Two subtypes of depression that appear to be quite distinct on numerous biological measures are the melancholic and atypical types. Melancholic depression tends to be associated with high activity in the HPA and NA systems, as well as the amygdala, and also involves 5-HT_{1A} receptor dysfunction (exacerbated by feedback from the HPA axis). Conversely, atypical depression is associated with reduced HPA activity owing to a strong inhibitory response to cortisol and hypoactivity of NA and 5-HT.[12] These biological differences appear to be related to the different treatment responsiveness of the 2 subtypes. In people with melancholic depression, TCAs and SNRIs are more effective than SSRIs, and they tend to respond well to ECT, but poorly to psychotherapy.[78] Their reduced responsiveness to SSRIs may stem from impaired 5-HT_{1A} receptor function.[12] People with atypical depression tend to show better responsiveness to MAOIs than TCAs or SSRIs, and also respond well to cognitive-behavioural therapy.[78]

Recently, Antonijevic[15] reported differences in the sleep profiles of patients with melancholic, compared with atypical, depression. Only patients of the melancholic subtype consistently showed the typical sleep pattern of depression: low sleep efficiency, NREM deficiency, and increased REM pressure. This result is consistent with the strong links between HPA overactivity, central nervous system hyperarousal, and monoamine–ACh imbalance. Conversely,

patients of the atypical subtype did not show the typical depressive sleep profile. Instead, they showed reduced delta wave production in the first NREM sleep period, possibly owing to diminished 5-HT activity. Kaplan and Harvey[79] additionally suggest that the atypical subtype is associated with hypersomnia, possibly as a consequence of reduced HPA activity. They describe the sleep pattern of people with atypical depression as: increased TST, significant nocturnal insomnia, frequent daytime napping, and excessive daytime sleepiness. Unfortunately, the literature on hypersomnia in depression is currently small because different diagnostic systems place different importance on sleep features in the diagnosis of depression. As with many other sleep measures, the study of hypersomnia also suffers from a lack of a consistent definition across laboratories.

Therefore, while sleep measures appear to have potential utility to differentiate melancholic from atypical depression, not all patients are easily placed along the melancholic–atypical spectrum. About 30% of patients are purely melancholic, while 12% are purely atypical. The remaining 58% exhibit either fluctuation between the 2 syndromes, or suffer depressive episodes that fail to match either subtype.[80] Sleep measures may be useful as an additional specifier for differential diagnosis between the melancholic and atypical subtypes; this distinction appears to have implications for treatment strategy. A nocturnal PSM may also prove useful in the establishment of new biological subtypes of depression. Undoubtedly, sleep measures will need to be used alongside other biological and psychological traits, such as gene polymorphisms,[46] early-life trauma,[81] and gender.[82]

Our paper has attempted to connect modern neurochemical research in depression with sleep research in depression. We have not attempted a review of the equally important clinical issue of whether sleep that is disrupted by physical illnesses, such as sleep apnea, can cause psychiatric symptoms or even simulate depression. In the companion article to this one, Dr Lee and Dr Douglass[1] consider this question, as do several other recent reviews and studies.[83–86] Unfortunately, these phenocopies of depression are rarely screened for in current psychiatric practice, even though they are likely the cause of numerous cases of treatment-resistant depression. Much work remains to be done.

In conclusion, there is an intimate relation between the anatomical–neurochemical systems controlling both sleep and mood. Arguments that sleep abnormalities are only epiphenomena of depression are likely incorrect, given the strong antidepressant effect of sleep deprivation, and the rapid return of depression when sleep is allowed. However, the scientific literature on sleep in depression is regarded by many as of historical interest only. Recent findings about the important role of novel neurochemical systems (CRH neurotransmission, BDNF, adenosine, and CREB) both in sleep and in depression suggest that sleep physiology in depression deserves a second look. At the very least, modern clinical sleep medicine can assist patients with refractory depression by ruling out or treating comorbid sleep disorders. However, our review suggests that the study of sleep using modern digital recordings and mathematical analysis may be of even greater benefit in diagnosing depression. It may allow the separation of melancholic from atypical depression and provide insight into their respective neurochemistry and treatment response. Of course many more patients need to be studied in uniform protocols to confirm this hypothesis, but it is possible that a sleep study could eventually become psychiatry's first real laboratory test; that is, a physiological measure closely tied to subjective mood symptoms that can also identify people at risk for depression before it occurs.

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Résumé : Les pathologies du sommeil dans la dépression et l'utilité clinique de la polysomnographie

Le sommeil anormal accompagne de nombreuses affections psychiatriques, mais il a longtemps été reconnu comme étant un attribut particulièrement visible des troubles affectifs. Plus qu'un simple épiphénomène, le lien puissant entre le sommeil et la régulation de l'humeur est démontré très clairement par l'extrême efficacité de la privation de sommeil pour atténuer la dépression. En effet, les anomalies du sommeil qui accompagnent la dépression peuvent être attribuables aux mêmes neuropathologies qui sont responsables de ses symptômes de l'humeur et cognitifs. Ce lien puissant entre le sommeil et la régulation de l'humeur fait de la polysomnographie (PSG) une fenêtre utile sur la pathophysiologie sous-jacente de la dépression, et pourtant, elle est sous-utilisée, particulièrement en diagnostic clinique. La recherche récente sur la dépression met l'accent sur l'importance d'établir des sous-types de la dépression biologiquement pertinents, avec une spécificité de traitement et une valeur de pronostic. Les mesures de la PSG, entre autres marqueurs biologiques, peuvent être importantes pour établir ces sous-types. Il a récemment été démontré que deux sous-types de la dépression qui semblent avoir des différences biologiques robustes, les sous-types mélancoliques et atypiques, ont des profils du sommeil différents qui peuvent aider au diagnostic différentiel. En outre, l'usage courant de la PSG dans l'investigation d'un patient souffrant de dépression minimiserait les risques de diagnostic erroné chez ceux qui souffrent des troubles du sommeil primaires comme l'apnée du sommeil, qui peut présenter des symptômes de l'humeur secondaires semblables à la dépression. Le recours accru à la PSG dans la pratique psychiatrique clinique enrichirait l'ensemble des données disponibles pour définir les nouveaux sous-types dépressifs à l'avenir. Il servirait aussi l'objectif immédiat de la séparation de la dépression atypique, comparativement à la dépression mélancolique, et du diagnostic différentiel des troubles du sommeil primaires.