Clinical research

Sleep disorders as core symptoms of depression

David Nutt, DM, FRCP, FRCPsych, FMedSci; Sue Wilson, PhD; Louise Paterson, PhD

There is a very strong association between sleep disturbance and major depression. The link between the two is so fundamental that some researchers have suggested that a diagnosis of depression in the absence of sleep complaints should be made with caution.[1] Sleep disturbance is one of the key symptoms of the disease, may be the reason that depressed patients first seek help, and is one of the few proven risk factors for suicide.[2] If sleep problems remain after other symptoms are ameliorated, there is a significantly increased risk of relapse and recurrence. Another aspect of the association is the remarkable, if paradoxical, temporary improvement in mood seen after total sleep deprivation in a high proportion of depressed patients.

Incidence of sleep symptoms in depression

Symptoms of disturbed night-time sleep in people with depression have been described extensively in both clinical and epidemiological studies. In clinical samples, difficulty in initiating or maintaining sleep (including early-morning wakening) or both have been reported in about three quarters of all depressed patients.[3,4] In epidemiological samples examining insomnia symptoms and depression, sleep symptoms occurred in 50% to 60% in a sample of young adults aged 21 to 30.[5] In a UK population sample (n=8580),[6] the incidence of insomnia symptoms in a wide age range of patients with depression increased with age. Overall, 83% of depressed patients had at least one insomnia symptom, compared with 36% who did not have depression. This varied from 77% in

Links between sleep and depression are strong. About three quarters of depressed patients have insomnia symptoms, and hypersomnia is present in about 40% of young depressed adults and 10% of older patients, with a preponderance in females. The symptoms cause huge distress, have a major impact on quality of life, and are a strong risk factor for suicide. As well as the subjective experience of sleep symptoms, there are well-documented changes in objective sleep architecture in depression. Mechanisms of sleep regulation and how they might be disturbed in depression are discussed. The sleep symptoms are often unresolved by treatment, and confer a greater risk of relapse and recurrence. Epidemiological studies have pointed out that insomnia in nondepressed subjects is a risk factor for later development of depression. There is therefore a need for more successful management of sleep disturbance in depression, in order to improve quality of life in these patients and reduce an important factor in depressive relapse and recurrence.

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Keywords: *sleep; depression; insomnia*

Author affiliations: Psychopharmacology Unit, University of Bristol, UK

Address for correspondence: Professor David Nutt, Psychopharmacology Unit, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol, BS1 3NY, UK
(e-mail: david.j.nutt@bris.ac.uk)

Clinical research

- Insomnia is common in depression and may be the presenting complaint
- Sleep disturbance may predict treatment outcome, including relapse and recurrence
- Sleep manipulation alters mood
- Sleep architecture is abnormal in depression
- Antidepressants change sleep architecture in the opposite direction

Table I. Sleep and depression are strongly linked.

the 16-to-24-year age group to 90% in the 55-to-64-year age group. When the authors looked at the value of sleep symptoms as a screening aid for depression, the proportion of participants with depression who reported symptoms of insomnia sufficient to warrant a diagnosis of insomnia (DSM-IV) was 41%, and the proportion without depression and without a diagnosis was 96%. This supports the statement mentioned above that diagnosing depression without sleep complaints needs care.

Hypersomnia is less common, and tends to be a feature of atypical depression, and more prevalent in the young, with about 40% of patients under 30 and 10% of those in their 50s experiencing the symptom,[7] and a higher incidence in females of all ages. Some patients experience both insomnia and hypersomnia during the same depressive episode.

Distress and quality of life

Disturbed sleep is a very distressing symptom which has huge impact on quality of life in depressed patients.[8] We surveyed the views of patients with depression about their symptoms and associated sleep difficulties.[9] In this study, 2800 members of Depression Alliance, a UK-based charity for people with depression, were sent a postal questionnaire. Respondents were asked if, when they are depressed, they suffer from sleep difficulties *(Table II)*. Some 97% reported sleep difficulties during depression and 59% of these indicated that poor sleep significantly affected their quality of life. The majority believed their sleep difficulties started at the same time as their depression. About two thirds had sought extra treatment—such as prescribed sleeping pills, over-the-counter sleeping aids, and extra visits to their doctor—for their sleep problems. In another recent study,[10] depressed patients reported significantly poorer perceptions of sleep quality and poorer perceptions of life quality and mood than the control group, even though estimates of sleep disturbance were similar. This may indicate that depressed individuals experience more "sleep distress" than healthy individuals.

Physiological findings in depression

As well as the distressing symptoms of sleep disturbance experienced by patients, changes in objective sleep architecture are well-documented in depression.[11] Compared with normal controls, sleep continuity of depressed sub-

Nature of sleep and daytime symptoms	%
Sleep disturbance symptoms (n=496)	
Any	97
i) I can't get off to sleep	58
ii) I keep waking up in the night	59
iii) I wake early and can't get back to sleep	61
iv) I sleep for too long	31
Insomnia only (i, ii and/or iii)	69
Hypersomnia only (iv)	10
Mixed insomnia/hypersomnia	21
Associated daytime symptoms (n=491)	99
I can't concentrate	81
I feel exhausted and lethargic	80
I have no energy	77
I feel very sleepy	41
I nap during the day	40
Extra treatment sought (n=341)	69
Prescribed sleeping pills	48
Over-the-counter sleeping aids	29
Extra visits to the doctor	24
Effect on QOL (n=495)	
Not at all	2
A little	10
Moderately	29
A lot	35
Very much	24
Onset of sleep problems (n=483)	
A long time before my depression	16
About the same time as my depression	68

Table II. Sleep disturbance symptoms: nature, onset, effect on quality of life (QOL), and further treatment sought.[9]

jects is often impaired, with increased wakefulness (more frequent and longer periods of wakefulness), and reduced sleep efficiency. Sleep onset latency is significantly increased and total sleep time reduced. Rapid eye movement (REM) latency is often shortened, and the duration of the first REM period is increased *(Figure 1)*. The number of eye movements in REM (REM density) is also increased.
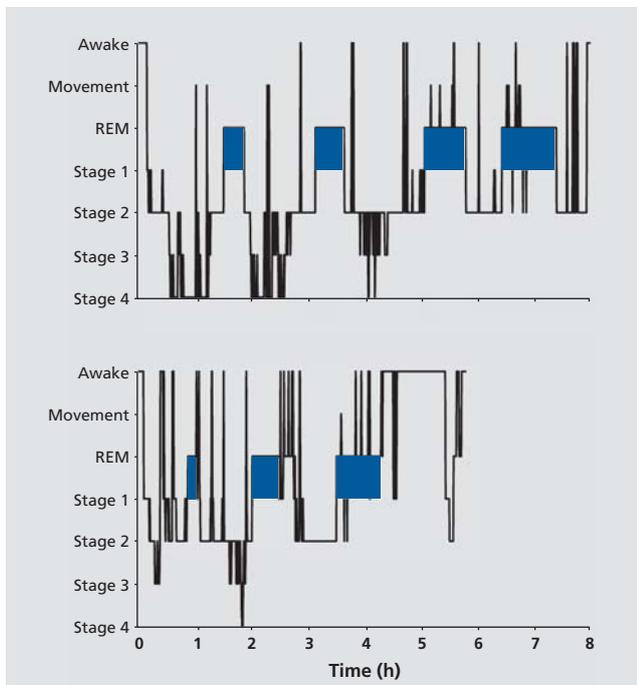

Figure 1. Hypnograms from a normal subject (upper) and a depressed patient (lower). The depressed patient has a shortened REM sleep latency, very little slow-wave (stages 3 and 4) sleep, particularly in the first sleep cycle, more awakening, and a long period of waking at about 0430.

Slow-wave activity (SWA) seen on the electroencephalogram (EEG) during non-REM sleep is a marker of the homeostatic drive to sleep; thus, the amount of SWA is greatest in the first sleep cycle when sleep propensity is high, and gradually diminishes in subsequent cycles as sleep debt is made up and sleep drive diminished. The total amount of SWS is often decreased in depression, compared with normal controls.[11] This reduction may be related to decreased regional cerebral blood flow seen in the orbitofrontal and anterior cingulate cortex during slow-wave sleep (SWS) in imaging studies,[12] and it may be a consequence of the abnormalities in this area described in depression.[13] In addition,

reduction in SWS can reflect fragmented sleep in general, such as is seen in depression.

Another anomaly seen in depressed patients is that the normal pattern of SWA decreasing from the first to the last NREM episode is disrupted, with less of a decrease in SWA occurring from the first to the second episode in depressed patients[14,15] *(Figure 2)*. This is sometimes expressed as a lower delta sleep ratio (DSR) that is the quotient of SWA in the first to the second non-REM period of sleep.
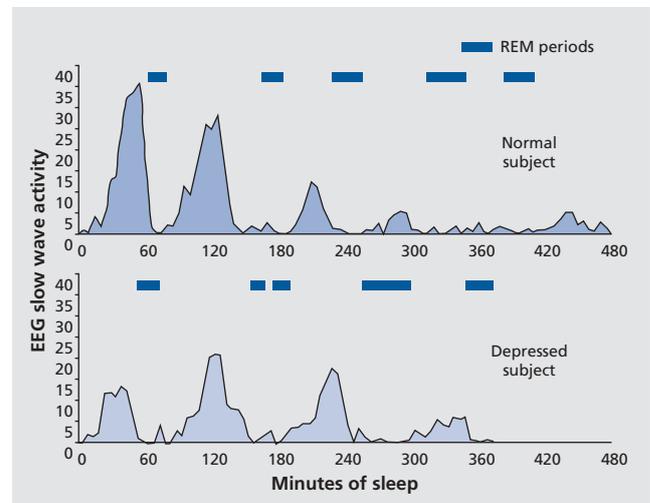
Figure 2. Evolution of slow-wave activity over the night in a normal subject (upper) and a depressed patient (lower). In the normal subject the amount of slow-wave activity is high in the first non-REM period, then diminishes over the night. In the depressed patient, the highest activity is in the second non-REM period.

Some of these sleep architecture abnormalities are present during full clinical remission, and also appear to be associated with an increased risk for relapse.[16-18] High REM density and reduced SWS in the first cycle were also present in first-degree relatives of depressed patients in the Munich Vulnerability Study on Affective Disorders, measured on two occasions 4 years apart,[19] and in a more recent study, REM density predicted those who had subsequently developed a major depressive episode.[20]

Mechanisms of sleep regulation and disturbances in depression

Research over the past 25 years has revealed that the sleep-wake cycle is regulated by two separate but interacting processes,[21] the circadian (C) process and the homeostatic (S), or recovery process.

The C process is that which regulates the daily rhythms of the body and brain. Circadian (24-h) patterns of activity are found in many organs and cells, and the main circadian pacemaker is found in a group of cells in the suprachiasmatic nucleus (SCN) of the hypothalamus. These cells provide an oscillatory pattern of activity which drives rhythms such as sleep-wake activity, hormone release, liver function, etc. This drive from the SCN is innate, self-sustaining, and independent of tiredness or amount of sleep. It is affected markedly by light and to some extent by temperature. Bright light in the evening will delay the clock, and bright light in the morning is necessary to synchronize the clock to a 24-hour rhythm; in constant light or darkness the cycle length is about 24.3 h. All animals have such a clock, and the period and timing appear to be dependent on particular genes, which are similar in fruit flies and mammals.

The drive to sleep from the circadian clock in normal sleepers starts to increase slowly at about 11 PM and gradually reaches a peak at about 4 AM. This provides a sleep-promoting process which continues into mid-morning and then provides a wakefulness-promoting process during the day. The timing of REM sleep is linked to the circadian rhythm, closely mirroring the core temperature. Thus, the maximum propensity for REM sleep is usually after the nadir of core temperature, around 6 AM, and it is less likely to occur during an afternoon and evening nap.[21]

The homeostatic or recovery drive to sleep (the S process) is wake-dependent, ie, it increases in proportion to the amount of time since last sleep. Its usual maximum is at about 11 PM, or about 16 hours after waking up in the morning, and then decreases during sleep, with a minimum at natural waking in the morning. When sleep has been shorter than usual there is a "sleep debt" which leads to an increase in the S process—this works to ensure that the debt is made up at the next sleep period, by accelerating the time to sleep and possibly by increasing sleep depth and duration.

These two processes interact to promote the onset of sleep when both are high (at the usual bedtime), and maintain sleep when the C process is high and the S process is declining (in the early hours of the morning). SWA (see above) is a marker of the homeostatic drive to sleep; thus, the amount of SWA is greatest in the first sleep cycle when sleep propensity is high, and gradually diminishes in subsequent cycles as sleep debt is made up and sleep drive diminished.

Sleep abnormalities in depression, both subjective and objective, point to a disruption in both homeostatic and circadian drives to sleep. A frequently occurring symptom is taking a long time to initiate sleep,[3] which is common to some other psychiatric conditions, particularly generalized anxiety disorder.[23] It may be that general hyperarousal, or psychic anxiety, which is present in about 80% of depressed patients, may be a contributory factor in this early insomnia. The alteration in timing or evolution of SWA may be thought of as a disruption in the normal S process, resulting in a decreased pressure to sleep. This hypothesis has never been tested properly in depressed patients, although its validity may be supported by the effects of sleep deprivation (see below). In addition, effective treatment with antidepressant drugs tends to restore the profile of SWA towards normal,[23] but it is difficult to disentangle these effects on SWA from those on REM sleep.[14]

In contrast, alterations in REM latency, increase in waking and stage 1 sleep, and waking early point to the C process being affected; in depression patients would have an earlier onset of key sleep rhythms. Whether the circadian rhythm disruption is a cause, a consequence, or a comorbid condition of depression is the subject of much research at present, as the underlying genetic control of the mammalian clock is becoming clearer, and investigation of clock genes in depression more common. Some interesting data has emerged linking some of these genes with sleep in bipolar disorder[25] and with the response of insomnia in depression to treatment with antidepressants[26]; however, there is little as yet which clarifies the relationship between circadian genes and sleep in unipolar depression. Another theory relates to deficiencies in key neurotransmitters such as serotonin (5-HT), noradrenaline, or acetylcholine leading to phase advance of sleep rhythms in depression.

Evidence for both S and C processes being implicated in depression is contained in the phenomenon of total sleep deprivation improving mood the next day in major depression, which has been known and used for many years.[27] This is an extension of the well-known feature seen in many patients with severe depression that mood is worse in the mornings and gradually improves during the day, to the point that it can be in the normal range just before bed—only to revert back to depression during sleep. However, keeping patients awake all night is difficult to perform, and once they are allowed uninterrupted sleep all the beneficial effects of sleep deprivation disappear. Recent research

has refined the methods of manipulation of sleep and circadian rhythm to maximize its effects on mood by bringing the sleep period forward,[27] and there have been several strategies proposed to prolong the therapeutic effect such as adding drug interventions and strictly controlling the amount and type of sleep allowed in the following days.[28,29] It can be argued that this intervention works to increase the pressure for sleep (homeostatic process) and on basic circadian function in the brain, supporting a "phase advance" of circadian rhythm in depression which is corrected by sleep manipulation. Further evidence is gained from studies showing that those patients who respond to sleep deprivation and to light treatment are those in whom phase advance has been demonstrated by actimetry (a technique which measures sleep-wake cycles using movement sensors worn for many weeks on the wrist).[30]

There is evidence from animal studies of an immediate increase in 5-HT, noradrenaline, and dopamine function in rat brain after sleep deprivation.[31] Neuroimaging studies provide some evidence that in depressed patients, the metabolic hyperactivity seen in the anterior cingulate in depression is corrected by sleep deprivation.[32,33] Thus the effects of sleep deprivation may be mediated via multiple brain systems.

Sleep in depressed patients may be more sensitive to life events which disrupt daily rhythms. Haynes et al[34] rated these events in a group of depressed patients and measured sleep disruption by actigraphy. Depressed patients who had experienced social rhythm-disrupting events, for instance overseas travel, being fired from a full-time job without immediately starting another, starting full-time college, or marital separation, had much more wakefulness during the night compared with those patients without these events, and this difference was not evident in normal controls.

Increased risk of depression in insomnia

The National Institute of Mental Health Epidemiologic Catchment Area study 20 years ago interviewed 7954 adults on two occasions a year apart, and this study first highlighted the strong association between sleep disturbance and subsequent depression. They found that 14% of those who had insomnia at the first interview had developed new major depression a year later.[35] This data has been augmented by several more recent reports of increased risk. Breslau et al,[5] in a survey of 1200 young adults in Michigan, found that the odds ratio of new

depression in was 4 times increased in those subjects who had insomnia 3 years earlier, and in a questionnaire survey of adults over 18 in the UK there was a 3-fold increased risk of new depression if subjects had reported one sleep problem occurring "on most nights" a year earlier.[36] Doctors in a prospective study who had complained of insomnia during medical school in the 1950s and 1960s were twice as likely to have developed depression at follow-up in 1990s.[37]

It is apparent that sleep problems often appear before other depression symptoms,[38] and that subjective sleep quality worsens before onset of an episode in recurrent depression.[39]

Residual insomnia: relapse and recurrence

There is much evidence that effective antidepressant treatments can successfully elicit significant response in depression, but is much less evidence that effective treatment fully addresses the problem of sleep disturbance. Persistent insomnia is one of the most common residual symptoms in patients with incomplete remission.[40] This presents a problem, given the fact that residual insomnia confers greater risk of subsequent depression: in a study of "remitted" patients maintained on a selective serotonin reuptake inhibotor (SSRI) and psychotherapy,[41] subjective sleep problems and anxiety were each found to be predictors of early recurrence. The origin of these residual symptoms of insomnia is probably multifactorial, reflecting ongoing functional brain abnormalities as well as adverse effects of some drug treatments, for example SSRIs, particularly fluoxetine, can lead to insomnia.

Implications for treatment

Anomalies in sleep architecture in depression are linked with treatment outcome; for instance they may predict poor response to cognitive behavioral therapy (CBT)[42] and interpersonal therapy,[43] and more patients experience a recurrence of depression after successful CBT treatment if they have an abnormal sleep profile.[42] Response to antidepressant drug treatment is not predicted by sleep EEG abnormalities; however, placebo nonresponse is more likely in those patients with an abnormal sleep profile.[44]

Selective serotonergic drugs are the present first-line therapy for depression, and there is much evidence for the involvement of 5-HT in the pathogenesis of both depres-

sion and sleep disturbance. For instance, rapid tryptophan depletion, which reduces brain 5-HT function, results in a temporary return of depressive symptoms in recovered depressed patients,[45] and a reduction in REM latency. [46] SSRIs which increase 5-HT function increase REM latency, and reduce REM sleep.[47] However, although SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and venlafaxine are effective and widely used, they may worsen sleep disturbance early in treatment[48,49] and may leave residual sleep symptoms once mood is improved.[50] Benzodiazepine and Z-drug hypnotics (non-benzodiazepine hypnotics, such as zolpidem and zopiclone) are often required to deal with these adverse effects, which can lead to problems with dependence and withdrawal. However, in a study in which eszopiclone was added to fluoxetine in depressed patients[51] there were significant beneficial effects, even in depressive symptoms other than insomnia items.

Some antidepressants can have a beneficial effect on sleep. These include mianserin, trazodone, nefazodone, and mirtazapine, as well as the older tricyclic antidepressants. The mechanisms underlying this are complex and relate to interactions (blockade) of certain neurotransmitter receptors—with significant 5-HT antagonist properties being a common theme—though antagonism at histamine H_1 and noradrenaline α_1 receptors also plays a part for some of these drugs.

In conclusion

Subjective and objective sleep disturbance in depression is prevalent, distressing, and often unresolved by treatment. It indicates significant alterations in brain neurotransmitter function, as well as leading to significant impairments in quality of life and further treatment-seeking by sufferers, so increasing the burden on health care services. There is therefore a need for more successful management of sleep disturbance in depression, in order to improve quality of life in these patients and reduce an important factor in depressive relapse and recurrence. ❏

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Los trastornos del sueño como síntomas nucleares de la depresión

El sueño y la depresión están fuertemente relacionados. Cerca de tres cuartas partes de los pacientes depresivos tienen síntomas de insomnio, y la hipersomnia se presenta en alrededor del 40% de los adultos jóvenes con depresión y en el 10% de los pacientes de mayor edad, con un predominio entre las mujeres. Los síntomas provocan un inmenso distrés, tienen un gran impacto en la calidad de vida y constituyen un potente factor de riesgo para el suicidio. Además de la experiencia subjetiva de los síntomas del sueño, en la depresión existen cambios bien documentados en la arquitectura objetiva del sueño. En este artículo se discuten los mecanismos de la regulación del sueño y cómo ellos pueden estar alterados en la depresión. Los síntomas del sueño a menudo no se resuelven con el tratamiento, y aportan un mayor riesgo de recaídas y recurrencias. Los estudios epidemiológicos han señalado que el insomnio en los sujetos sin depresión es un factor de riesgo para que más adelante se desarrolle este cuadro. Por lo tanto, se requiere de un manejo más exitoso de los trastornos del sueño en la depresión para mejorar la calidad de vida de estos pacientes y para reducir un factor importante en las recaídas y recurrencias depresivas.

Les troubles du sommeil, symptôme majeur de dépression

Le sommeil et la dépression sont fortement liés. Environ trois quarts des patients déprimés souffrent d'insomnie et l'hypersomnie existe chez à peu près 40 % des jeunes adultes déprimés et 10 % des patients plus âgés avec une prédominance féminine. Ces symptômes sont responsables d'une grande souffrance, ils diminuent beaucoup la qualité de vie et sont un facteur de risque important de suicide. Les modifications de l'architecture objective du sommeil dans la dépression sont aussi bien documentées que les troubles subjectifs du sommeil. Les mécanismes de régulation du sommeil et la manière dont ils peuvent être perturbés lors de la dépression sont discutés. Les troubles du sommeil persistent souvent en dépit du traitement, et représentent un grand risque de récidive et de rechute. Des études épidémiologiques ont souligné que l'insomnie chez des sujets non déprimés est un facteur de risque de dépression ultérieure. Il est donc nécessaire que les troubles du sommeil soient mieux pris en charge dans la dépression afin d'améliorer la qualité de vie chez ces patients et de réduire ce facteur important de récidive et de rechute dépressive.

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