

REVIEW ARTICLE

The relationship between sleep disturbance and depression

ANDREW G. MAYERS^{1,2} & DAVID S. BALDWIN¹

¹University of Southampton, and ²Southampton Solent University, Southampton, UK

Abstract

This paper focuses on several aspects of the relationship between sleep and depression, with particular attention to objective factors and subjective perceptions. It does not address the effect that antidepressants have on sleep, nor does it explore the wider implications of the types and course of depression, age, or other psychiatric conditions. “Normal sleep” is explored, examining typical sleep architecture in individuals without sleep disorders, psychiatric conditions or physical illness. Sleep disorders are reviewed and examined to present the nature of the disturbance and the role that they may play in depression, with particular attention paid to insomnia. Studies have identified a sub-group of insomnia patients (highly distressed poor sleepers), who appear to be less satisfied with their sleep quality than “low distressed poor sleepers”, even though they did not differ on sleep timing perceptions. Recent work has shown that depressed individuals to be less satisfied with sleep quality than healthy controls, even though they did not differ on sleep timing perceptions. The evidence presented here supports the view that subjective sleep perceptions play an important role in depression. Poor subjective perceptions of sleep in depression may be associated with faulty cognitions. This has been found extensively in insomnia, but is under-researched in depression.

Key Words: *Sleep, depression, perception, electroencephalography*

Normal sleep

The average adult human spends between 6½ and 8 hours sleeping, usually at a regular time each night [1]. It is argued that circadian rhythms regulate sleep over an approximate 25-hour daily schedule [2], managed by the individual, using cues from the environment, such as clocks and sunlight/darkness, to maintain a 24-hour cycle [3].

Sleep electroencephalography (EEG) has shown that sleep progresses through a series of stages that represent the depth of sleep [4]. Traditionally, these stages are defined by guidelines that are universally accepted [5], although not entirely without critics [6]. Stage 1 is a light sleep represented on sleep EEG by mixed frequency, low amplitude, waves. It is similar to alert wakefulness [7], but is easily distinguished from it [8]. Stage 1 sleep accounts for about 2–5% of the overall sleep episode in healthy young adults. Stage 2 is characterised by sleep spindles (rapid bursts of high amplitude activity) and K-complexes (bi-phasic waves of sharply contrasting high and low amplitude). This stage represents about 55% of the sleep episode [8]. Stage 3 is represented by slower sleep waves of higher amplitude, and lower frequency. In Stage 4, the deepest sleep, the delta activity of low frequency, high-amplitude,

waves become more pronounced [7]. Stages 3 and 4 represent slow-wave sleep (SWS) and occupy about 13–25% of the overall sleep episode [8].

Across the night, sleep is normally divided into four to six cyclic progressions. In normal young adults SWS predominates the first third of the sleep episode. After the first cycle, Stage 1 sleep becomes punctuated by periods of intense brain activity, known as rapid-eye-movement (REM) sleep [9], so called because of the appearance of frequent and intense bursts of eye movement, but with an almost total lack of muscle tone elsewhere in the body. REM sleep is commonly associated with dreaming. Sleep stages 1–4, are regarded as non-REM (NREM) sleep. After the initial progression to deeper SWS sleep the progression between sleep stages is erratic, although cycling between NREM/REM stages is more predictable, typically following a 90–120-minute cycle [8].

The first REM period in normal sleep occurs between 60 and 110 minutes after sleep initiation [3], and REM sleep periods generally get progressively longer and denser, as the night progresses (a few minutes in the initial REM stages to 30 minutes or more in the final stages). Figures 1 and 2 demonstrate sleep, produced by sleep EEG;

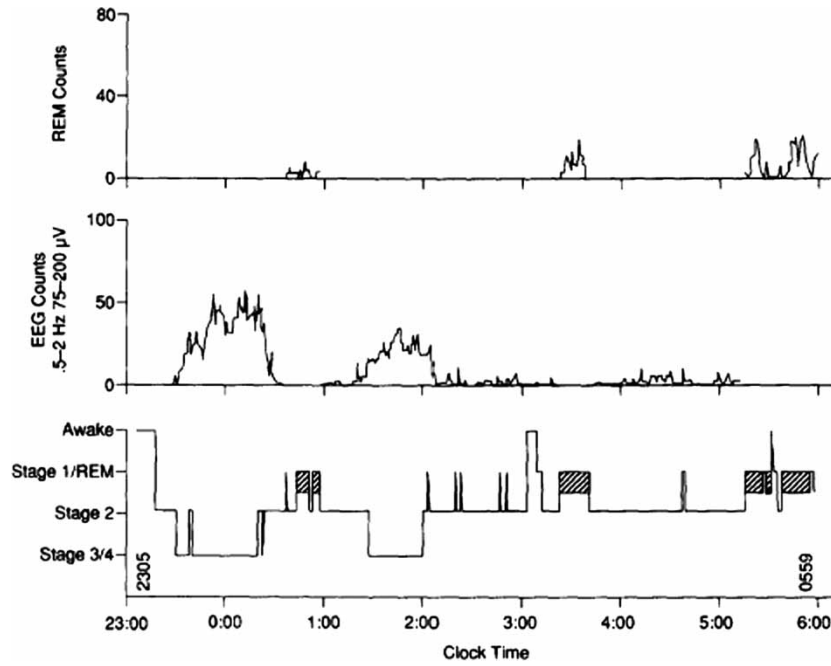


Figure 1. Sleep EEG representing a healthy individual (from [130]).

Figure 1 represents a healthy individual, Figure 2 shows sleep for a depressed individual.

The debate over the individual functions of REM versus NREM remains largely unresolved. Hartmann [4] argued that there are distinct types of sleep, represented by the sleep stages, which provide separate functions for the sleeper. It has been proposed that SWS provides physical restoration, and is fairly constant between sleepers [4]. Factors such as daytime exercise can lead to variations in SWS, with increased activity resulting in more SWS

in the subsequent sleep episode [4]. On the other hand, lighter sleep, and particularly REM sleep appears to fluctuate more according to the sleeper's psychological needs [10].

It has also been shown that human growth hormone (GH) is secreted during SWS; several studies have confirmed the positive relationship between SWS and GH [11]. GH depletion may be associated with poor quality of life. One recent study showed that nine patients with deficient GH presented less SWS, less overall sleep, greater sleep

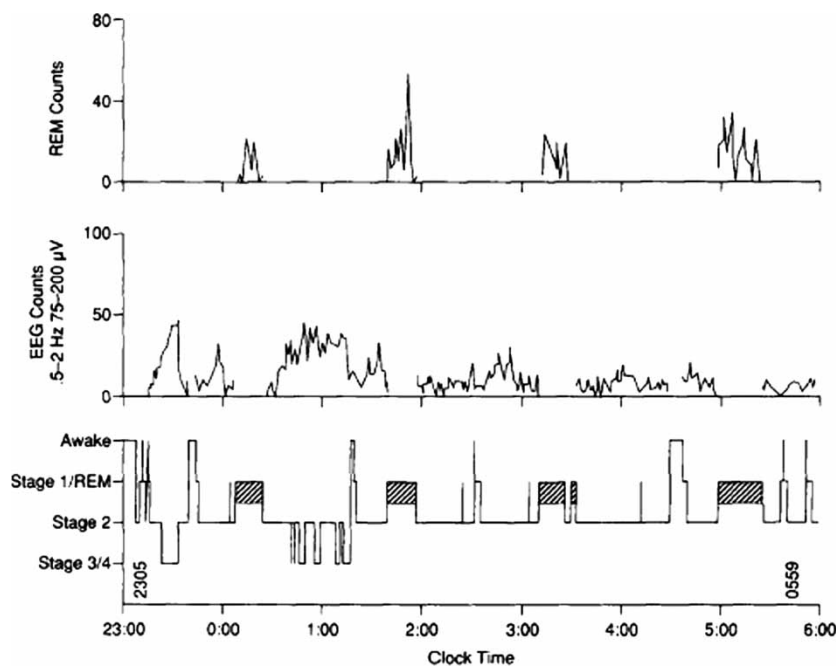


Figure 2. Sleep EEG representing a depressed patient (from [130]).

fragmentation and poorer quality of sleep than nine healthy controls [12]. Poorer sleep quality may be associated with subsequent quality of life.

REM sleep is commonly associated with dreaming. Dreams can often reflect current thinking styles and mood. Consequently, most dreaming is pleasurable [13]. As will be seen later, depressed individuals have been found to spend more time in REM sleep than healthy controls. Given the earlier discussions, a predominance of REM sleep at the expense of SWS, may be associated with less physical restoration, less GH release, more sleep fragmentation and poorer quality of life. Depression is associated with generally negative cognitions [14], so it could be expected that depression is also associated with negative dreams. However, this may help with the self-regulation of mood. One study [15] demonstrated that 39 of 61 participants presented symptoms of depression, using the Beck Depression Inventory (BDI; [16]). Of these, more than three-quarters reported negative dreams. They were more likely to be remitted at follow-up than those who did not report negative dreams. This may represent a within-sleep mood regulation, particularly earlier in the condition. Later sleep negativity may be associated with poorer cognition. On the other hand, the continuation of negative thoughts in sleep, as well as daytime cognition, may serve to exacerbate the condition. Furthermore, most antidepressants suppress REM sleep and reduce dreaming and yet are associated with an improvement in mood; this is more likely to support the latter argument rather than the former.

Nevertheless, trying to precisely define a specific role for either REM sleep or NREM sleep may be fruitless, given the complexity and interactive nature of sleep stages and architecture [17]. Part of the problem may be the way in which sleep is measured and scored. The gold standard for "scoring" sleep was defined in 1968 by Rechtschaffen and Kales [5]. Since then, much has been learned about sleep that suggests this reference system may need to be updated to reflect current knowledge and research. Several researchers have suggested revision; a recent review summarises the points and draws upon clinical and research experience [6].

Himanen and Hasan [6] argue that the Rechtschaffen and Kales system is sufficient for most normal sleepers, but is unable to address those with more complex and disturbed sleep. A single channel of EEG, supported by electrooculography (EOG) to detect eye movement and electromyography (EMG) to measure muscle activity, detects electrical activity and movement from a very limited source across the scalp; it is possible that several areas need to be examined, particularly in disturbed sleep. Normal sleep is associated with fewer sleep-stage changes; current EEG scoring techniques fail to account for the rapid and frequent changes

observed in disturbed sleep. The complexity of sleep, particularly for those with disturbed sleep, presents conflicts when making decisions on scoring ambiguous sleep stages. There may be features of more than one sleep stage in any one epoch; currently the most predominant stage is selected. However, it is possible that there should be several sub-stages within each stage, or more stages to reflect current knowledge of sleep complexity [6].

Dyssomnias

The dyssomnias refer to disruptions to the timing, quality and amount of sleep, and are dominated by research focusing on insomnia. The association between insomnia (and to a lesser extent hypersomnia) and depression is well documented and is reviewed later.

Narcolepsy

Narcolepsy is a neurological disorder, in which the patient may present excessive daytime sleepiness (EDS), frequent daytime naps or lapses into sleep, hypnagogic hallucinations, cataplexy, and sleep paralysis [18]. EDS is a primary diagnostic criterion for narcolepsy. It can present as subjective feelings of sleepiness, or as sudden irresistible sleep attacks [19]. Although sleep attacks can be frequent, nocturnal sleep is still disturbed, and patients' total 24-hour sleep is rarely longer than normal. Hypnagogic hallucinations refer to often frightening images that occur at sleep onset. They are usually visual, but can be auditory. Frequently these hallucinations relate to perceptions of intruders, or people (or animals) standing over the patient (or being under the bed) [20]. The perception of these experiences appears so real that the patient often needs reassurance from their bed partner [19]. Some perceptions can be so intense that the patient is considered psychotic.

Cataplexy is represented by sudden collapsing, in association with intense emotion (usually laughter, but occasionally anger) with total loss of muscle tone. Frequently, the knees give way leading to collapse but, whilst abrupt, the patient usually has sufficient time to find support to avoid injury; consciousness is preserved [19]. Sleep paralysis is often experienced just before or immediately after sleep. The individual is unable to move, but remains awake and conscious; this can be very frightening. Patients cannot open their eyes but yet feel awake. This state is often associated with hypnagogic hallucinations (or hypnopompic hallucinations if waking), which make the experience more frightening [19]. Narcoleptic patients often experience disturbed and fragmented nocturnal sleep, albeit with short sleep onset. Nocturnal disturbances can also be associated with periodic limb movement disorders (such as restless legs), sleep apnea, REM

sleep behaviour disorders and sleep talking, all of which add to the unpleasant nature of this experience [19].

Several studies suggest that there is an association between narcolepsy and depression. In one study examining 305 members of the UK Narcolepsy Patient Association [21], subjects demonstrated significantly poorer quality of life perceptions, as measured by the short-form 36 scale (SF-36 [22]), compared to normative data. In contrast, when 45 narcoleptic patients were compared to 50 controls, the lifetime frequency of depression did not differ [23].

By definition, narcolepsy is associated with sleep-onset REM (SOREM) and increased REM density; shortened REM latency and greater REM density are also common with depression [24]. The narcoleptic symptoms of EDS may also explain the association with depression, as can frequent nocturnal disturbance. Cataplexy in narcolepsy is often treated successfully with antidepressants associated with REM sleep suppression. This action appears to improve mood and reduce cataplexy, sleep paralysis and hypnagogic hallucinations. The most common treatment is the tricyclic antidepressant clomipramine, which has also been found to alleviate EDS, although some selective serotonin reuptake inhibitors (SSRIs), such as fluvoxamine and paroxetine, have also shown positive results [19] and psychostimulants such as modafinil can be used [25].

Sleep apnea

Obstructive sleep apnea (OSA) patients experience repetitive cessations of breathing during sleep, similar to choking, which cause brief arousals followed by “snoring” that marks the return to normal breathing [1]. Whilst primarily a physical condition, OSA can be associated with personality changes, depression and anxiety, as well as poor daytime function [26]. Several studies have sought to examine the association between OSA and depression. In one study [27], 2271 patients with suspected OSA, were examined for psychiatric symptoms. Females showed significantly higher levels of depression in severe OSA than in milder cases, although males showed no such relationship. Another study [28], demonstrated that OSA patients ($n=60$) showed poorer SF-36 scores than controls ($n=34$), and poorer perceptions on the Epworth Sleepiness Scale (ESS; [29]) and the Zung Self-rated Depression Scale (SDS; [30]). In a recent epidemiological study [31], patients with breathing-related sleep disorders, including OSA, had higher rates of major depressive disorder, and vice versa, even after controlling for obesity and hypertension.

A number of correlation studies have examined the extent of the relationship between OSA and depression. For example, in a study of 49 OSA

patients [32], 32% demonstrated high depression scores on the Minnesota Multiphasic Personality Inventory (MMPI; [33]) compared to 49 healthy controls. On the other hand, some studies have failed to find an association between OSA and depression. One study [34] examined 95 elderly subjects at baseline, of whom 42 were available at 5-year follow-up; 10 of these had presented mild OSA at baseline and 32 had no symptoms. Depressive symptoms did not differ between these groups. The problem here is that OSA was only measured at baseline, telling us nothing about follow-up profiles. Even so, the severity of OSA at baseline was mild, perhaps explaining the low level of association with depression.

It is possible that the association between OSA and depression has been overstated. One review [26], examined 16 studies that explored the relationship. The authors categorised those studies which highlighted a strong relationship (nine), those which suggest that depression is secondary to OSA, or at least resolved by treating the OSA (five), and two studies which claimed no association at all. Those studies which propose that the relationship between OSA and depression is secondary also claim that the association is no more prevalent than in any other chronic illness [35]. In one study, although OSA was associated with depression, that relationship disappeared when controlling for age, body mass and hypertension [36].

Those who claim that there is no relationship at all (e.g., Lee, 1990 [37]) argue that depression in OSA is overstated because the primary condition is “psychologised” by using scales such as MMPI and BDI, which use vegetative symptoms in the depression cluster, thus giving a false positive. The authors prefer to use “clinical experience” to observe for signs of mental disorder. However, this is only replicable if observations are made through standardised interviews and quantifiable scales [26].

A partial explanation for the association between OSA and depression can be found in sleep architecture. OSA is associated with frequent arousals from sleep, which have an impact on EDS [38]. This is probably a key factor in associated depression [39]. OSA also presents significant increases in Stage 1 sleep, usually at the expense of REM sleep and SWS. In some cases SWS is completely abolished; the patient will not be aware of this, but may feel like they are not refreshed upon waking. This may also explain some of the association with depression. However, the reduction in REM sleep would not explain such an association [40]; depression is often related to increased REM sleep, especially shorter REM latency [41]. On the other hand, it has been shown that OSA patients with depression present greater REM sleep percentage than OSA patients without depression [42]. This perhaps highlights the

interaction of OSA and depression and indicates that sleep EEG produces confounding results in each condition [38].

Treatment studies also provide some insight into the relationship between OSA and depression. The standard treatment for OSA is a mechanical device called “continuous positive airway pressure” (CPAP). Several studies have shown that the use of CPAP reduces depressive symptoms, in addition to successfully treating the OSA [43], although not all studies agree [44]. A possible explanation for conflicting results is that CPAP treatment involves patients wearing an intrusive device over the nose (and sometimes mouth). This may affect compliance, especially in depressed populations [45]. Another problem is that there is no direct correlation between OSA severity and mood improvement after CPAP, but depression severity does affect response to CPAP [46].

A final point relates to the direction of relationship between OSA and depression. It seems logical that OSA is more likely to cause depression, rather than vice versa. However, treatments for depression and related insomnia may have an impact on OSA. Some depressed patients require additional medication as an adjunct to their antidepressant to treat insomnia. Hypnotic medications may adversely affect the dilator muscles responsible for OSA and make the situation worse [47].

Restless legs syndrome and periodic limb movement disorder

Restless legs syndrome (RLS) is the subjective feeling of unpleasant physical sensations in the legs, often accompanied by observable “periodic limb movements”, or “leg jerks”. RLS tends to occur near bedtime, often associated with early or middle insomnia and can result in EDS [48]. RLS can present from childhood to old age, but is more common with increasing age [49], and in women [50]. The diagnostic criteria for RLS require all of the following to be met: an urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs; those feelings and urges begin or worsen during periods of rest or inactivity (such as lying or sitting); those feelings and urges are relieved, at least partially, by moving the legs, but only for as long as that activity continues; those feelings and urges are worse in the evening or night than during the day [51]. RLS is often reported in obstructive sleep apnea, narcolepsy, and REM sleep behaviour disorder [52]. RLS can also be associated with depression. In one study [53], RLS patients ($n=103$) demonstrated significantly poorer Hamilton Rating Scale for Depression (HAMD [54]) scores than controls. In another study [55], 369 participants were assessed for RLS. Overall prevalence was 9.8% and was significantly more common

in women (13.9%) than men (6.1%); participants with RLS presented a significantly greater incidence of depression than those without RLS.

More recently, Winkelmann et al examined the risk factors for depression in RLS [56]. Healthy controls ($n=4181$) were drawn from an earlier community survey. RLS patients reported significantly higher 12-month rates of depression than controls (Odds Ratio (OR)=2.6) and were significantly more likely to present with comorbid depression (OR 2.1). RLS patients were significantly more likely to attribute their depression as being the result of RLS (OR 24.9). However, significant associations were also found with several anxiety symptoms. RLS can be a side effect of antidepressant treatment, e.g., with mianserin [57] or mirtazapine [58].

Circadian rhythm sleep disorders (CRSD)

CRSD represent a group of sleep disorders that share a common profile: a misalignment between the patient’s sleep patterns and those considered to the societal norm [59]. Typically, sleep occurs at the wrong time of day, or is out of phase with normal, and includes sleep disorders such as jet lag, shift work, and sleep phase syndromes, each of which are explored separately below. However, each of them shares features that might explain any possible association with depression. CRSD not only present changes in timing, which may be associated with EDS, but also with other circadian rhythm-related factors, such as melatonin release and body temperature [60]. Melatonin may be of particular relevance, as it is also implicated in depression; several studies have shown reduced melatonin levels in depression [61]. Melatonin depletion is observed in CRSD [62]. Melatonin is easily administered, and has been shown to successfully treat shift work [63] and delayed sleep phase syndrome [64].

Time zone change (jet lag) syndrome

Jet lag is a phenomenon associated with travel across time zones, which may be associated with fatigue, poor concentration, irritability and depression. The effect appears to be most pronounced on trips over several zones involving forward shifts in time. In one study [65], sleep was disrupted, and depression ratings were poorer, in male volunteers whose flight involved a 7-hour forward time shift, but not in one involving a 7-hour backward time shift. Further analyses suggested that the forward-time-shift flights were associated with increased REM production [66]. The authors suggest that daylight may be implicated in changes to the melatonin rhythm, although melatonin treatment for jet lag is less well supported than other CRSD [60].

Shift work sleep disorder

Individuals who are subject to regular shift work appear to be more prone to significant problems relating to physical and mental health, including depression. In one study [67], nearly 82% of Japanese shift workers ($n = 174$) presented insomnia, autonomic dysfunction and other physical complaints, while 18.4% were diagnosed with depression. A community study involving 2570 participants included 360 working rotating shifts, 174 on night shifts, with the remainder on normal day shifts [68]. Those working abnormal shifts, who presented EDS or insomnia, also presented significantly more depression, absenteeism and sleep-related accidents.

Sleep phase syndromes

Advanced sleep phase syndrome (ASPS) is typical in older people, and is represented by earlier retirement to bed and early morning awakening. Delayed sleep phase syndrome (DSPS), often seen in younger people, involves later sleep onset times (often beyond normal social hours) and late morning waking [69]. ASPS has been associated with depression [70], but DSPS receives most attention in the literature. In one study [71], three-quarters of sleep-disorder patients ($n = 33$), with a mean bedtime of 04:00 and a mean wake time of 10:38, had a current, or historical, diagnosis of depression; for one-half of these the depression was resistant to treatment.

Parasomnias

Parasomnias are represented by undesirable physical and behavioural abnormalities during sleep that are frequently disturbing (and occasionally hazardous) to the sleeper or their bed partner. Typically these involve unusual arousals, movements or perceptions.

Nightmares, night terrors and sleepwalking

Nightmares occur during REM sleep; the sleeper usually recalls the dream, often waking soon after as a result [1]. Night terrors and sleepwalking tend to occur during non-REM sleep, with the sleeper usually having no recall of the event. Night terrors are an abrupt arousal from sleep, often accompanied by panic and screaming [72]. Sleepwalking is relatively mild, compared to the often dramatic characteristics of sleep terrors. Sleepwalkers appear to be oblivious to the surrounding environment, presenting a blank expression, and clumsy purposeless activity [1].

Studies that address the relationship between these conditions and depression are scarce. One study of more than 5000 French participants [73],

found that 18.3% of those with insomnia ($n = 1049$) reported nightmares. These were significantly associated with multiple awakenings, increased sleep latency, poor memory and greater anxiety during the proceeding day. Nightmares were also significantly associated with depression in women, but not men. However, it has been suggested that it is the distress associated with those reports of nightmares that are related to depression, rather than the nightmare itself [74]. In a large British sample ($n = 4972$) [72], 30.4% of those reporting night terrors, and 14.6% of those reporting sleepwalking, were significantly more likely to have diagnosis of major depression than controls (5.7%).

REM sleep behaviour disorder

Normally, dreaming is devoid of physical activity because of reduced (almost paralysed) muscle tone during REM sleep. REM sleep behaviour disorder is a rare condition, whereby the dreamer “acts out” the dream, sometimes violently [75]. There is some evidence suggesting an association with depression [76]. In the Ohayon study [72], violent behaviour in sleep was reported in 2.1% of participants. This group reported more night terrors, daytime sleepiness, and hypnagogic hallucinations (often visions of being attacked), than those not reporting the behaviour. They were also more likely to have reported symptoms of depression and anxiety in the prior year.

Because so little research has been conducted specifically examining the association between REM sleep behaviour disorder and depression, and never in controlled conditions, this should be viewed with caution. This is true of any sleep disorder, but particularly parasomnias, which have been less rigorously examined than narcolepsy, OSA and RLS. A recent study sought to rectify the paucity of research in some sleep disorders and their association with depression [77]. They recruited 917 patients from a Dutch sleep disorders clinic (aged 18–84 years). The authors examined the prevalence of associated depression with the primary sleep disorder using the BDI; a score of 10 or more indicates the possible presence of depression. At least some presence of depression was found in OSA (41%), insomnia (43%), narcolepsy (37%), RLS (53%), DSPS (41%), ASPS (83%), and parasomnias (29%). However, the detection of depression, using the BDI, was based on subjective feelings, rather than clinical syndromes; the sample sizes in some disorders (e.g., ASPS, $n = 5$) was low; and the findings probably have little reliability in clinical settings. There is still a need for larger, more controlled studies to fully understand the relationship between sleep disorders and depression.

Insomnia and hypersomnia

Insomnia is the most common of the dyssomnias and is diagnosed when the patient reports at least 2 weeks of problems initiating or maintaining sleep, or with early morning awakening, nearly everyday [1]. DSM-IV specifies that these symptoms prevail for a month or more, and are associated with significant distress and impairment in normal functioning [78]. Hypersomnia is marked by excessive sleep [79], defined as sleeping too much nearly every day for 2 weeks.

The relationship between sleep disturbance, particularly insomnia, and depression has received much attention, and is divided between those studies that focus on subjective assessment of sleep, and those that examine objective measurement. In one review [80], it was noted that one-third of patients with chronic sleep problems present mood disorders and that most patients with mood disorders experience insomnia and, less often, hypersomnia. The relationship between sleep and psychiatric conditions is illustrated in an earlier meta-analysis [81]. They studied data from 177 research investigations, involving over 7000 patients and controls. Poor sleep was implicated in most psychiatric disorders, but only affective disorders showed a significant difference to controls on all variables. Sleep EEG analyses showed that depressed patients demonstrated shorter total sleep time, longer sleep latency, less slow-wave sleep, shorter REM latency, and greater REM density, compared to controls. No other psychiatric disorder demonstrated the same contrast to controls.

Disturbed sleep may be a symptom of depression, or it may be a prodrome. The causal direction of insomnia and depression is not clear, but longitudinal studies have helped to provide some indication. In one seminal study [82], nearly 8000 US patients were examined at baseline and followed-up 1 year later. At baseline, the prevalence of insomnia and hypersomnia was 10.2 and 3.2%, respectively. Furthermore, 40% of those with insomnia and 46.5% with hypersomnia had a comorbid psychiatric disorder (16.4% had no sleep complaint). Follow-up measures indicated that the risk of developing new cases of depression was nearly 40 times greater when insomnia was present at both interviews, compared to an absence of insomnia. The risk of developing new cases of depression was less than two times greater for those whose insomnia was resolved, compared to those who did not have insomnia at baseline either. These findings underlie the risk for depression associated with persistent insomnia.

In another study [79], conducted over 3.5 years, 1007 patients were examined. At baseline 31.1% of participants with insomnia, 25.3% with hypersomnia, and 54.3% with the combined condition also reported symptoms of major depression. When a revised "diagnosis" of depression (excluding sleep

disturbance as a criterion) was used the association of depression was reduced, but remained significant (22%; 18%; 37%). The relative risk of developing a "first" diagnosis of depression by the 3.5-year follow-up period was found to be 15.9% of participants who had presented a history of insomnia at baseline, compared to 4.6% of participants without that history. Adjusted figures demonstrated that patients with history of insomnia at baseline were four times more likely to develop new depression, and almost three times more likely to do so with a history of hypersomnia.

In a more specific longitudinal study [83], more than 1000 US medical school graduates were examined while students, and then followed up since leaving (up to 45 years). One-tenth of former students developed depression. The relative rate of depression was more than twice as great for those who had reported insomnia at medical school, and 1.8 times greater for those reporting sleep difficulty (compared to those who did not). This shows the risk that insomnia presents for depression can persist over time.

The relationship between insomnia and depression also appears to depend on the severity of the sleep complaint. In a study of more than 2500 German patients in primary care [84], assessed at baseline, 4 months and 2 years, the presence of depression at follow-up was much stronger if patients presented severe insomnia at baseline. This was also confirmed in a US study involving 1814 primary care patients over 2 years [85]. At baseline, 16% of patients presented severe insomnia, and 34% mild. At follow-up, 59% of those with mild insomnia, and 83% of those with severe insomnia, still had sleep problems. Odds ratio risk factors associated with depression were 2.6 for those with mild insomnia, and 8.2 with severe insomnia, compared to rates of depression with those not presenting insomnia at all.

Using data from the HAM-D and BDI for 14 subjects remitted from depression [86], it was found that recurrence was associated with increased levels of sleep disturbance prior to that recurrence. Chi-square analyses showed that a significantly greater proportion of recurrent subjects complained of insomnia symptoms than those who were still in remission (85.7 vs. 28.7%; $P < 0.05$). The same authors demonstrated subjective sleep complaints and EEG sleep abnormalities are associated with risk of the onset of "first ever" depression, and to recurrence of depression [87].

Objective factors

The most common form of objective sleep measuring technique is the sleep EEG. This involves placing small electrodes on the scalp of the participant. From these, the EEG recording device detects

minuscule traces of electricity between pairs of these electrodes. Sleep EEG differs from traditional EEG, in that it uses fewer electrodes; the purpose of sleep EEG is to detect amplitude and waveform of electrical signals across sleep stages, and to measure eye-movement and muscle activity to illustrate REM sleep.

An obstacle to using traditional EEG, particularly in research, is the cost of equipment, the need for specialist training in application of electrodes and “reading” EEG output, the time need to attach electrodes for each night of recording, and the inconvenience to participants. Also, most EEG recordings are conducted in the laboratory, thus losing ecological validity. Even with portable EEG devices, the participant needs to visit the laboratory daily to have the electrodes refitted. The journey home from the laboratory can cause some embarrassment whilst wearing the electrodes. Consequently, some researchers prefer to use other methods.

Wrist actigraphy involves strapping a small, watch-sized, device to the non-dominant wrist [88]. It is easier to fit, can be worn for several days at a time, and is considered to be more acceptable to the wearer [89]. It is also cheaper (typically one device costs £250) and downloads data to software programmes without the need for much expertise. The actigraph detects motor activity (body movement) and the researcher is able to accurately establish whether the subject is asleep or awake [89]. Actigraphy has been shown to have a high correlation with traditional EEG, particularly in respect of “total sleep” [89]. However, wrist actigraphy cannot be used for sleep staging [88], nor can it recognise the appearance of REM sleep.

The Nightcap [90,91], involves two crucial sensors: one that is applied to the eyelid using adhesive tape to detect rapid-eye-movements, and a mercury switch to monitor body movement. The sensors are attached to a headband or cap, which is easily fitted by the participant. The Nightcap is relatively inexpensive, is easy to fit and can be worn in the patient’s home and has shown good correlation with subjective sleep reports [91] and objective EEG

recordings [90]. The Nightcap has been found to reliably detect sleep states (in normal populations) and has an 87% accuracy rate compared to sleep EEG [92], 93% concordance for NREM states and 80% for REM states [91], and has been found to reliably distinguish between good and poor sleepers [92]. However, the Nightcap cannot detect sleep stages, nor can it measure the depth of sleep and density of REM counts.

EEG variables

EEG studies consistently report their findings using a standardised set of sleep variables and associated abbreviations. Those abbreviations help reduce the length and complexity of reported data; a list of variables and abbreviations is displayed in Table I. Typical sleep EEG hypnograms for a healthy individual and a depressed patient are presented in Figures 1 and 2, respectively. The depressed patient presents more trouble initiating sleep, attempting sleep on several occasions and waking again, before finally progressing to maintained sleep; sleep initiation is much quicker for the healthy individual. The depressed patient shows the first appearance of REM sleep much earlier than the healthy individual (as shown by the shaded boxes), and wakes more frequently (demonstrated by the spindle peaks in the lower display). The healthy individual spent more time in the deeper stages of sleep (stages 3 & 4) than the depressed patient and shows fewer and less intense occurrences of REM sleep.

Several EEG studies report the extent of sleep disruption in depression. In one study [93], depressed patients ($n=56$) demonstrated reduced TST, greater SL, more REM sleep, less SWS, less SE, more WASO, and shorter REML sleep than controls ($n=41$), and more WMINS, shorter REML, and greater REMD compared to primary insomnia patients ($n=18$). In addition to those findings, a review [41] confirmed that depressed patients spent longer time in REM during the first REM period, compared to non-depressed controls. In the Benca review [81], depressed patients consistently demonstrated shorter TST, longer SL, less

Table I. Sleep variable abbreviations.

Sleep variable	Abbreviation	Refers to
Total Sleep Time	TST	Total time spent asleep during the measured episode
Time in bed	TIB	Time spent in bed, whether asleep or not
Sleep latency	SL	Length of time taken to initiate sleep
Sleep efficiency	SE	Proportion of time spent asleep during the episode ($TST \div TIB$)
Wakings after sleep onset	WASO	Number of times awake during the sleep episode, once sleep initiated
Waking minutes	WMINS	The length of those awakenings
Rapid eye movement (sleep)	REM	Light, almost wake-like, sleep typified by rapid eye movements but associated with a lack of movement elsewhere
Non-REM sleep	NREM	Any sleep not involving REM
Slow wave sleep	SWS	Periods of deeper NREM sleep
REM sleep latency	REML	Length of time from sleep onset to first appearance of REM
REM sleep density	REMD	The number of REM counts within a single period of REM sleep

SWS, shorter REML and greater REMD than controls. Whilst several sleep abnormalities also appeared in other psychiatric disorders only depressed subjects presented all of them in such magnitude. In particular, the degree of REM sleep variation appears to be the factor most associated with depression.

While insomnia and depression are frequently associated, the profile of sleep disturbance is quite different between them. One study [94], found that sleep onset times did not differ between those rated with primary insomnia ($n=21$) and major depression ($n=21$), or healthy controls ($n=21$). However, the control group presented significantly fewer problems maintaining sleep than experimental groups, in respect of TST, SE and WMINS; the depressed group slept more productively than the insomnia group. Both experimental groups exceeded healthy volunteers in respect of WASO, but the depressed group spent significantly more time in Stage 1 sleep and REM sleep than the insomnia group, who spent significantly longer in SWS than the depressed group. Whereas the healthy volunteers, and to lesser extent the insomnia group, showed increases in SWS activity in the first NREM-REM period, the depressed group demonstrated no change.

Studies also suggest that the abnormal sleep architecture observed in depression persists beyond the index episode [95]. Thirteen depressed patients were examined while depressed and when remitted for 6 months. There was no significant difference between when the patient was depressed to when remitted in respect of REMD, REML, TST, or the amount of time spent in REM sleep. Eleven of depressed patients showed reduced REML whilst ill; eight of these were still reduced at remission.

REM latency

There is consistent and conclusive evidence that shortened REM latency is a key indicator for the vulnerability for depression. Kupfer [96] confirmed that shortened REML is a strong predictor of depression, present in almost all primary depressed patients, but absent in those with secondary conditions. One way of examining the potential for REML as a predictor for depression is to explore its presence in (non-depressed) first-degree relatives of depressed patients. Studies suggest that sleep may have a genetic component [97]. There is also evidence that suggests that psychiatric conditions, including depression, may be genetically transmitted [98]. Therefore, it seems reasonable to expect that the risk factor for depression posed by sleep abnormalities is also genetic.

REM sleep and family concordance in depression has been examined extensively by Donna Giles and her colleagues. In one study [99], the relative risk of

depression in relatives with reduced REML was almost three times greater than for relatives without shortened REML. In a later study [100], first-degree relatives of depressed probands, with reduced REML, were shown to present similar polysomnography in other sleep parameters as those seen in the depressed group, even though none of the relatives were depressed at assessment. Reduced REML also appears to be stable regardless of whether depression is new or recurrent [101]. In a more recent study [102], it was demonstrated that REML predicted lifetime history of depression. This risk was almost twice as high in relatives of depressed probands, where the relatives had reduced REML, compared to relatives with normal REML. This suggests that reduced REML is associated with a risk for depression beyond the normal family risk, and that sleep abnormalities may precede depression and be a risk factor for it.

Subjective factors

While objective measures of sleep disturbance clearly have their place in addressing the nature of the relationship with depression, there is a need to address the key role that subjective factors play; this is an area that has been under researched previously. The perception of sleep is a very personal one; each individual can place a different emphasis on the importance of sleep. Insomnia in particular is regarded as a subjective complaint, confirmed by the clinician's observation. The extent that insomnia can precede depression indicates the importance of subjective perceptions of sleep. Furthermore, depression has a large subjective element, especially in respect of cognitive aspects, such as guilt, self-esteem, pessimism, memory, concentration, motivation, and mood.

Methods of measurement

Sleep perceptions are usually collated from diaries, which can be compared to self-reported quality of life questionnaires or to clinician-rated scales that diagnose the nature and severity of psychiatric conditions. These can be very useful in obtaining important information about how an individual assesses the length and quality of their sleep.

The Pittsburgh Sleep Quality Index (PSQI; [103]) is a self-rated questionnaire of sleep quality and disturbance that is completed over one month. It comprises seven components (subjective sleep quality, sleep latency, total sleep time, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction), which lead to one global score. A study of 168 subjects indicated that PSQI was able to significantly distinguish good and poor sleepers, with a sensitivity of 89.6% and specificity of 86.5% [103].

The Leeds Sleep Evaluation Questionnaire (LSEQ; [104]) uses 10 self-rated questions relating to sleep and early morning behaviour, which produce four sleep factors: ease of getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS), and behaviour following wakefulness (BFW). The questionnaire has been used widely in psychopharmacological studies to examine subjective sleep reports as the results of drug-taking behaviour [105]. It has been shown to have good internal consistency across each of the four factors (GTS, $\alpha=0.83$; QOS, $r=0.72$; AFS, $r=0.77$; BFW, $\alpha=0.91$) [106]. The LSEQ has been shown to reliably measure the effects of antidepressants on sleep [107].

The Pittsburgh Sleep Diary (PghSD; [108]) includes two diaries. The bedtime diary requires participants to record events from the preceding day, including meals, caffeine, alcohol, and tobacco consumption, medication taken, levels of exercise and the number of naps taken. The wake time diary, completed the next morning, asks participants about various aspects of the previous night's sleep, including time to bed and length of sleep initiation, and the number and length of nocturnal awakenings. The diary also requires the subject to rate various aspects of their sleep satisfaction. In a cohort of 234 participants, subjective sleep ratings correlated well with objective (actigraphy) measures, and the diary was sensitive to distinguish between poor and good sleepers [108]. Insomnia patients were found to report significantly more, and longer, nocturnal awakenings and reported poorer perceptions of sleep-quality, mood on awakening and alertness on awakening than controls.

Accuracy of subjective sleep reporting

A potential criticism of subjective sleep perceptions focuses on how accurate these perceptions are, compared to objective measures (such as sleep EEG). Most of the published work here focuses on insomnia, and some on healthy populations; few studies have explored this in depression. In a study of 173 patients presenting with insomnia [109], it was shown that insomniacs generally tend to underestimate TST. Differences between subjective reports of sleep and objective measures have also been found in patients with sleep apnea [110]. All the patients with suspected sleep apnea ($n=84$) were shown to overestimate SL and underestimate TST, but the differences were greater for those diagnosed with sleep apnea. In a study of eight healthy participants, measured over eight nights, subjective ratings appeared to correlate to sleep efficiency, but not to stages, suggesting inaccuracy in respect of depth of sleep, but not to quantity [111].

In depression, one study suggested that there was good correlation on all measures except the number

of wakings after sleep onset (WASO), between depressed outpatients ($n=52$) and healthy controls ($n=49$) [112]. However, there was a poorer correlation for perceptions of sleep quality, depth of sleep and feelings of being "rested" on waking, in the depressed group. Another study suggested that all participants were inaccurate, but depressed patients ($n=30$) were more inaccurate than controls ($n=10$) [113]. The authors illustrated that objectively measured slow wave sleep in depressed patients was synonymous with subjective estimates of TST, while the density of REM sleep was related to perceptions of WASO. The extent of accuracy may be related to illness severity. One study of 23 depressed patients sought to examine this [114], and found that the extent of inaccurate subjective sleep reporting increased with the severity of depression. However, the extent of any difference in the accuracy of sleep reporting may prove less important than the way in which depressed patients react differently to perceived changes in sleep timing.

Sleep satisfaction

Perhaps one of the key aspects in subjective sleep reporting in depression is the extent that patients present negative perceptions. This might reflect the pervasive nature of cognitions in depression [14]. Negative cognition in the sleep perceptions of insomniacs has been widely researched, but depression gets very little attention in this respect. Argyropoulos et al [115] conclude that sleep disturbance in depression has a strong (negative) cognitive element that may explain the inaccuracy of subjective sleep reporting in depression. Lee et al [116] found that depressed patients in remission reported improvements in subjective sleep quality, even though EEG recordings of sleep did not show improvements.

However, cognitive models of sleep tend to focus on insomnia [117]. Cognitive disturbance, such as worry and fear of insufficient sleep has been implicated in maintaining insomnia [118]. In particular, pre-sleep cognitive activity has been associated with negative thoughts and worry, especially about getting to sleep [119]. A study of 30 insomnia patients [118] showed significantly higher Beck Anxiety Inventory (BAI; [120]) scores than 30 healthy controls, but did not differ on BDI scores; perhaps studies are needed to explore these cognitions in the sleep of depressed individuals.

Furthermore, not only do insomniacs tend to worry about getting to sleep, they also worry about the consequences of not getting enough sleep, "catastrophising" the impact on daytime function, work performance, social relationships and self-esteem [121]. This serves to exacerbate the sleep problem. Given the emphasis on cognitive models for insomnia, it is not surprising that cognitive behaviour therapy (CBT) has been identified as a potential

treatment [122]. Should negative cognition also be shown to maintain negative subjective sleep in depression then CBT may be useful in treating those thoughts. One possible indication to the presence of faulty cognition in depression focuses on another theory for the function of REM sleep. Johnson argues that the suppression of noradrenergic activity in REM sleep may be associated with reduced rationality and logical sequencing (often a feature of dreams), and with perpetuating emotion [123]. For the depressed individual that may be represented by increased negative emotion. Since many antidepressants suppress REM sleep, this may partly explain the lifting of mood and the improvement in subjective sleep perception observed by Lee [116].

Fichten and colleagues [124,125] described a subgroup of insomnia patients who demonstrated "sleep distress". Highly distressed poor sleepers demonstrated more reports of difficulty with daytime function, tension and depression than those low distressed poor sleepers, even though those groups did not differ in respect of perceived sleep timing. From this, it could follow that "poor sleepers", who report least satisfaction with their sleep, may be at greater risk for future depression than those who are less distressed by sleep perceptions.

More recently, subjective sleep satisfaction has been extended to depressed populations. In one study [126], 20 depressed patients were compared to 20 healthy controls. The depressed group reported significantly poorer perceptions of sleep quality, perceptions of "sufficient sleep", and perceptions of feeling "rested upon waking", even though perceptions of sleep timing were similar between the groups. Clearly the depressed group were demonstrating poorer sleep satisfaction than controls. A similar finding was found in a second cohort of 18 depressed patients and 18 healthy controls [127]. On this occasion, a group of 10 first-degree relatives of each group were also recruited. In addition to the sleep dissatisfaction factor, there was a non-significant trend for the relatives of the depressed group to report sleep in similar way to their depressed relatives; no such correlation was seen between the healthy controls and their relatives.

In a sample of 26 participants, recruited from a depression self-help group [128], perceptions of sleep timing were not related to perceptions of sleep satisfaction or mood/quality of life perceptions. However, perceptions of sleep satisfaction were related to mood/quality of life perceptions. Furthermore, perceptions of current depression were related to sleep satisfaction; history of insomnia was not. Sleep timing perceptions could not be explained by any factor, nor did they predict other variables, whereas variance in sleep satisfaction was explained by subjective depression. Participants with current subjective depression showed greater changes to

sleep satisfaction perceptions, in reaction to sleep timing changes, than those without current subjective depression.

Conclusions

The relationship between disturbed sleep and depression has been widely researched. While everyone probably experiences some kind of sleep disturbance during their lifetime, this is generally brief and rarely interferes significantly with daily living. However, for some sleep disturbance is chronic. Sometimes that disturbance is perceived, with no apparent objectively measured difference in the timing of their sleep patterns to those not reporting sleep problems. Nevertheless, their distress poses a significant enough problem that might contribute to depression.

Other, more observable, sleep disturbances are also associated with depression. Studies have suggested associations between depression and narcolepsy [21]; obstructive sleep apnea [27,28,31,32] and restless legs syndrome [53,55,56], but not all research agrees [23,34,36,37]. The propensity to sleep depends on environmental cues to maintain a fully functional 24-hour circadian cycle [2]. It would seem logical that any disruption to these cues may lead to problematic sleep, possibly affect mood in the process. Time zone changes, shift work and sleep phase abnormalities have all been associated with depression [65,67,68,70,71]. Parasomnias have been linked less with depression, and any association may be the result of distress with the individuals' reports of frequent nightmares or other violent disruptions from sleep (such as night terrors or sleepwalking) [72,74,76].

Most studies support a significant relationship between insomnia and depression [80]. The key studies in this respect have focused on longitudinal analyses, each showing that a baseline diagnosis or history of insomnia presents a significantly greater risk of depression at follow-up than when there is no such diagnosis [79,82,83]. The severity and chronicity of insomnia also appears to be positively correlated with depression severity [84,85].

Objectively measured observations of sleep confirm the extent and nature of disruption to sleep architecture in depression [81]. Depressed individuals consistently demonstrate less total sleep time, greater problems initiating sleep, more trouble maintaining sleep and poorer sleep efficiency than healthy controls [93]. REM sleep variables are also significantly altered in depression; patients frequently show shorter REM sleep latency, more frequent and more intense REM production, and less deeper, slow-wave, sleep than healthy individuals [41]. While these profiles are seen individually in other forms of mental disorder, none other shows the same extent and intensity of REM sleep disruption, especially in the first NREM-REM period

[81]. Although insomnia and depression are frequently associated, studies have shown sleep disruption in depression to be different to those seen in insomnia. Depressed individuals particularly differ to insomniacs in respect of REM latency and density [93]. REM latency may represent a significant marker for the risk of depression [102].

Subjective factors are also important. Sleep EEG may demonstrate what is happening to the structure of sleep, but the individual's perception of sleep sufficiency and quality might illustrate how people react to even small changes in sleep patterns. Whether those subjective assessments of sleep are accurate when compared to objectively measured techniques may not be as crucial as some researchers argue. Indeed, subjective sleep satisfaction has been shown to be an important factor in insomnia [124,125] and depression [126–128], and may represent a cognitive bias towards negativity in the poor sleeper [115,117–119,121,123,129]. However, this research tends to focus more on insomnia patients; more work is needed to explore cognitive biases towards sleep in depression.

Key points

- There is a strong relationship between sleep disturbance and depression
- Longitudinal studies suggest that insomnia or poor sleep may precede depression
- Objective (EEG) studies demonstrate a specific profile of sleep disturbance in depression, particularly in respect of a dominance of REM sleep
- Depressed individuals may show greater subjective sleep distress than non-depressed individuals

Statement of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article. AGM is Editorial Assistant, and DSB Joint Editor of *International Journal of Psychiatry in Clinical Practice*, but neither was involved in the independent peer review process for the original manuscript or in the review of subsequent revisions.

References

- [1] Vgontzas AN, Kales A. Sleep and its disorders. *Annu Rev Med* 1999;50:387–400.
- [2] Borbély AA. A two process model of sleep regulation. *Hum Neurobiol* 1982;1(3):195–204.
- [3] Thase ME. Depression, sleep, and antidepressants. *J Clin Psychiatry* 1998;59(Suppl 4):55–65.
- [4] Hartmann E, Baekeland F, Zwilling G, Hoy P. Sleep need: How much and what kind? *Am J Psychiatry* 1971;127(8):1001–8.
- [5] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring for sleep stages of human subjects. Washington, DC: US Government Printing Office; 1968.
- [6] Himanen S-L, Hasan J. Limitations of Rechtschaffen and Kales. *Sleep Med Rev* 2000;4(2):149–67.
- [7] Dement WC, Kleitman N. The relation of eye movement during sleep to dream activity: An objective method for the study of dreaming. *J Exp Psychol* 1957;53(5):339–46.
- [8] Idzikowski C, James R. Sleep. In: Idzikowski C, Cowen PJ, editors. Serotonin, sleep and mental disorder. Petersfield: Wrightson Biomedical Publishing; 1991. p 23–32.
- [9] Aserinsky E, Kleitman N. Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 1953;118:273–4.
- [10] Baekeland F, Lasky R. Exercise and sleep patterns in college athletes. *Percept Mot Skills* 1966;23:1203–7.
- [11] Van Cauter E, Copinschi G. Interactions between growth hormone secretion and sleep. In: Smith RG, Thorner MO, editors. Human growth hormone: Research and clinical practice, vol. 19. Totowa, NJ: Humana Press; 1999. p 261–83.
- [12] Van Cauter E, Latta F, Nedeltcheva A, et al. Reciprocal interactions between the GH axis and sleep. *Growth Horm IGF Res* 2004;14(Suppl A):S10–17.
- [13] Horne JA. Human sleep, sleep loss and behaviour: Implications for the prefrontal cortex and psychiatric disorder. *Br J Psychiatry* 1993;162:413–9.
- [14] Beck AT. Cognitive models of depression. *J Cogn Psychother* 1987;1:5–37.
- [15] Cartwright R, Young MA, Mercer P, Bears M. Role of REM sleep and dream variables in the prediction of remission from depression. *Psychiatry Res* 1998;80(3):249–55.
- [16] Beck AT, Ward CH, Mendleson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:53–63.
- [17] Horne JA. Why we sleep – The functions of sleep in humans and other mammals. Oxford: Oxford University Press; 1988.
- [18] Kryger MH, Walid R, Manfreda L. Diagnoses received by narcolepsy patients in the year prior to diagnosis by a sleep specialist. *Sleep* 2002;25(1):35–41.
- [19] Overeem S, Mignot E, van Dijk JG, Lammers GJ. Narcolepsy: Clinical features, new pathological insights, and future perspectives. *J Clin Neurophysiol* 2001;18(2):78–105.
- [20] Thorpy M. Current concepts in the etiology, diagnosis and treatment of narcolepsy. *Sleep Med* 2001;2:5–17.
- [21] Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. *J Sleep Res* 2001;10(1):75–81.
- [22] Ware JJE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473–83.
- [23] Vourdas A, Shneerson JM, Gregory CA, et al. Narcolepsy and psychopathology: Is there an association? *Sleep Med* 2002;3(4):353–60.
- [24] Pollmächer T, Mullington J, Lauer CJ. REM sleep disinhibition at sleep onset: A comparison between narcolepsy and depression. *Biol Psychiatry* 1997;42(8):713–20.
- [25] Black J, Guilleminault C. Medications for the treatment of narcolepsy. *Expert Opin Emerg Drugs* 2001;6(2):239–47.
- [26] Andrews JG, Oei TPS. The roles of depression and anxiety in the understanding and treatment of Obstructive Sleep Apnea Syndrome. *Clin Psychol Rev* 2004;24:1031–49.
- [27] Pillar G, Lavie P. Psychiatric symptoms in sleep apnea syndrome: Effects of gender and respiratory disturbance index. *Chest* 1998;114(3):697–703.
- [28] Akashiba T, Kawahara S, Akahoshi T, et al. Relationship between quality of life and mood or depression in patients

- with severe obstructive sleep apnea syndrome. *Chest* 2002; 122(3):861–5.
- [29] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14(6):540–5.
- [30] Zung WW. A self-rating depression scale. *Arch Gen Psychiatry* 1965;12:63–70.
- [31] Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. *J Clin Psychiatry* 2003;64(10):1195–200.
- [32] Aikens JE, Mendleson WB. MMPI correlates of sleep and respiratory disturbance in obstructive sleep apnea. *Sleep* 1999;22(3):362–9.
- [33] Hathaway SR, McKinley JC. A multiphasic personality schedule (Minnesota): 1. Construction of the Schedule. *J Psychol* 1940;10:249–54.
- [34] Phillips BA, Berry DT, Lipke-Molby TC. Sleep-disordered breathing in healthy, aged persons. Fifth and final year follow-up. *Chest* 1996;110(3):654–8.
- [35] Klonoff H, Fleetham J, Taylor DR, Clark C. Treatment outcome of obstructive sleep apnea. Physiological and neuropsychological concomitants. *J Nerv Ment Dis* 1987; 175(4):208–12.
- [36] Bardwell WA, Berry CC, Ancoli-Israel S, Dimsdale JE. Psychological correlates of sleep apnea. *J Psychosom Res* 1999;47(6):583–96.
- [37] Lee S. Depression in sleep apnea: A different view. *J Clin Psychiatry* 1990;51(7):309–10.
- [38] Schroder CM, O'Hara R. Depression and obstructive sleep apnea (OSA). *Ann Gen Psychiatry* 2005;4(1):13–20.
- [39] Sforza E, de Saint Hilaire Z, Pelissolo A, Rochat T, Ibanez V. Personality, anxiety and mood traits in patients with sleep-related breathing disorders: Effect of reduced daytime alertness. *Sleep Med* 2002;3(2):139–45.
- [40] Reynolds CF III, Kupfer DJ, McEachran AB, et al. Depressive psychopathology in male sleep apneics. *J Clin Psychiatry* 1984;45(7):287–90.
- [41] Reynolds CF III. Sleep and affective disorders. A minireview. *Psychiatr Clin North Am* 1987;10(4):583–91.
- [42] Bardwell WA, Moore P, Ancoli-Israel S, Dimsdale JE. Does obstructive sleep apnea confound sleep architecture findings in subjects with depressive symptoms? *Biol Psychiatry* 2000;48(10):1001–9.
- [43] Means MK, Lichstein KL, Edinger JD, et al. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. *Sleep Breath* 2003;7(1):31–42.
- [44] Henke KG, Grady JJ, Kuna ST. Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypopnea syndrome. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2001;163(4): 911–7.
- [45] Edinger JD, Carwile S, Miller P, Hope V, Mayti C. Psychological status, syndromatic measures, and compliance with nasal CPAP therapy for sleep apnea. *Percept Mot Skills* 1994;78(3 Pt 2):1116–8.
- [46] Millman RP, Fogel BS, McNamara ME, Carlisle CC. Depression as a manifestation of obstructive sleep apnea: Reversal with nasal continuous positive airway pressure. *J Clin Psychiatry* 1989;50(9):348–51.
- [47] Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990;83(3A):25–8S.
- [48] Poceta JS. Restless legs syndrome and nocturnal myoclonus. In: Poceta JS, Mitler MM, editors. *Sleep disorders: Diagnosis and treatment*. Totowa, NJ: Humana Press; 1998. p 75–93.
- [49] Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. *Arch Intern Med* 2000;160(14): 2137–41.
- [50] Hogl B, Kiechl S, Willeit J, et al. Restless legs syndrome: A community-based study of prevalence, severity, and risk factors. *Neurology* 2005;64(11):1920–4.
- [51] Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4(2):101–19.
- [52] Wetter TC, Pollmacher T. Restless legs and periodic leg movements in sleep syndromes. *J Neurol* 1997;244(4 Suppl 1):S37–45.
- [53] Sevim S, Dogu O, Kaleagasi H, et al. Correlation of anxiety and depression symptoms in patients with restless legs syndrome: A population based survey. *J Neurol Neurosurg Psychiatry* 2004;75:226–30.
- [54] Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
- [55] Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: The MEMO study. *Memory and Morbidity in Augsburg Elderly*. *Neurology* 2000;54(5):1064–8.
- [56] Winkelmann J, Prager M, Lieb R, et al. "Anxietas tibiarum". Depression and anxiety disorders in patients with restless legs syndrome. *J Neurol* 2005;252(1):67–71.
- [57] Markkula J, Lauerma H. Mianserin and restless legs. *Int Clin Psychopharmacol* 1997;12(1):53–8.
- [58] Agargun MY, Kara H, Ozbeck H, Tombul T, Ozer OA. Restless legs syndrome induced by mirtazapine. *J Clin Psychiatry* 2002;63(12):1179.
- [59] Thorpy M. *Diagnosic Classification Steering Committee. ICSD – International classification of sleep disorders: Diagnostic and coding manual*. Rochester, MN: American Sleep Disorders Association; 1990.
- [60] Dagan Y. Circadian rhythm sleep disorders (CRSD). *Sleep Med Rev* 2002;6(1):45–55.
- [61] Brown R. Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. *Am J Psychiatry* 1985;142:811–6.
- [62] Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. *J Biol Rhythms* 1999;14(1): 72–6.
- [63] Folkard S, Arendt J, Clark M. Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. *Chronobiol Int* 1993;10(5):315–20.
- [64] Dagan Y, Yovel I, Hallis D, Eisenstein M, Raichik I. Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome (DSPS). *Chronobiol Int* 1998;15(2):181–90.
- [65] Fevre-Montange M, Van Cauter E, Retetoff S, et al. Effects of 'jet-lag' on hormonal patterns: II. Adaptation of melatonin circadian periodicity. *J Clin Endocrinol Metab* 1981; 52(4):642–9.
- [66] Desir D, Van Cauter E, Fang VS, et al. Effects of 'jet-lag' on hormonal patterns. I. Procedures, variations in total plasma proteins, and disruption of adrenocorticotropin-cortisol periodicity. *J Clin Endocrinol Metab* 1981;52(4):628–41.
- [67] Sasaki M, Takahashi T. Human circadian rhythms and psychosomatic complaints. *Jpn J Psychosom Med* 1990; 30(3):299–307.
- [68] Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep* 2004;27(8): 1453–62.
- [69] Kripke DF. The uses of bright light in an office practice. In: Poceta JS, Mitler MM, editors. *Sleep disorders: Diagnosis and treatment*. Totowa, NJ: Humana Press; 1998. p 53–74.
- [70] Schrader H, Bovim G, Sand T. Depression in delayed sleep phase syndrome. *Am J Psychiatry* 1996;153(9):1238.
- [71] Regestein QR, Monk TH. Delayed sleep phase sleep syndrome: A review of its clinical aspects. *Am J Psychiatry* 1995;152(4):602–8.
- [72] Ohayon MM, Guilleminault C, Priest RG. Night terrors: Sleepwalking, and confusional arousals in the general population: Their frequency and relationship to other sleep

- and mental disorders. *J Clin Psychiatry* 1999;60(4):268–76.
- [73] Ohayon MM, Caulet M, Lemoine P. Comorbidity of mental and insomnia disorders in the general population. *Compr Psychiatry* 1998;39(4):185–97.
- [74] Levin R, Fireman G. Nightmare prevalence, nightmare distress, and self-reported psychological disturbance. *Sleep* 2002;25(2):205–12.
- [75] Dahl R. Common Sleep Problems in Children. In: Poceta JS, Mitler MM, editors. *Sleep disorders: Diagnosis and treatment*. Totowa, NJ: Humana Press; 1998. p 161–86.
- [76] Clarke NA, Williams AJ, Kopelman MD. Rapid eye movement sleep behaviour disorder, depression and cognitive impairment. *Br J Psychiatry* 2000;176:189–92.
- [77] Vandeputte M, de Weerd A. Sleep disorders and depressive feelings: A global survey with the Beck depression scale. *Sleep Med* 2003;4(4):343–5.
- [78] Eddy M, Walbroehl GS. Insomnia. *Am Fam Phys* 1999;59(7):1911–6.
- [79] Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;39(6):411–8.
- [80] Benca RM, Okawa M, Uchiyama M, et al. Sleep and mood disorders. *Sleep Med Rev* 1997;1(1):45–56.
- [81] Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: A meta-analysis. *Arch Gen Psychiatry* 1992;49(8):651–68.
- [82] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *J Am Med Assoc* 1989;262(11):1479–84.
- [83] Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. *Am J Epidemiol* 1997;146(2):105–14.
- [84] Hohagen F, Rink K, Kappler C, et al. Prevalence and treatment of insomnia in general practice. A longitudinal study. *Eur Arch Psychiatry Clin Neurosci* 1993;242(6):329–36.
- [85] Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med* 1998;158(10):1099–107.
- [86] Lustberg L, Reynolds CF. Depression and insomnia: questions of cause and effect. *Sleep Med Rev* 2000;4(3):253–62.
- [87] Perlis ML, Giles DE, Buysse DJ, et al. Which depressive symptoms are related to which sleep electroencephalographic variables? *Biol Psychiatry* 1997;42(10):904–13.
- [88] Wiggs L, Stores G. Children's sleep: How should it be assessed? *ACPP Rev Newsletter* 1995;17(3):153–7.
- [89] Jean-Louis G, Zizi F, Von Gizycki H, Hauri P. Actigraph assessment of sleep in insomnia: Application of the Actigraph Data Analysis Software (ADAS). *Physiol Behav* 1999;65(4/5):659–63.
- [90] Mamelak A, Hobson A. Nightcap: A home-based sleep monitoring system. *Sleep* 1989;12(2):157–66.
- [91] Ajilore O, Stickgold R, Rittenhouse CD, Hobson JA. Nightcap: laboratory and home-based evaluation of a portable sleep monitor. *Psychophysiology* 1995;32(1):92–8.
- [92] Pace-Schott EF, Kaji J, Stickgold R, Hobson A. Nightcap measurement of sleep quality in self-described good and poor sleepers. *Sleep* 1994;17(8):688–92.
- [93] Gillin JC, Duncan W, Pettigrew KD, Frankel BL, Snyder F. Successful separation of depressed, normal, and insomniac subjects by EEG sleep data. *Arch Gen Psychiatry* 1979;36(1):85–90.
- [94] Staner L, Cornette F, Maurice D, et al. Sleep microstructure around sleep onset differentiates major depressive insomnia from primary insomnia. *J Sleep Res* 2003;12:319–30.
- [95] Rush AJ, Erman MK, Giles DE, et al. Polysomnographic findings in recently drug-free and clinically remitted depressed patients. *Arch Gen Psychiatry* 1986;43(9):878–84.
- [96] Kupfer DJ. REM latency: A psychobiologic marker for primary depressive disease. *Biol Psychiatry* 1976;11(2):159–74.
- [97] Heath AC, Kendler KS, Eaves LJ, Martin NG. Evidence for genetic influences on sleep disturbance and sleep pattern in twins. *Sleep* 1990;13(4):318–35.
- [98] Kendler KS, Neale MC, Kessler RCJ, Heath AC, Eaves L. The lifetime history of major depression in women. *Arch Gen Psychiatry* 1993;50(11):863–70.
- [99] Giles DE, Biggs MM, Rush AJ, Roffwarg HP. Risk factors in families of unipolar depression. I. Psychiatric illness and reduced REM latency. *J Affect Disord* 1988;14(1):51–9.
- [100] Giles DE, Kupfer DJ, Roffwarg HP, et al. Polysomnographic parameters in first-degree relatives of unipolar probands. *Psychiatry Res* 1989;27(2):127–36.
- [101] Giles DE, Roffwarg HP, Rush AJ. A cross-sectional study of the effects of depression on REM latency. *Biol Psychiatry* 1990;28(8):697–704.
- [102] Giles DE, Kupfer DJ, Rush AJ, Roffwarg HP. Controlled comparison of electrophysiological sleep in families of probands with unipolar depression. *Am J Psychiatry* 1998;155(2):192–9.
- [103] Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
- [104] Parrott AC, Hindmarch I. Factor analysis of a sleep evaluation questionnaire. *Psychol Med* 1978;8:325–9.
- [105] Zisapel N, Laudon M. Subjective assessment of the effects of CNS-active drugs on sleep by the Leeds sleep evaluation questionnaire: A review. *Hum Psychopharmacol Clin Exp* 2003;18(1):1–20.
- [106] Tarrasch R, Laudon M, Zisapel N. Cross-cultural validation of the Leeds sleep evaluation questionnaire (LSEQ) in insomnia patients. *Hum Psychopharmacol* 2003;18(8):603–10.
- [107] Stephenson DA, Harris B, Davies RH, et al. The Impact of antidepressants on sleep and anxiety: A comparative study of fluoxetine and dothiepin using the Leeds Sleep Evaluation Questionnaire. *Hum Psychopharmacol Clin Exp* 2000;15:529–34.
- [108] Monk TH, Reynolds CF, Kupfer DJ, et al. The Pittsburgh Sleep Diary. *J Sleep Res* 1994;3(2):111–20.
- [109] Edinger JD, Fins AI. The distribution and clinical significance of sleep time misperceptions among insomniacs. *Sleep* 1995;18(4):232–9.
- [110] McCall WV, Turpin E, Reboussin D, Edinger JD, Haponik EF. Subjective estimates of sleep differ from polysomnographic measurements in obstructive sleep apnea patients. *Sleep* 1995;18(8):646–50.
- [111] Åkerstedt T, Hume K, Minors D. The meaning of good sleep: A longitudinal study of polysomnography and subjective sleep quality. *J Sleep Res* 1994;3(3):152–8.
- [112] Armitage R, Trivedi M, Hoffmann R, Rush AJ. Relationship between objective and subjective sleep measures in depressed patients and healthy controls. *Depress Anxiety* 1997;5:97–102.
- [113] Rotenberg VS, Indursky P, Kayumov L, Sirota P, Melamed Y. The relationship between subjective sleep estimation and objective sleep variables in depressed patients. *Int J Psychophysiol* 2000;37(3):291–7.
- [114] Tsuchiyama K, Nagayama H, Kudo K, Kojima K, Yamada K. Discrepancy between subjective and objective sleep in patients with depression. *Psychiatry Clin Neurosci* 2003;57:259–64.
- [115] Argyropoulos SV, Hicks JA, Nash JR, et al. Correlation of subjective and objective sleep measurements at different stages of the treatment of depression. *Psychiatry Res* 2003;120(2):179–90.

- [116] Lee JH, Reynolds CF III, Hoch CC, et al. Electroencephalographic sleep in recently remitted, elderly depressed patients in double-blind placebo-maintenance therapy. *Neuropsychopharmacology* 1993;8(2):143–50.
- [117] Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40(8):869–93.
- [118] Harvey AG. Pre-sleep cognitive activity: a comparison of sleep-onset insomniacs and good sleepers. *Br J Clin Psychol* 2000;39(Pt 3):275–86.
- [119] Watts FN, Coyle K, East MP. The contribution of worry to insomnia. *Br J Clin Psychol* 1994;33(Pt 2):211–20.
- [120] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psychol* 1988;56(6):893–7.
- [121] Harvey AG, Greenhall E. Catastrophic worry in primary insomnia. *J Behav Ther Exp Psychiatry* 2003;34(1):11–23.
- [122] Espie CA, Inglis SJ, Tessier S, Harvey L. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: Implementation and evaluation of a sleep clinic in general medical practice. *Behav Res Ther* 2001;39(1):45–60.
- [123] Johnson JD. REM sleep and the development of context memory. *Med Hypotheses* 2005;64(3):499–504.
- [124] Fichten CS, Creti L, Amsel R, et al. Poor sleepers who do not complain of insomnia: Myths and realities about psychological and lifestyle characteristics of older good and poor sleepers. *J Behav Med* 1995;18(2):189–223.
- [125] Alapin I, Fichten CS, Libman E, et al. How is good and poor sleep in older adults and college students related to daytime sleepiness, fatigue, and ability to concentrate? *J Psychosom Res* 2001;49:381–90.
- [126] Mayers AG, Van Hooff JC, Baldwin DS. Quantifying subjective assessment of sleep and life-quality in antidepressant-treated depressed patients. *Hum Psychopharmacol Clin Exp* 2003;18(1):21–7.
- [127] Mayers AG, Van Hooff JC, Baldwin DS. Assessing subjective sleep reports in the first degree relatives of antidepressant treated depressed outpatients. *Hum Psychopharmacol Clin Exp* 2003;18(3):207–14.
- [128] Mayers AG. Subjective sleep dissatisfaction in depression: Unpublished PhD Thesis. 2005.
- [129] Fichten CS, Libman E, Creti L, et al. Role of thoughts during nocturnal awake times in the insomnia experience of older adults. *Cogn Ther Res* 2001;25(6):665–92.
- [130] Kupfer DJ. Sleep research in depressive illness: Clinical implications: a tasting menu. *Biol Psychiatry* 1995;38(6):391–403.