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Aims and Scope

The International Journal of Sleep Disorders is designed to bring a critical analysis of the world literature on sleep disorders, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding of the treatment of sleep disorders across the global healthcare system by providing an active forum for the discussion of clinical and healthcare issues.

Leading Articles – These major review articles are chosen to reflect topical clinical and healthcare issues in sleep disorders. All contributions undergo a strict editorial review process.

Clinical Reviews – The most important papers from the best of the international literature on sleep disorders are systematically selected by an internationally recognized panel of experts. The Editors then prepare concise and critical analyses of each paper, and, most importantly, place the findings into clinical context.

Meeting Reports – The International Journal of Sleep Disorders also provides incisive reportage from the most important international congresses.

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Dear Colleagues,

Welcome to the third issue of *The International Journal of Sleep Disorders*.

In our first article this quarter, Wilfred R Pigeon and Michael L Perlis (University of Rochester, Rochester, NY, USA), review the overlap between insomnia and depression, questioning the view of insomnia as merely a symptom of major depressive disorder and suggesting that they are in fact separate entities. This review presents evidence for insomnia and depression as comorbid disorders, and considers whether targeted treatment for insomnia may influence the clinical course of major depression.

Tamar Shochat, Giora Pillar, and Atul Malhotra (University of Haifa, Rambam Medical Center, Haifa, Israel, and Brigham and Women's Hospital, Boston, MA, USA) provide an overview of the changes in sleep patterns seen with aging, discussing the vulnerability of this patient population to sleep abnormalities and reviewing the different presentations of these disorders and the treatments available. Due to the considerable morbidity that sleep disorders can cause, the authors suggest that further research into, and proper treatment of, these disorders could help improve satisfaction and quality of life in elderly patients.

The role of the γ-aminobutyric acid $(GABA)_A$ receptor in the pharmacology of insomnia is discussed by Matt T Bianchi (Massachusetts General Hospital and Brigham and Women's Hospital, Boston, MA, USA) in the third article of this issue. $GABA_A$ receptor function has frequently been used as a target for insomnia therapeutics, such as classical benzodiazepines. However, recent studies have provided further insights into the function of this receptor and its various subunits, underscoring the potential for rational drug design and offering new possibilities for treating specific aspects of insomnia, while minimizing the unwanted side effects.

As always, a synopsis of the latest and most important scientific findings are reviewed and placed into clinical context by our Editors, providing a digested read of the most critical developments from several key areas of sleep research. The issue concludes with highlights from the 8th World Congress on Sleep Apnea (Montréal, QC, Canada), presented by Nelly Huynh and Christian Guilleminault (Université de Montréal, Montréal, QC, Canada, and Stanford University Medical Center, Stanford, CA, USA).

We would like to thank you for the positive response to *The International Journal of Sleep Disorders* and look forward to receiving your future comments and suggestions to help us continue to provide a useful resource for clinicians working in this rapidly developing field.

Alan F Schatzberg
Editor-in-Chief

Contents

LEADING ARTICLE

Insomnia and Depression: Birds of a Feather?

Wilfred R Pigeon and Michael L Perlis

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Over the course of the last 30 years there has been a great deal of research into sleep abnormalities in patients with major depression. However, only a small proportion of this work has focused on sleep continuity disturbance (as opposed to abnormalities in sleep micro- and macroarchitecture), despite insomnia being a defining feature of depression. The lack of work in this area may be attributed to the view that insomnia is nothing more than a symptom of depression. Yet, in recent years, perceptions have shifted to the alternative point of view – that insomnia is less a symptom and more a comorbid disorder. The present article provides an overview of the data and suggests that insomnia and depression are separable entities, insomnia confers a risk for greater depressive morbidity, and targeted treatment for insomnia may influence the clinical course of major depression. *Int J Sleep Disorders* 2007;**1**(3):82–91.

It has often been said that sleep disturbance is a cardinal sign of major depressive disorder (MDD). However, this claim does not refer to a single abnormality but rather to a cluster of signs and symptoms that range from sleep continuity disturbance[1], to abnormalities in sleep architecture, to sleep electro-encephalogram (EEG) anomalies.

The relationships between depression and sleep architecture and/or sleep EEG anomalies have been extensively studied, well delineated, and thoroughly reviewed [1], whereas the relationship between depression and sleep continuity disturbance has not. This may be due to the prevailing assumption that, like headache or fever, insomnia is simply a symptom of an underlying disease process and, as a symptom (even as a defining feature of MDD), it cannot provide information on disease etiology or pathophysiology. In order to challenge this perspective, it is necessary to demonstrate that insomnia is not simply a symptom (i.e. occurs with the disease and is otherwise absent), but is instead a comorbid condition that may interact with the MDD to confer greater morbidity.

To make the case for comorbidity, one would need to demonstrate that insomnia has the following characteristics:

- It occurs in the absence of depression.
- It persists following effective therapy for depression.
- It can be distinguished from depression in terms of sleep and neurobiological abnormalities.

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To determine whether insomnia interacts with MDD to confer greater morbidity, the following must be established:

- Insomnia can exist as a predisposing, precipitating, and/or perpetuating factor for depression.
- Insomnia represents a modifiable factor, which, when subjected to targeted treatment, alters the course of depression.

The present review examines these lines of evidence.

Historical context: is insomnia a symptom or a comorbid disorder?

Up to 80% of patients with depression have sleep complaints consistent with insomnia [2]; this finding, along with the fact that first-generation antidepressants tend to have sedative effects, led to the pervasive point of view that insomnia occurs as a consequence of mood dysregulation.

Insomnia and depression are separable

The evidence that insomnia and depression may be separate, although related, disorders, is provided by the relatively recent observations that:

- Up to 25% of insomnia subjects do not have concomitant depression (or other psychiatric or medical illnesses) [3].

1. Sleep continuity refers to the collection of variables that correspond to sleep initiation and maintenance, including sleep latency, wake after sleep onset, number of awakenings, and total sleep time. While the term is not formally part of the sleep lexicon, it has the heuristic value of being a global term whose meaning may be contrasted with the class of variables that correspond to sleep architecture.

- Second-generation antidepressants (e.g. selective serotonin reuptake inhibitors) often exert their clinical effects without ameliorating the patient's insomnia complaints [4–8].
- Regardless of the type of intervention, it is often the case that insomnia persists and/or becomes chronic, despite successful resolution of the psychiatric illness [9–12].

While not refuting the alternative point of view, these data suggest that insomnia and depression could be considered separate entities or comorbid conditions. This evidence is further strengthened by a series of findings showing the two conditions to be distinct in terms of sleep and neurobiological measures.

Insomnia and depression exhibit different sleep and neurobiological abnormalities

Polysomnographically-measured sleep abnormalities

When sleep is measured using polysomnograpy (PSG), patients with depression reliably exhibit sleep continuity and sleep architectural abnormalities [1,13]. Within the sleep continuity domain, patients with depression tend to exhibit increased sleep latency, increased wake time, and decreased sleep efficiency. Typically, depressed patients take 15–40 min to fall asleep, spend 15–30 min awake after sleep onset, have early morning awakenings that last ≥15 min, and exhibit sleep efficiencies (total sleep time/total time in bed) that range from 85–95% [14,15]. While this profile clearly resembles that which is seen in patients with primary insomnia, the magnitude of the problem tends to be smaller. Patients with primary insomnia usually have more severe PSG-measured sleep continuity problems than those with insomnia in the context of depression [16,17]. However, it should be noted that this may be a selection artifact, as only patients with primary insomnia are selected for study on the basis of the severity of the insomnia complaint.

Sleep architecture refers to two kinds of PSG-defined variables: those related to non-rapid eye movement (NREM) sleep and those related to REM sleep. Within the NREM domain, slow-wave sleep (SWS) is the main variable of interest, and is thought to be related to sleep homeostasis (for a review of sleep homeostasis and insomnia see [18]). While the amount of SWS varies with age, healthy adults (aged, for example, 25–55 years) typically spend 10–15% of total sleep time in SWS (approximately 40–60 min) [19]. Deficiencies in SWS have been observed both in patients with primary insomnia [20–23] and in those with MDD [14,15,24,25], with an exhibited decrease in SWS to 5–10% of total sleep time.

With regard to REM sleep, patients with depression tend to exhibit a shorter REM latency (time between sleep onset and the first epoch of REM sleep), increased REM density (number of REMs during REM sleep), and increased REM sleep time. Typically, healthy subjects have REM latencies of 70–110 min [19]. Between 50% and 70% of patients with MDD have mean REM latencies of ≤65 min [14,15,24,26]. Patients with depression exhibit greater REM density than controls; this is particularly evident during the first REM period [14,15]. Finally, while the amount of REM sleep varies with age, healthy middle-aged adults typically spend 15–20% of total sleep time in this sleep stage [19]. Patients with depression tend to exhibit more than 20% – often as much as 30% – of sleep time in REM [14,15,24]. In contrast, patients with primary insomnia do not show any consistent REM abnormalities.

Quantitative EEG abnormalities

Power spectral analysis (PSA) of EEG activity from PSG recordings confirmed many of the PSG sleep architecture findings, and also produced a number of new results. A variety of studies based on PSA have reported that patients with depression exhibit either reduced NREM delta power (overall) or abnormal distributions of delta activity across the sleep period [27–29]. However, other studies have suggested that these findings are not replicable [30,31], are limited to men [32], and/or are characteristic of depressed cohorts from past, but not present, generations [33]. There have been fewer studies in patients with insomnia than depression, but the finding of diminished delta activity has been observed more consistently within these [20–23,34].

In addition to findings in the slow-wave portion of the EEG spectrum, differences have also been observed within the high-frequency (beta and gamma frequencies) domain. Patients with primary insomnia have been found to exhibit more beta and gamma activity than either good sleepers or patients with insomnia secondary to MDD [17,21,35–39]. Specifically, patients with primary insomnia exhibit more high-frequency EEG activity at sleep onset and during NREM sleep. This kind of activity has also been negatively associated with the perception of sleep quality [40,41], and positively associated with the degree of discrepancy between PSG and sleep diary measures of sleep continuity [39]. The latter finding regarding sleep state misperception is important as this clinical phenomenon is thought to occur with primary insomnia, and is not typically seen in insomnia associated with depression [42].

Taken together, these data suggest that, using PSG and PSA measures, depressed patients with insomnia do not exhibit the same sleep continuity, sleep architecture, or sleep EEG profiles as patients with primary insomnia.

Neuroimaging abnormalities

Using positron emission tomography (PET), Nofzinger and colleagues at the University of Pittsburgh (Pittsburgh, PA, USA)

have shown that depressed patients have a higher degree of activation of structures involved in REM sleep, from waking to REM sleep, than healthy controls [43]. In broad terms, these areas include brainstem structures, the limbic and anterior paralimbic cortex, and the executive cortex. Differences between depressed and normal patients have also been observed in PET studies of NREM sleep: depressed patients showed a higher overall brain metabolism and a smaller decrease in activation across a variety of frontal areas from waking to NREM sleep [44,45]. These findings are consistent with PSG findings of decreased SWS activity and increased REM sleep activity in depressed subjects.

In patients with primary insomnia[2], compared with good sleepers, the same Pittsburgh group found that:

- There was a smaller decline in metabolism from waking to NREM sleep in the ascending reticular activating system, the hippocampus, the amygdala, and anterior cingulate cortex in insomnia patients [47].
- Only the patients with insomnia exhibited elevated whole-brain metabolism across waking and NREM sleep [48].

These data suggest that both forms of insomnia are associated with increased central nervous system (CNS) metabolic activity during NREM sleep (and in structures related to the promotion of sleep and/or wakefulness), but only patients with depression exhibit increased metabolic activity in regions associated with the generation of REM sleep. These differences, while entirely consistent with PSG and PSA findings, await replication by multiple investigators using more standardized groups and procedural criteria in larger samples.

Neuroendocrine abnormalities

When acutely ill, patients with depression exhibited elevated levels of cortisol and adrenocorticotropic hormone (ACTH), both during the night and over the course of the 24-h day, compared with healthy controls [49]. Data from longitudinal studies suggest that these hypothalamus–pituitary–adrenal (HPA) axis abnormalities normalize with the resolution of the acute illness [50]; however, it is unclear from these studies whether the sleep continuity disturbance persists into remission.

Studies of non-depressed young adults who were good or poor sleepers found that the poor sleepers have significantly higher mean 24-h levels of urinary-free 11-hydroxycorticosteroids [51]. Parallel findings have been observed in studies of patients with primary insomnia versus good sleepers. The insomnia patients exhibited significantly higher mean levels of ACTH and cortisol over 24 h, with the largest group differences observed in the evening and first half of the night [52,53]. Correlation analyses show that increased HPA axis activation is associated with increased amounts of Stage 1 sleep, increased wakefulness following sleep onset, and lower sleep efficiency [52]. It should be noted that there is at least one study that has failed to show a difference between patients with primary insomnia and good sleepers with regard to cortisol levels [54].

To date, only one study has concomitantly evaluated EEG sleep and nocturnal plasma levels of catecholamines in patients with primary insomnia, patients with acute major depression, and healthy controls [55]. The insomnia group showed disordered sleep continuity and nocturnal increases in levels of circulating norepinephrine compared with the control group, whereas depressed patients showed no differences in EEG sleep or nocturnal catecholamines (Fig. 1). Sleep efficiency was negatively correlated with nocturnal elevations of norepinephrine in the patients with insomnia, but not in the patients with depression or in the healthy controls.

The finding that hypercortisolemia can occur in the absence of depression suggests that insomnia and depression are separate entities and that it is the insomnia (as opposed to the depression) that appears to account for the HPA abnormalities. Alternatively, there may be a sequential effect, such that stress leads to acute activation of the HPA axis, insomnia, and then depression, but in the long-term the insomnia that persists beyond acute illness leads to a tonic activation of the HPA axis.

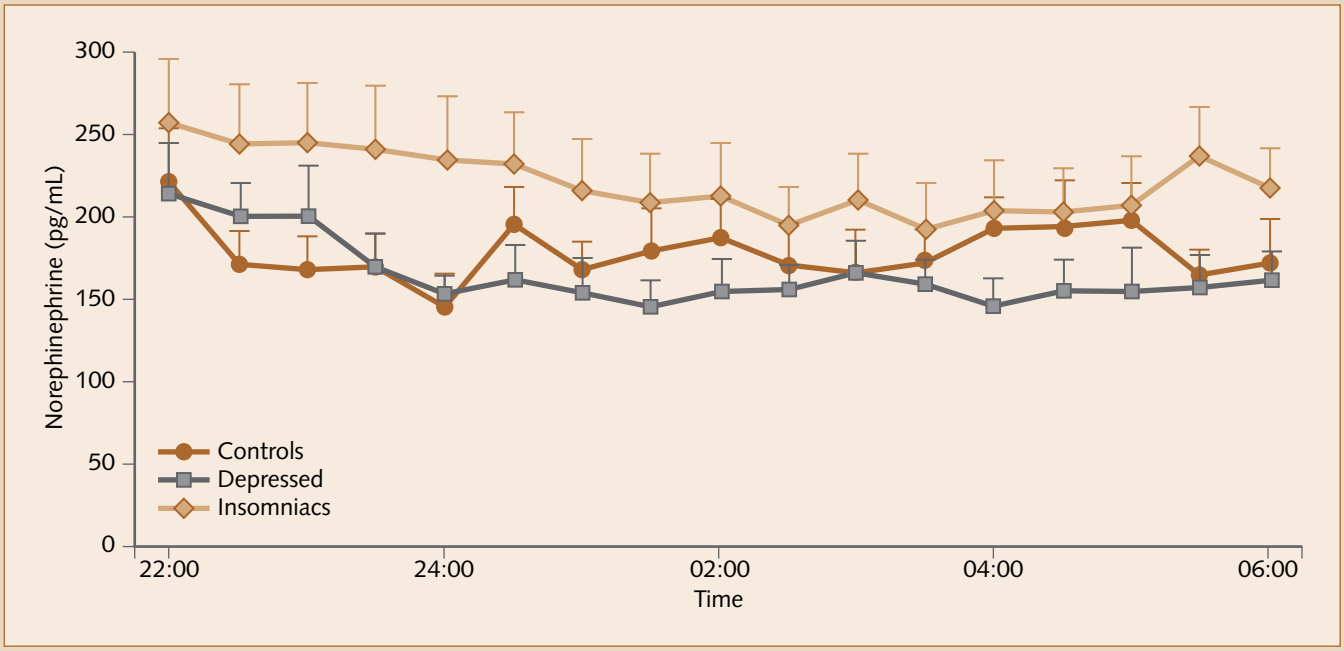
Neuroimmune abnormalities

Depression is associated with diminished cellular immune competence (e.g. lymphocyte proliferation and reduced natural killer [NK] cell activity) and elevated markers of systemic inflammation (e.g. elevated circulating levels of interleukin-6 [IL-6] and C-reactive protein) [56–58]. In a study that assessed both types of measures simultaneously, depressed males had reduced NK cell activity and increased IL-6 levels compared with never-depressed controls [59].

In vitro stimulation of proinflammatory cytokines with lipopolysaccharide (LPS), which tests the ability of circulating white blood cells to produce cytokines (as would occur in an innate immune response to infection), have yielded mixed findings when sampling depressed inpatients and/or outpatients [60]. In non-clinical samples, where depression is measured using validated depression scales, higher scores were associated with greater LPS-stimulated expression of

2. It should be noted that there is one additional imaging study that has been conducted in patients with primary insomnia [46]. In this study, single-photon emission computed tomography (SPECT) was used to assess CNS metabolic activity in patients with primary insomnia and in good sleepers. Patients with insomnia exhibited lower levels of activation following sleep onset, particularly in the basal ganglia. While these results appear entirely inconsistent with the PET findings, numerous methodological differences may account for the differences. The most likely explanation is that the short time resolution of SPECT captured a more transient phenomenon that occurs when subjects first achieve persistent sleep, whereas the PET study, with its longer time resolution, captured a more stable phenomenon that occurs throughout NREM sleep.

Figure 1. Nocturnal catecholamines and immune function in insomnia patients, depressed patients, and control subjects. The bars represent the standard error of the mean.



Redrawn with permission from [55].

tumor necrosis factor-α (TNF-α) and IL-1β (the latter only in men) [61,62]. In contrast, higher depression scores have been associated with diminished *in vitro* production of IL-6 and increased circulating levels of IL-6 [63]. Another study found that higher depression scores were associated with lower *in vitro* stimulated IL-6, IL-1β, and TNF-α, but were not associated with circulating levels of IL-6 or TNF-α [60]. Interestingly, in this latter study, the somatic symptom cluster of depression (including sleep-related items) was most strongly associated with stimulated cytokine production.

Chronic insomnia (as compared with good sleep) tends to be associated with decreased NK activity [55,64,65] and a shift in the circadian distribution of IL-6 and TNF-α from the night to the daytime, despite higher evening levels of IL-6 [53]. Burgos et al. found that IL-6 secretion is inversely correlated with self-reported sleep quality and PSG-measured SWS in patients with insomnia [66].

These neuroimmune findings are less conclusive than the other areas reviewed in terms of whether insomnia and depression are distinct disorders. While some of the findings show that the disorders are associated with similar abnormalities (e.g. decreased NK cell activity, elevated IL-6), there is some indication that these findings may differ when the measurement strategy is *in vitro* stimulation of immune responses [60]. Furthermore, there are no data on whether the neuroimmune findings persist into remission. If, like the neuroendocrine findings, these changes are persistent, it is possible that insomnia (as opposed to depression) accounts for neuroimmune abnormalities. Alternatively, a sequence effect may be responsible.

Taken together, this overall set of neurobiological findings provides evidence for a distinction between insomnia and depression. Given that the two disorders appear to be separate, the nature of their relationship remains in question.

How are insomnia and depression related?

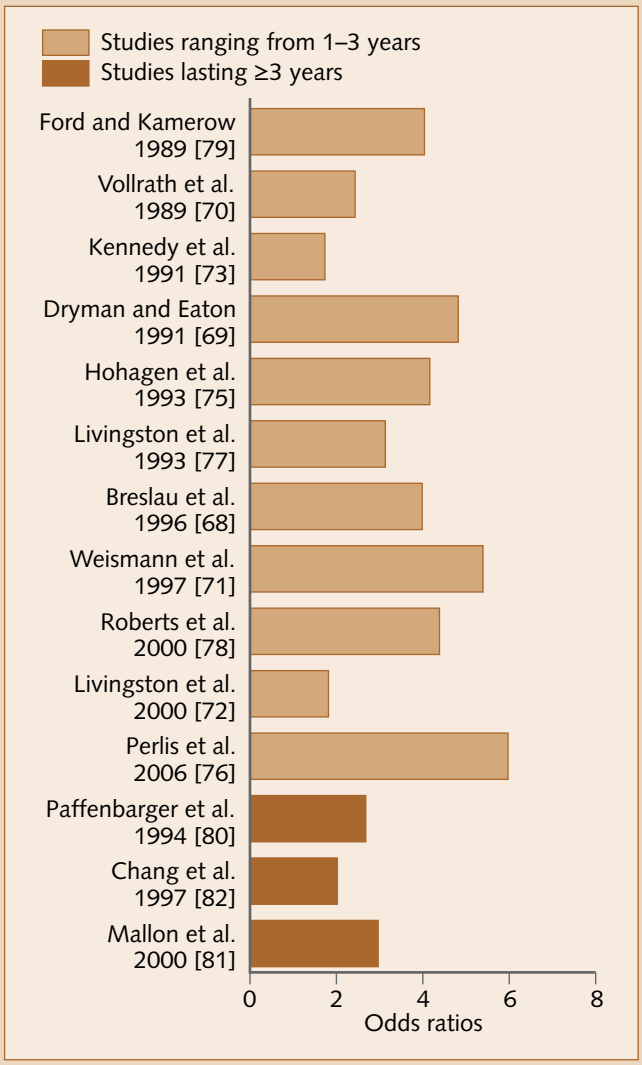
A useful way of assessing the relationship between insomnia and depression is to consider whether insomnia serves as a predisposing, precipitating, or perpetuating factor for depression. This conceptual framework is the basis for Spielman's three factor model of insomnia and is applied here for its heuristic value [67].

In the present context, insomnia would be labeled a predisposing factor if it temporally preceded and conferred risk for the development of new-onset or recurrent depression; a precipitating factor if its occurrence (or increase in severity) preceded, and was immediately contiguous, with new onsets of depression; and a perpetuating factor if its occurrence (or severity) was associated with treatment non-response, treatment resistance, or reduced rates of remission.

Insomnia as a predisposing factor for depression

There are at least 12 longitudinal studies reporting that insomnia carries an increased risk of new-onset and

Figure 2. Odds ratios from longitudinal studies showing the elevated risk for the development or presence of depression when there are symptoms of sleep disturbance consistent with persistent insomnia.



recurrent depression over time frames of between 6 months and 3 years [68–79]. Reports also show that insomnia can confer depression risk for a period that extends over decades [80–82]. In general, these studies show that patients with persistent insomnia have an approximately 3.5-fold increase in the risk of depression compared with subjects without complaints of insomnia. A graphical representation of these data is shown in Figure 2.

Several of these investigations have evaluated insomnia as a predisposing factor for depression in terms of age and gender interactions. In the three studies that focused on older adults [76–78], this trend was found to be characteristic of the elderly; that is, insomnia conferred an approximately three-fold increase in risk of depression. It is difficult to infer age interactions in the remaining investigations as the samples tended to be heterogeneous for age, which was statistically controlled. What was evident from these studies was that the relative risk estimates were reliably higher in the investigations that controlled for age. This suggests that insomnia is not a uniform risk factor for all age cohorts and/or that the effects of persistent insomnia are larger when age effects (which are significantly more predictive than sleep factors) are adjusted for. With respect to gender differences, the majority of the studies calculated odds ratios that were adjusted for gender [68,70,71,77–79], and one study only included men [82]. In the studies that evaluated gender differences [69,81], the association between insomnia and depression was predominantly observed in women.

In addition to these considerations, it should be remembered that the definition of a "risk factor" i.e. how insomnia is measured and how it is defined in terms of type, severity, and chronicity, varies widely between studies. These caveats notwithstanding, data from the above studies strongly support the hypothesis that insomnia represents one of the predisposing factors for MDD.

Insomnia as a precipitating factor for depression

To our knowledge, only one study has examined whether insomnia is a precipitant, or at least a prodromal, sign of MDD [83]. In this, patients with recurrent MDD (remitted) were followed for up to 42 weeks. Subjects were monitored on weekly basis using the Beck Depression Inventory (BDI) and if an exacerbation of their symptoms was noted on this scale, they were formally evaluated for recurrence.

Two groups were identified from this cohort: an index group of subjects who experienced a recurrence and a comparison group of individuals who were matched to the index group with respect to age, gender, and clinical history. Weekly sleep disturbance complaints were evaluated using the single sleep item on the BDI (question 16) for the 5 weeks prior to recurrence in the index group and for a temporally equivalent period in the non-recurrent control group. The time series data from this period showed that the non-recurrent group exhibited an elevated, but stable, level of sleep disturbance and the recurrent group exhibited an increased level of sleep disturbance that began 5 weeks prior to, and was of highest severity at, the week of recurrence.

These data strongly suggest that insomnia may be a prodromal symptom of depression, and lend weight to the possibility that insomnia may trigger or precipitate new depressive episodes. To properly assess the latter, it would be necessary to experimentally manipulate sleep continuity in what would most likely be an ethically challenging and difficult experiment (see Summary and future directions).

Insomnia as a perpetuating factor for depression

We are only aware of one preliminary study that addresses the possibility that insomnia perpertuates depression. In this investigation, data were drawn from a large interventional study of late-life depression that enrolled 1801 elderly patients with MDD and/or dysthymia based on the Structured Clinical Interview for Diagnostic and Statistic Manual-IV edition [84]. MDD subjects from this cohort (n=1221) were assessed for their clinical status at baseline and at 6 months to determine whether insomnia (classified as no insomnia, transient insomnia, and persistent insomnia) was associated with clinical improvement and/or the occurrence of remission. The groups were significantly different in terms of the percentage of subjects who remained ill at 6 months according to two measures of depression (remission and <50% improvement). Overall, patients with persistent insomnia were 10–12-fold less likely to achieve remission or an improvement of ≥50% in depressive symptoms compared with patients with no insomnia. These data, which await replication, suggest that insomnia may perpetuate depression.

There are therefore good data to suggest that insomnia is a significant predisposing factor for depression, although further investigations are required to address the possible precipitating and perpetuating roles of insomnia in the depressive clinical course. In all three cases, it is unclear whether insomnia as a comorbid disorder interacts with other variables for the development of depression, or whether insomnia itself only represents an as yet unknown factor.

Does treatment of insomnia modify the course of depression?

From the historical symptom-only perspective of insomnia, one would predict that treatment of insomnia in the context of depression is either futile in the absence of treatment for the parent disorder, or, if successful, merely an example of good symptom management. Alternatively, if insomnia is a comorbid condition that predisposes, precipitates, or perpetuates depression, then insomnia should be treatable in the context of depression, and the benefits of such treatment should accrue to the depressive condition. There are now two sets of data that refute the former perspective, and support the latter. First, two clinical case series [85,86] and two randomized clinical trials [87,88] have shown that patients with co-occurring psychiatric or medical illnesses derive benefit from standard cognitive behavioral treatment for insomnia (CBT-I), with effect sizes comparable to meta-analytical norms.

Second, in another clinical case series, 56 patients presenting with insomnia and depression were enrolled in a structured, self-help insomnia program [89]. On average, patients not only showed improved sleep parameters, but 57% no longer exceeded depression cut-off scores, and an additional 13% of the total sample had a >40% decrease in depression scores. In a preliminary, uncontrolled study of CBT-I, eight patients with insomnia and mild depression showed improved sleep continuity measures, and seven of eight had depression scores below the cut-off at the end of treatment and at a 3-month follow-up [90].

Finally, in a large clinical trial (n=545), depressed patients with insomnia were randomized to receive fluoxetine with either placebo or eszopiclone. The group receiving eszopiclone not only showed significantly improved sleep continuity, but also had a greater reduction in depression scale scores and a shorter time-to-event for improved depression than the group receiving fluoxetine plus placebo [91].

These data suggest that the treatment of insomnia is feasible and efficacious in the context of current depression, and that successful treatment of insomnia attenuates depressive symptoms beyond those that are sleep-specific. When coupled with data showing that insomnia can persist following otherwise successful antidepressant treatment [4–8], this strengthens the case for considering insomnia not only as a risk factor in the course of depression, but also as a potentially modifiable risk factor for new-onset, episodic, or unremitting depression.

This, in turn, raises two additional questions:

- Can the treatment of insomnia in remitted depression prevent recurrence?
- Can the treatment of primary insomnia, in an at-risk non-depressed group, be protective against new-onset depression?

To our knowledge, there is one ongoing trial regarding the former (Is Insomnia a Modifiable Risk Factor for Insomnia? Primary Investigator: ML Perlis, University of Rochester, Rochester, NY, USA), but there are currently no published data that respond to either question.

Theoretical perspectives: how could insomnia modify the course of depression?

There are two broad perspectives from which to consider how insomnia may affect the development and course of depression. From a psychological perspective, the mood and cognitive consequences of insomnia may diminish the capacity to cope with interpersonal, social, and vocational stressors, thereby increasing the likelihood of negative life events or poor responses to such events. It is also possible that "lack of control" issues related to insomnia may activate other depressive schema related to helplessness and hopelessness.

From a neurobiological perspective, the association of persistent insomnia with neuroendocrine imbalances (e.g. hypercortisolism, increases in aminergic tone, serotonin deficiency), may directly or indirectly predispose the individual to the full clinical syndrome of MDD. These neuroendocrine abnormalities may, in turn, represent some of the biological factors that make insomnia a risk factor for MDD.

These two perspectives are not mutually exclusive. In fact, a surprising marriage of these perspectives comes from evidence revealing that acute sleep deprivation has antidepressant effects [92]. This raises the question of how insomnia can be a risk factor for MDD, when sleep deprivation acts as a form of antidepressant therapy. Clearly, insomnia and sleep deprivation are not the same, especially since insomnia as it presents in MDD is not comparable in magnitude or form to the sleep deprivation that has antidepressant effects. It has been proposed that insomnia initially occurs as a compensatory phenomenon in MDD to increase serotonergic tone but, unlike its sleep deprivation counterpart, cannot reach a level that exerts an antidepressant effect [93–95]. We would add that insomnia may also be an attempt to regulate other features of depression. If part of the pathogenesis of MDD relates to increased somatic arousal and/or to increased CNS arousal, then insomnia may represent a systemic response i.e. insomnia that occurs with MDD may be an attempt to increase homeostatic pressure to a point where the resultant fatigue and sleepiness counterbalance somatic and/or CNS hyperarousal. While such a position is entirely speculative, it is consistent with reports that sleep deprivation results in decreased core body temperature and decreased CNS metabolism in depressed subjects who have an antidepressant response to sleep deprivation [96–98].

In agreement with this perspective, there is a cascade effect that occurs with new onsets of depression. Following the biopsychosocial events that precipitate the initial CNS concomitants of depression (e.g. limbic hyperarousal induced by life stress), insomnia occurs both as a consequence and as a systemic response. The resultant increase in homeostatic pressure diminishes the CNS hyperarousal but also exacerbates or produces a set of "secondary" depressive symptoms. These secondary symptoms (anhedonia, fatigue, and memory and concentration problems) may, in turn, give rise to tertiary symptoms that include interpersonal problems, social withdrawal, and/or cognitive distortions (Fig. 3). When viewed in this way, onset of new episodes of MDD would be expected to unfold over time in such a way that some symptoms of depression reliably occur before others.

In remitted patients, persistent insomnia may indicate that the depression is not entirely resolved. Alternatively, insomnia may persist for reasons other than those that initiated the depressive episode. In keeping with the behavioral model of insomnia [99], an acute episode of depression may initiate insomnia, but the insomnia (as in primary insomnia) may persist due to perpetuating or maintaining factors, such as extending sleep opportunity and staying in bed while awake, which can result in conditioned insomnia. When insomnia exists as a result of behavioral contingencies, it may set the stage for other depressive symptoms. The occurrence of these symptoms, now secondary to a conditioned insomnia, could lower the threshold for the recurrent episodes of depression. This may be true in at least two ways. First, more defining criteria are met because of insomnia, thereby requiring fewer additional symptoms to make the diagnosis. Second, and more importantly, insomnia may increase general psychobiological vulnerability.

If it is true that insomnia represents a failed attempt at somatic and/or CNS homeostatic regulation, then the regulated sleep deprivation that is a cornerstone of both sleep restriction therapy and stimulus control interventions of CBT-I may succeed where the endogenous form fails. This may be because therapeutic sleep restriction, while of a short duration, is of a greater magnitude than the loss of sleep that occurs with natural insomnia. Thus, it may allow for a downregulation of somatic and/or CNS hyperarousal but may not be sufficiently chronic to exacerbate or precipitate the "secondary" depressive symptoms. This perspective suggests that the behavioral treatment of insomnia might exert direct antidepressant effects in addition to prophylactic effects, and bears further scrutiny in controlled trials.

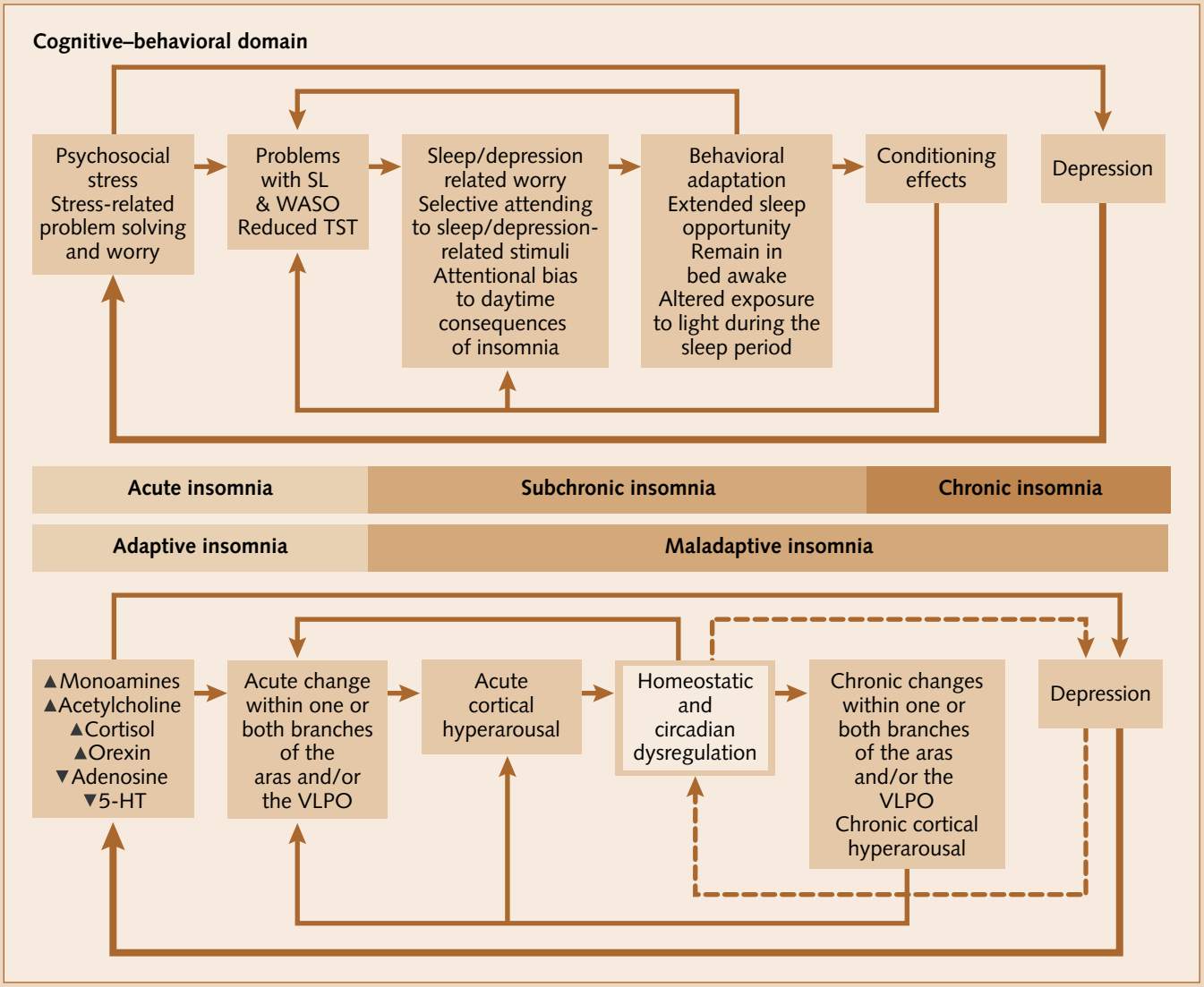
Finally, as has been argued throughout this paper, insomnia may confer risk for new-onset depression in that it may be a normative "first response" to biopsychosocial stress. Such a response, one might argue, is likely to be adaptive to the extent that the stressor appropriately and acutely activates the fight-or-flight system. If, however, the insomnia response continues beyond the biopsychosocial stress event, one might expect this form of insomnia (i.e. chronic insomnia) to represent a risk factor for the development of new-onset depression in a manner that is similar to the sequence (kindling) effect described above. For a graphical representation of this idea, see Figure 3.

Summary and future directions

In the present paper we have argued that there is sufficient evidence to consider insomnia and depression comorbid disorders, and that it is at least possible that insomnia and depression interact synergistically. The evidence supporting this includes:

- Each disorder may appear in the absence of the other disorder.

Figure 3. Etiology and pathophysiology of insomnia and depression. The box delineating the homeostatic and circadian factors is highlighted because the neurobiological control mechanisms are not detailed.



5-HT: serotonin; SL: sleep latency; TST: total sleep time; VLPO: ventrolateral preoptic area of the hypothalamus; WASO: wake after sleep onset.

- Insomnia remains a common residual symptom in remitted depression.
- Insomnia can be successfully targeted in the context of ongoing depression.
- Insomnia is a predisposing factor for depression (with preliminary evidence that it may also precipitate and/or perpetuate depression).

In addition, the two disorders present with different PSG findings, and to a less impressive degree, with different neurobiological profiles.

In order make a more compelling case for this theory, there are a variety of studies that need to be undertaken. These include:

- Large-scale longitudinal studies with multiple time point assessments (using validated insomnia instruments) to determine the time course between the onset of acute insomnia, the onset of chronic insomnia, and the development of new-onset depression. Such trials could also assay potential moderating/mediating factors as the ability to cope with interpersonal, social, and vocational stressors, the contribution of a sense of helplessness as opposed to control, and the level and type of neuroendocrine and neuroimmune abnormalities. These studies could also be designed to compare those individuals for whom insomnia appears to be only a symptom of depression that ameliorates with the depression, with those for whom insomnia persists.

Similarly, it would be useful to characterize and distinguish between depressed subjects who develop hypersomnia as opposed to insomnia.

- Intervention trials (both pharmacological and behavioral), which treat persistent insomnia in subjects with remitted depression or in subjects at risk of depression, would help assess whether this delays or aborts recurrent or first-onset episodes of depression.
- Studies that replicate the work by Fava and colleagues [91], which showed that adjuvant treatment for insomnia hastens recovery from depression.
- An inpatient intervention trial to assess the effects of treatment for insomnia in acute depression, where both pharmacological and behavioral anti-insomnia treatments are applied as monotherapies.
- An inpatient trial where subjects at risk for depression are exposed to a transient insomnia condition (such as those used by industry for Phase II trials) to determine whether insomnia can "trigger" new-onset episodes of depression. As noted earlier, this study (while a powerful demonstration) is likely to be too ethically challenging to conduct. The alternative would be to create an animal model of insomnia and use this to determine whether chronic insomnia predisposes, precipitates, or perpetuates an analogue form of depression in this context.

Disclosures

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LEADING ARTICLE

Sleep and Aging

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As the population ages and awareness of sleep disorders grows, issues that concern both sleep and aging are becoming increasingly important. The elderly appear to be particularly susceptible to a variety of different sleep complaints. At the present time, little is known regarding the mechanisms underlying the development of these disorders, despite some excellent research in this arena. This review summarizes the existing knowledge on this topic, focusing on insomnia, sleep apnea, circadian rhythm disorders, rapid eye movement behavior disorder, and periodic limb movements/restless legs syndrome. Sleep disorders can lead to considerable morbidity, particularly in the elderly, and we therefore strongly support further research in this area. Such research should focus on the mechanisms underlying the aging predispositions, the susceptibility of the elderly to these disorders, and potential therapeutic targets to treat these disorders and minimize their complications. *Int J Sleep Disorders* 2007;**1**(3):92–101.

The high prevalence and substantial consequences of sleep disorders are being increasingly recognized, and older age has been determined a major risk factor for many sleep disorders. The aging of the population as a result of increases in life expectancy and survival of the "baby boomers" is therefore likely to contribute a variety of sleep-related problems. Important progress has been made regarding our understanding of the various disorders; however, a number of questions remain unanswered. This review summarizes the existing knowledge related to aging and sleep disorders, focusing on insomnia, sleep apnea, circadian rhythm disorders, rapid eye movement (REM) sleep behavior disorder (RBD), and periodic limb movement disorder (PLMD)/restless legs syndrome (RLS).

Insomnia

Definition and etiology

Insomnia is defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as a complaint of difficulty initiating or maintaining sleep, and/or non-restorative sleep lasting at least 1 month, with major negative consequences on daily functioning [1,2]. A distinction is made between primary insomnia as a separate clinical entity, and insomnia that is secondary to primary psychiatric or medical conditions. However, studies have shown that despite the high prevalence of insomnia in chronic illnesses, insomnia can be a cause, a consequence, or unrelated to comorbidity [3–8]. Thus, some researchers have suggested that secondary insomnia should be more appropriately termed comorbid insomnia.

In the elderly, insomnia is often related to psychiatric or medical comorbidities, medications for the treatment of these illnesses, or primary sleep disorders such as sleep-disordered breathing (SDB), PLMD and RLS, and circadian rhythm disorders (Table 1) [9,10]. As all of these factors are highly prevalent in the elderly population, insomnia is not considered to be a part of the aging process *per se* [9–11].

Epidemiology and risk factors

The overall prevalence of insomnia is estimated as affecting approximately one-third of the adult population, with 10–15% suffering from insomnia on a long-term or chronic basis [3,12–14]. The prevalence of insomnia has been found to increase with age, particularly in women. Foley et al. reported results on the epidemiology of insomnia in the elderly [15], based on data from The National Institute on Aging's EPESE (Established Populations of Epidemiological Studies of the Elderly) [16]. In this sample of >9000 older adults, over 50% reported at least one sleep complaint, and 35–40% reported disorders of initiating and/or maintaining sleep on a chronic basis. Sleep complaints increased with age and were significantly higher in women; in a 3-year follow-up of this sample, the annual incidence rate was 5% per year [17]. Risk factors included chronic disease, depression, poor perceived health, physical disability, widowhood, and the use of sedatives. Remission occurred in nearly half of those with insomnia at baseline, and was related to improvements in perceived health.

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Table 1. Risk factors associated with insomnia in the elderly.

Mental illness – depression, anxiety, psychosis, dementia, delirium
Medical illness – cardiovascular disease, chronic obstructive pulmonary disease, asthma, stroke, Parkinson's disease, malignancies, arthritis, gastroesophageal reflux, peptic ulcer, nocturia, menopause
Primary sleep disorders – sleep-disordered breathing, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorders (advanced/delayed sleep phase syndrome/shift-work disorder), rapid eye movement sleep behavior disorder
Medications – antidepressants, anti-Parkinsonian agents, β-blockers, diuretics, antihypertensives, decongestants, bronchodilators, anticholinergics, sedatives, stimulants, alcohol

Similar findings from the National Sleep Foundation 2003 Sleep in America Survey have shown that depression, heart disease, pain, and memory decline were associated with symptoms of insomnia in older adults [18].

In a comprehensive review of the epidemiological studies of insomnia, prevalence rates and risk factors were compared based on the different definitions for insomnia [19]. Interestingly, whereas studies focusing on symptoms of insomnia have shown an increased prevalence with age, studies focused on global sleep dissatisfaction and insomnia based on the DSM-IV diagnosis have not shown age dependence.

Collectively, these findings support the widely held view that insomnia is not a part of aging, but rather increases in relation to the increased prevalence of comorbid conditions.

Consequences

Insomnia in older adults has been associated with decreased cognitive performance, including difficulty sustaining attention, slowed response time, and memory problems [20]. However, the evidence for cognitive decline in insomnia is not clear. In a study of sleep and cognition in elderly women, shorter sleep periods and insomnia complaints were related to lower scores on cognitive tests at the initial assessment, but not at 2-year follow-up [21]. In a 3-year longitudinal study, chronic insomnia was found to be an independent risk factor for cognitive decline in men, but not in women [22]. In a separate longitudinal study, daytime sleepiness, but not insomnia, was related to incident dementia and cognitive decline in men [23]. Similar results have been reported for elderly individuals in assisted-living residences [24]. Gooneratne et al. reported that insomnia with comorbid SDB was associated with lower daytime functioning and increased psychomotor reaction times [25]. These studies collectively suggest that the relationship between sleep disorders and cognitive functioning may be mediated by daytime sleepiness. However, insomnia can be an early sign of Alzheimer's disease, and may therefore be a harbinger of subsequent cognitive decline rather than a causal factor. Moreover, therapeutic studies using pharmacological and non-pharmacological techniques did not improve cognitive function, as measured by objective assessments, in the elderly.

Other daytime consequences of insomnia include adverse effects on mood, social and occupational functioning, perceived health, and overall quality of life (QoL) [20,26–29]. In addition, insomnia may increase economic burden via poor work productivity, absenteeism, and increased healthcare costs [26,30,31].

Evaluation and diagnosis

Despite its widespread prevalence in the adult population, insomnia is under-recognized and often inadequately treated in healthcare systems [4]. The Standards of Practice Committee of the American Academy of Sleep Medicine (AASM) has suggested guidelines for the evaluation of insomnia in the adult population [32], which include determining a thorough sleep history to identify a sleeping disorder, and also the specific type, i.e. sleep onset or sleep maintenance insomnia. Although overnight polysomnography (PSG) is not necessary for the assessment of insomnia, symptoms and signs of other sleep disorders, such as SDB, do warrant such a study. The effectiveness of actigraphy for the evaluation of insomnia is still debatable and is not recommended by the AASM guidelines (Fig. 1). Sleep logs and questionnaires completed by the patient and bed partner can provide a useful supplement to the sleep history for assessing sleep patterns and habits [33].

Useful questions when taking a sleep history in elderly patients include the occurrence and timing of daytime sleep, timing of bedtime and wake-time, number and length of nocturnal awakenings, and effects of the sleep problem on daytime functioning. It is essential to identify coexisting conditions such as medical or psychiatric illness, medications being taken, poor sleep hygiene, or other sleep disorders.

Treatment

Traditionally, insomnia has been widely accepted as secondary to a medical or psychiatric illness and, therefore, treatment of the underlying disorder should alleviate the insomnia [8,34]. However, regardless of the origin of the insomnia, many pharmacological and non-pharmacological treatments have proven effective for late-life insomnia. The following section reviews the evidence for their efficacy (Tables 2, 3, and 4).

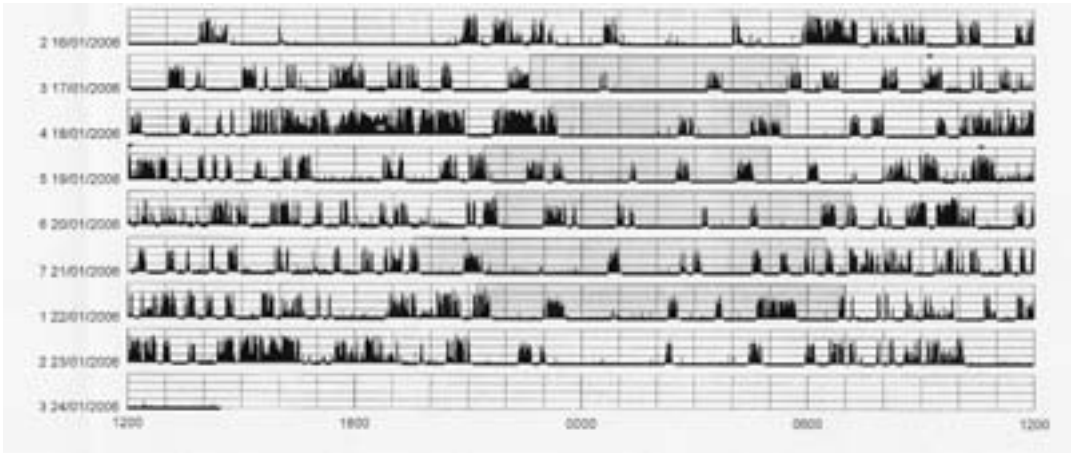

Figure 1. Actigraphy of a patient with insomnia. Recording over a period of a week is shown. Note the intermittent movements indicative of awakenings for long periods of time throughout the study period. In addition, note the frequent naps this individual takes during the day.

Non-pharmacological treatments

In a review by the AASM [35], stimulus control, progressive muscle relaxation, and paradoxical intention met the American Psychological Association (APA) criteria for empirically supported psychological treatments for insomnia. Sleep restriction, biofeedback, and multifaceted cognitive–behavioral therapy (CBT) met APA criteria for probable efficacious treatments.

Clinical trial studies of recent years have clearly demonstrated that CBT has been successful for elderly adults with primary and secondary or comorbid insomnia, and for those with hypnotic dependency [36–39]. In a long-term (1-year) follow-up, improvements were maintained and hypnotic use was reduced [39]. Of note, these improvements were not age-dependent, indicating that older insomnia patients with long-term use of hypnotic medication may benefit from CBT. In fact, one could argue that given the high prevalence of drug side effects and drug interactions in the elderly, non-pharmacological therapies may have more of a role in this group than they do in younger patients.

Pharmacological treatments

Hypnotic prescription medications for the treatment of insomnia include the traditional benzodiazepine sedative hypnotics (temazepam, estazolam, flurazepam, quazepam, triazolam), sedating antidepressants (trazodone), the newer non-benzodiazepine sedative hypnotics (zolpidem, zaleplon, eszopiclone), sedating antipsychotics (e.g. quetiapine), and melatonin agonists (e.g. ramelteon). Self-treatment strategies for insomnia include over-the-counter medications, such as sedating antihistamines and herbal or dietary supplements (e.g. melatonin, valerian–hops) [40,41].

General recommendations for the use of sedative hypnotics in the elderly include consideration of the type of insomnia complaint (sleep onset insomnia, sleep maintenance insomnia, or early morning awakening) in order to select the appropriate drug (short versus long acting), starting with a low dosage, consideration of drug interactions, and monitoring for residual effects of daytime sleepiness. The adverse consequences of hypnotic use may outweigh the benefits, and should be taken into consideration, particularly in those at high risk for falls or in individuals who suffer cognitive impairment [42]. In addition, underlying causes, such as depression in the case of early morning wakening in the elderly, should be considered.

Recent double-blind, case–controlled studies that have tested the efficacy, tolerability, safety, adverse events, and level of rebound insomnia for relatively new pharmacological agents commonly used in older adults are briefly presented below.

Zolpidem

Roger et al. compared the efficacy of two doses of zolpidem (5 and 10 mg/night) with triazolam (0.25 mg/night) in older adults aged >58 years [43]. Zolpidem was found to be at least as effective as triazolam, with good tolerability and safety, few side effects, and no rebound insomnia.

Ezopiclone

The efficacy of two doses of ezopiclone (1 and 2 mg/night) was evaluated in elderly patients by Scharf et al. [44]. Although 1 mg/night was sufficient to significantly shorten sleep latency, 2 mg/night shortened sleep latency and increased total sleep time, reduced wake-after-sleep onset, and improved sleep quality.

Zaleplon

Ancoli-Israel et al. reported that zaleplon (5 and 10 mg/night) and zolpidem (5 mg/night) significantly improved sleep parameters in elderly patients with insomnia. Rebound

Table 2. Cognitive–behavioral therapies for insomnia in the elderly [110].

Therapy	Description
Sleep hygiene education	Rules for better sleep include: maintain consistent bedtimes and wake times, minimize daytime naps, adjust bedroom environment (quiet, cool), avoid looking at clock during the night, avoid caffeine and nicotine in the evening, avoid heavy meals and excessive fluid intake in the evening, perform relaxing activities before bedtime, use bed only for sleep
Stimulus control therapy	Patient is instructed to go to bed only when tired; if sleep is not achieved within 20 min patient must leave the bedroom and return when tired. Process is repeated as needed. Bedroom is used only for sleep and sex. Wake times are consistent and no napping is allowed
Sleep restriction therapy	Time in bed is limited to the self-estimated total sleep time; no daytime sleep is allowed. Patient gradually increases sleep efficiency, estimated as the ratio between time asleep and time in bed. Time in bed may be gradually increased with improvement
Paradoxical intention	Patient is instructed to lie in bed and maintain wakefulness as much as possible. Bedroom must be dark and quiet; reading and television are not allowed
Cognitive therapy	Modification of sleep-related dysfunctional beliefs and attitudes that exacerbate the insomnia, and enhancement of sense of control
Relaxation therapies	Various techniques (e.g. muscle relaxation and meditation) aimed to reduce somatic and/or cognitive arousal

Table 3. Pharmacological treatments for insomnia.

Medication	Considerations when prescribing to the elderly
Benzodiazepines: temazepam, estazolam, flurazepam, quazepam, triazolam	Long half-life (except for triazolam) rendering these hypnotics effective for sleep maintenance. May have residual effects on next day functioning
Non-benzodiazepine hypnotics: zolpidem, ezopiclone, zaleplon	Effective especially for sleep onset insomnia, little evidence for residual effect. Zaleplon can be taken again in the middle of the night
Melatonin agonist: ramelteon	Effective for sleep-onset insomnia, no rebound insomnia or side effects reported
Sedating antidepressant: trazodone	Not recommended for non-depressed elderly patients due to side effects
Sedating antipsychotic: quetiapine	For treating elderly schizophrenia patients with insomnia
Over-the-counter medications: sedative antihistamines (diphenhydramine)	Inconclusive efficacy results
Herbal/dietary supplements: melatonin, valerian–hops	Inconclusive efficacy results

Table 4. Principles of sleep hygiene.

Maintain a regular sleep–wake schedule, go to bed and get up at the same times every day including weekends and holidays
Avoid daytime naps; if necessary, take a scheduled nap in the early afternoon and limit the nap to up to 1 h only
Avoid caffeine, alcohol, and nicotine, especially later in the day
Avoid heavy meals near bedtime
Avoid drinking fluids after dinner
Perform physical exercise during the day, but not before bedtime
Perform relaxing activities before bedtime
Create a comfortable bedroom environment; avoid light, noise, and extreme temperatures
Do not go to bed unless tired
Do not read or watch television in bed
Avoid trying to sleep
Avoid looking at the clock at night
Relax and focus on pleasant thoughts rather than stressful worrisome thoughts; make use of relaxation techniques

effects were observed in the zolpidem, but not the zalepon groups [45]. In a subsequent open trial with 6–12 months follow-up, long-term use of zaleplon was safe and effective, and the improvement in sleep measures was maintained, with no rebound insomnia [46].

Ramelteon

Roth et al. compared doses of ramelteon (4 and 8 mg/night) with placebo over 5 weeks in older adults [47,48]. Both doses significantly decreased sleep latency and caused no rebound insomnia or side effects.

Combination therapy

Morin et al. examined the separate and combined effects of sedative/hypnotic medication (temazepam) with CBT in older adults. Good short-term efficacy was reported for each treatment separately; however, better long-term management and reduced drug use was seen using the combined approach [49].

Circadian rhythm sleep disorders

The daily alternation between sleep and wake in humans is orchestrated by an interaction between the endogenous circadian pacemaker and the homeostatic drive for sleep. Evidence has accumulated to show that the circadian pacemaker provides a wakefulness signal that becomes progressively stronger throughout the day, with a peak in the late evening hours, and a sleepiness signal that becomes progressively stronger throughout the night, with a peak in the early morning hours [50].

Older adults typically complain of sleepiness early in the evening and of early morning awakenings. These complaints likely reflect systematic age-related changes in circadian rhythm. Thus, Munch et al. reported a diminished circadian arousal signal, characterized by increased sleep and reports of sleepiness during the early evening hours in healthy older adults, compared with their younger counterparts [51]. Likewise, the circadian-driven peak in sleepiness and the nadir in core body temperature, which both occur in the early morning hours, are phase advanced in older adults, resulting in less consolidated sleep and earlier arousal times [52]. Furthermore, both early morning light exposure and evening naps are likely to contribute to the advanced wake-times seen in older adults [52,53].

Healthy elderly individuals with an advanced sleep phase should be reassured that such age-related changes are normal, and treatment may not be necessary. Alternatively, if the phase advance is perceived as disruptive, bright light treatment in the evening hours has been shown to delay circadian rhythms and improve sleep efficiency and daytime performance [54]. However, a subsequent study failed to demonstrate improvement in objective sleep quality, despite circadian phase delay [55]. Similarly, several studies have examined the efficacy of melatonin for the treatment of age-related sleep disturbances, with mixed results. While some studies have found few or no improvements in sleep parameters, others have reported improved sleep efficiency [56,57]. Thus, the practical usefulness of both bright light and melatonin treatments in the elderly is still debatable.

Another circadian disorder that may affect older adults is shift-work disorder. Older adults still in the workforce may have more difficulty adjusting to rotating shifts and, in particular, to night shifts [58]. Advanced sleep may be the cause of poor tolerance to nighttime shiftwork, and early morning shifts should be favored in such cases. Studies examining the effects of melatonin for improving adaptation to shift-work have shown some benefits; however, as these studies recruited young adults, findings cannot be generalized to the older adult population [59]. Bright light exposure in the evening has proven effective.

In addition to the normal age-related changes in the circadian phase, pathological changes of the circadian system have been reported in elderly patients with dementia [60,61]. These changes include reduced amplitude of the sleep–wake cycle, characterized by increased nocturnal activity and increased daytime sleep episodes, as well as delayed and desynchronized circadian rhythms of core body temperature and activity. In nursing home patients with dementia, increased bright light exposure has been found to enhance circadian amplitude and consolidate nighttime sleep and daytime activity [62,63]. Recent studies on the efficacy of melatonin for the treatment of sleep disturbances in Alzheimer's disease have, in general, failed to find any major improvements in sleep [64].

PLM in sleep

PLM in sleep (PLMS) is characterized by involuntary leg kicks during sleep, which appear in repetitive clustered episodes, and may cause arousals from sleep. PLMS has traditionally been associated with insomnia and excessive daytime sleepiness (Fig. 2) [65], and has also been found to co-occur with other sleep disorders, including sleep apnea syndrome, narcolepsy, and RBD [66,67]. PLMS is a common finding in 80% of patients who suffer from RLS, a neurological disorder characterized by dysesthesia in the legs causing an irresistible urge to move them, with symptoms increasing during the evening and at night, causing sleep disturbance [68]. PLMS may also appear unrelated to RLS, with distinct sleep characteristics [69].

The etiology of PLMS is currently unknown; however, due to its successful treatment with levodopa, as well as other dopaminergic agents (see below), and from observations of

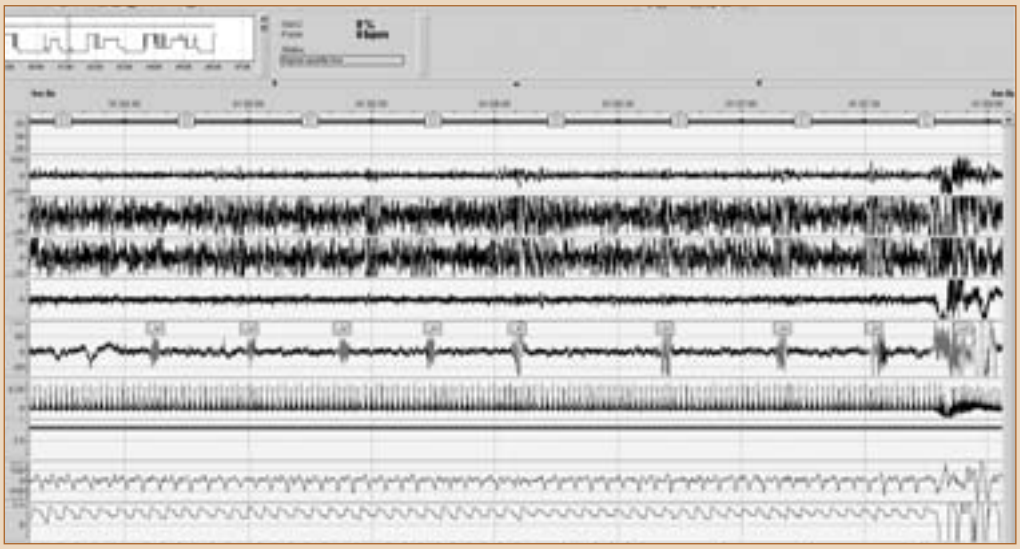

Figure 2. Periodic limb movements. The channels shown (from top to bottom) are: EOG (left and right), EEG (FP2-A1, FP1-A2), submental EMG, tibialis anterior EMG, ECG, respiration (flow: thermistor, nasal pressure; effort: thoracic belt), O_2 saturation, and pulse. Note the intermittent leg movements in the anterior tibialis EMG channel and the arousals seen with each leg movement.

ECG: electrocardiogram; EEG: electroencephalography; EMG: electromyography; EOG: electrooculography.

narcoleptic dogs with human-like PLMS, a dopaminergic deficiency has been suggested [70,71].

The prevalence of PLMS has been shown to increase with age. Prevalence rates reported in community-dwelling, elderly individuals for a PLM index >5 events/h ranged between 34–58% [72–74]. However, long-term follow-up of the elderly sample studied by Ancoli-Israel and colleagues has shown no overall change in PLMS with increasing age [75].

Despite its high prevalence, the pathological significance of PLMS in the elderly is debatable. Investigators found no relationship between PLMS severity and subjective reports of sleep disturbances or daytime sleepiness [74]. Youngstedt et al. reported PLMS in 86% of elderly volunteers with poor sleep or depression; however, PLMS severity was not related to any measures of sleep disturbance [76]. Gosselin et al. found that heart rate variability associated with PLM events was decreased in elderly subjects compared with younger adults [77].

The impact of PLMS is assessed based on the International Classification of Sleep Disorders diagnostic criteria of ≥5 PLM events/h of sleep, and clinical consequences of insomnia and/or daytime sleepiness. Regardless of whether PLMS is secondary to RLS or stands as a separate diagnosis, treatment strategies for both these conditions are similar.

Pharmacological treatments for PLMS have been studied in adult populations, and although these have included adults aged ≥65 years, no studies have thus far been dedicated exclusively to older adults. The treatments of choice for PLMS in symptomatic individuals with secondary insomnia and/or daytime sleepiness are dopaminergic agents, including levodopa with the dopa decarboxylase inhibitor carbidopa, and the dopamine agonists pergolide, pramipexole, and ropinorole. However, such agents may actually worsen daytime sleepiness in the elderly, and their usefulness is debated, particularly given the arguable significance of the limb movements themselves. Second-line treatments include sedative hypnotics, anticonvulsants, opioids, and adrenergic medications [78,79].

Sleep apnea syndrome

Sleep apnea syndrome is a disorder characterized by repetitive cessations of breathing during sleep. Apnea can be central (in which there is no respiratory effort) or obstructive (where effort to breathe continues but there is no airflow due to airway obstruction) [80]. Although both types of apnea may be affected by age, this review will focus primarily on obstructive sleep apnea (OSA), the more common manifestation. Several pathogenic mechanisms are, however, common to both obstructive and central apnea [81].

The principle abnormality in the individual with OSA is an anatomically small pharyngeal airway [82]. During wakefulness, the individual is able to compensate for the deficient anatomy by increasing the activity of upper airway muscles that maintain airway patency [83]. However, with sleep onset, this compensation is lost and airway collapse occurs. The physiological consequences of apnea are a rise in $PaCO_2$, a fall in PaO_2, and an increased ventilatory effort against an occluded airway. Ultimately, transient arousal from sleep occurs, which re-establishes airway patency and ventilation. The individual subsequently returns to sleep and the cycle repeats throughout the night.

OSA is usually associated with loud snoring, morning headache, dry mouth upon awakening, nocturia, fragmented sleep, and daytime sleepiness. During recent years, extensive

research has led to the realization that OSA is a major public health problem, with a large impact on healthcare utilization, increased morbidity (predominantly cardiovascular disorders), and mortality rate. Both the sleep apnea *per se* and its consequences may change over time, emphasizing the importance of a patients' age during clinical evaluation.

Epidemiology

Classically, OSA is defined as a respiratory disturbance index (RDI) of >5 events/h of sleep plus a complaint of daytime somnolence. When this definition is considered, the prevalence of OSA syndrome is 2–3% and 4–5% in middle-aged women and men, respectively [84,85]. In addition to obesity, other risk factors include male gender, genetic factors, hormonal disorders such as hypothyroidism, acromegaly, polycystic ovary syndrome, and specific diseases such as renal failure or diabetes. OSA is also prevalent in syndromes associated with predisposing airway collapse, such as Down's syndrome, Crouzon, or Pierre-Robin sequence. Aging has also been reported as a major factor affecting the incidence of OSA, with an increased prevalence from 2–5% in middle-aged individuals, to 5–8% in patients aged 50–60 years, and higher again in the elderly [86]. Kripke et al. reported that age was the second most important predictor of SDB (following obesity) in a population-based survey of over 350 people [87]. Ancoli-Israel et al. found that 81% of elderly individuals in a community-based sample had an RDI >5 events/h, and 44% had an RDI >20 events/h [88]. In a separate study, the reported overall prevalence of OSA in a sample of 358 randomly selected elderly volunteers, as diagnosed by home monitoring, was 17% [89]. Many epidemiologically based studies have noted the age-related increase in RDI [90–92], and the menopause also represents a major risk factor for sleep apnea in women [93]. In the extremes of aging, some data suggest a survivor effect, such that apnea prevalence may decrease among elderly patients. This is presumed to reflect death of apnea patients from the associated comorbidities prior to reaching the elderly age groups [101,102].

Mechanism

The explanation for the increased prevalence of OSA in aging remains unknown, although several potential mechanisms have been proposed. Martin et al. reported that upper airway dimensions (as assessed by acoustic reflection technique) decreased with increasing age [94]. Age has also been reported to correlate with pharyngeal resistance in men, but not in women [95], to be associated with a decrement in respiratory effort during an obstruction [96], and in protecting genioglossus muscle activation [97]. An age-related decrement in hypercapnic ventilatory response has also been reported, although its relevance to OSA is questionable. The age-related anatomical and pathophysiological potential mechanisms that could predispose to pharyngeal collapse in older individuals have recently been studied by the authors' group [98]. Upper airway anatomy was investigated in 38 subjects using volumetric analyses of magnetic resonance images in order to quantitatively assess the structures of interest. Physiological assessments of the activity of upper airway dilator muscles (using intramuscular genioglossus electrodes) during basal breathing and in response to respiratory stimuli were also performed, including pulses of negative pressure. The pharyngeal dilator muscles of older subjects were found to be less responsiveness to negative pressure stimuli than those of younger subjects ($R=0.55$; $p=0.005$). In addition, anatomical changes associated with aging included increased parapharyngeal fat pad size ($R=0.59$; $p=0.001$). Pharyngeal airway length correlated significantly with aging in women ($R=0.56$; $p=0.007$), but not in men ($R=0.18$; $p=0.47$). Since the longer the airways, the more prone they are to collapse; these findings may be of importance in the age-related increase in OSA, at least in women. More recently, a significant aging effect on airway collapsibility, as measured during stable non-REM (NREM) sleep, has been observed [98]. Thus, there are both anatomical and physiological age-related changes leading to an increased vulnerability to OSA in the elderly.

Outcome

Although most studies agree that the prevalence of OSA increases with age (based on standard definitions used in adults), the associated symptoms and consequences may change with age and be different in the elderly. Bixler et al. reported that the prevalence of sleep apnea tends to increase with age, but its clinical significance and severity decreases [99]. A later study concluded that although in a middle-aged population the most prevalent disorder accounting for excessive daytime sleepiness is OSA, in the elderly, depression and chronic disease such as diabetes becomes much more important [100]. Interestingly, although OSA probably results in increased morbidity and mortality rates during middle age, OSA most likely has a protective role in patients aged ≥70 years [101,102]. The reason for this paradoxical improvement in survival in OSA versus non-OSA subjects after 70 years of age has several potential explanations. First, it could relate to genetic inherited survival factors (i.e. those who survived OSA after the age of 70 have "genetically programmed" long life expectancies). In other words, if OSA is acting as a nightly stress test, those patients who have survived the stress test for multiple decades are likely to have an overall good prognosis from a cardiovascular standpoint. Second, it is plausible that patients with OSA

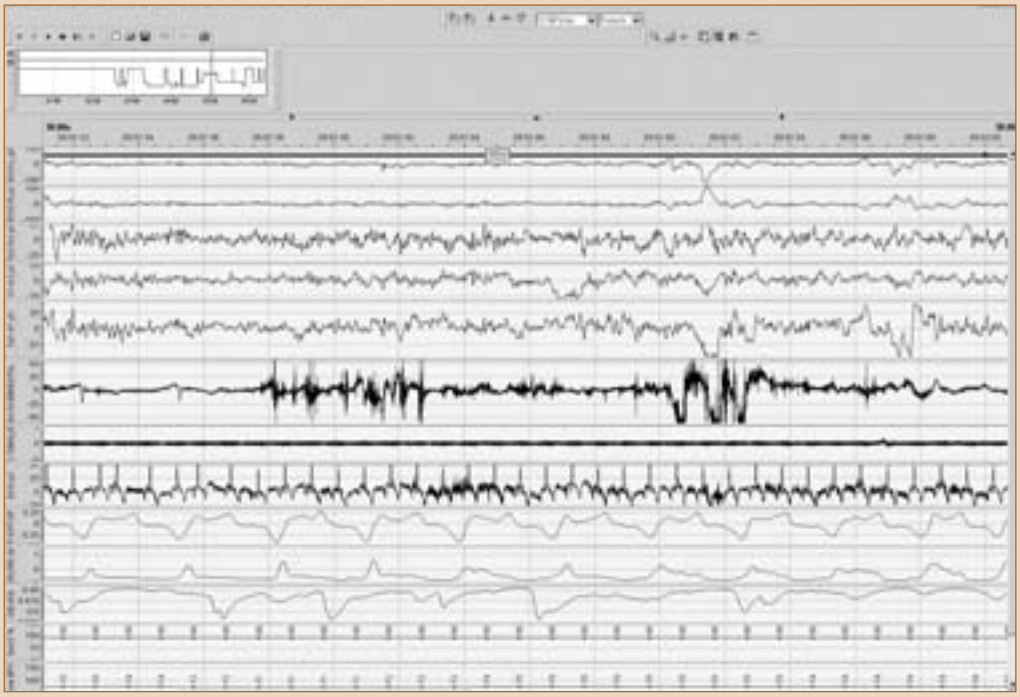

Figure 3. REM sleep without atonia. The channels shown (from top to bottom) are: EOG (left and right), EEG (FP2-A1, FP1-A2), submental EMG, EKG, respiration (effort: abdominal belt; flow: nasal pressure), snoring (db), O_2 saturation. Two REM spochs are shown. Note the submental EMG bursts on a background or relative atonia.

ECG: electrocardiogram;
EEG: electroencephalography;
EMG: electromyography;
EOG: electrooculography.

who have survived until the age of 70 years have developed protective mechanisms such as collateral coronary blood vessels. Regardless of the mechanism, it appears that OSA does increase with age, although at a certain age it becomes less harmful. Thus, when clinically evaluating a patient for suspected OSA, age appears important in the assessment of both complaints and prognosis. Thus, treatment decisions for sleep apnea need to be individualized, particularly in the elderly where the benefits may be modest. Similarly, in those patients unlikely to respond with improvements in symptoms (e.g. asymptomatic apnea or those with an apnea–hypopnea index <15 events/h), aggressive treatment may not be indicated. Ongoing, large-scale population-based studies will hopefully provide some guidance on these issues in the future.

REM sleep behavior disorder

RBD is a parasomnia characterized by undesired vocal and/or complex motor activities occurring during REM sleep (dreaming) (Fig. 3). The pathophysiology involves a decrement or loss of the REM-associated atonia [103]. Major diagnostic features include complaints of potentially harmful behaviors that occur during this sleep period, and dreams in affected patients may contain an elevated proportion of aggressive content [104,105]. As the events occur in REM sleep, they are usually expected during the latter part of the night. When PSG is performed in patients with RBD, even if events do not occur, REM sleep is commonly associated with increased electromyography activity [106]. RBD is hypothesized to be caused by a dysfunction of brainstem structures and basal ganglia [103], and hence may be associated with or precede the development of various neurodegenerative disorders such as multiple system atrophy, Parkinson's disease, and dementia with Lewy bodies [107], although many cases are idiopathic. With extended long-term follow-up, some recent series suggest that the majority of patients eventually develop either dementia or a synucleinopathy (e.g. Parkinson's disease). RBD is rarely seen in children and young adults, and it clearly increases with age, being most prevalent in the elderly. This finding may be partially explained by age-related central nervous system degeneration. In a summary study of 93 (81 men) consecutive patients seen at the Mayo Clinic Sleep Disorder Center (Rochester, MN, USA), it was reported that the mean age of onset was 60.9 years (range 36–84 years) and the mean age at presentation was 64.4 years (37–85 years) [108].

The classic treatment of choice for RBD is clonazepam, which is usually beneficial and well-tolerated by patients; however, as RBD is common among elderly individuals, in whom OSA and risk of falls can be a contraindication to clonazepam, alternative medications may be considered. For example, although data are somewhat sparse, the authors have experienced good clinical results with shorter-acting benzodiazepines and non-benzodiazepine sedative/hypnotics in RBD. Melatonin in doses of 3–12 mg has recently been suggested as a promising alternative therapy, with a good clinical response and tolerance reported in elderly patients [109]. Infrequent and mild side effects, such as morning headaches, morning sleepiness, and delusions/hallucinations,

were all resolved with decreased dosage. Anticholinesterase inhibitors and dopaminergic agents are not of clear benefit, and monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonergic reuptake inhibitors, and noradrenergic antagonists can induce or aggravate RBD symptoms and should therefore be avoided these in patients [103].

Summary

Sleep disorders are exceedingly common in the elderly. These diseases have been traditionally under-recognized and under-treated due to either a lack of awareness or a belief that treatment is unnecessary if the symptoms occur in association with a comorbid condition. Increasing evidence of the importance of these disorders advocates careful assessment and treatment planning for sleep symptoms in this population. For the clinician, we would argue that as many of these conditions are amenable to therapy, treatment of sleep disorders can improve satisfaction and quality of life in the elderly patient. For the researcher, further work will be required to determine why certain conditions increase with aging, the consequences of sleep disorders in the elderly population, and how these processes can be treated and/or prevented.

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LEADING ARTICLE

The Pharmacology of Insomnia: Targeting $GABA_A$ Receptor Function

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Among the wide array of neurotransmitters and neuropeptides that mediate neuronal communication, γ-aminobutyric acid (GABA) has emerged as the canonical inhibitory signal, and extensive *in vitro* studies have identified an enormous diversity in the signaling capabilities of the $GABA_A$ receptor. As a target for benzodiazepines (BZDs), barbiturates, and anesthetics, the clinical relevance of the $GABA_A$ receptor complex as a therapeutic target spans neurology, psychiatry, and anesthesiology. This review will focus on $GABA_A$ receptor function as a target for insomnia therapeutics, which until recently have been dominated by classical benzodiazepines. Recent experimental investigations targeting specific subsets of $GABA_A$ receptors, including genetic and pharmacological dissection of BZD mechanisms, underscore the potential for rational drug design. In addition, recent developments in a novel type of signaling mediated by non-synaptic (BZD-resistant) $GABA_A$ receptors offer new possibilities for insomnia therapeutics. *Int J Sleep Disorders* 2007;**1**(3):102–10.

This review focuses on recent developments in γ-aminobutyric acid A ($GABA_A$) receptor pharmacology that are relevant for insomnia therapeutics. Benzodiazepines (BZDs) have been the mainstay of prescription treatment for various forms of insomnia, and the recent development of next-generation hypnotics emphasizes the potential for optimizing hypnotic medications by targeting the specific neuronal pathways relevant for sleep [1]. A survey of $GABA_A$ receptor structure and function provides a framework for the translational research insights stemming from two main fronts. The first combines genetic engineering and novel pharmacological agents to dissect the specific mechanisms underlying the manifold behavioral effects of BZDs. The second targets a novel type of $GABA_A$ receptor that is excluded from synapses and therefore does not mediate the canonical synaptic form of signaling; it may therefore respond to distinct therapeutic agents. The end goal of both of these fronts, partly realized already with next-generation BZDs, is to provide a basis for rational drug design to target specific aspects of insomnia, while minimizing unwanted side effects.

$GABA_A$ receptor structure, function, and regulation

The simplistic view of the $GABA_A$ receptor as a single entity controlling "inhibition" is being replaced by the growing evidence for extensive diversity in signaling potential, derived primarily from an extensive array of genes encoding $GABA_A$ receptor subunits. GABA interacts with three types of membrane receptors, two of which comprise ion channels (types A and C), and one that is a G-protein coupled metabotropic receptor (type B). $GABA_A$ receptors are members of a superfamily of structurally similar neurotransmitter-gated ion channels [2], which also includes ion channel-coupled receptors for acetylcholine (nicotinic type), glycine, and serotonin (5HT-3 type). Five structurally homologous subunits, each encoded by a separate gene, assemble to form a chloride-permeable $GABA_A$ receptor channel complex. This molecular heterogeneity confers subunit-specific properties to the receptor complex; in fact, almost every property examined to date is regulated by subunit composition, including affinity for GABA, efficiency of channel opening, desensitization kinetics, sensitivity to allosteric modulators (including BZDs), neuroanatomic expression patterns, and subcellular targeting.

$GABA_A$ receptor molecular diversity

The diversity of $GABA_A$ receptor function begins with at least 16 genes, encoding various subtypes, grouped into several subunit families: α, β, γ, δ, ε, π, and θ. Some of the subunit families include multiple subtypes: α(1–6), β(1–3), γ(1–3). Each receptor complex consists of two α, two β, and one other subtype unit, with the majority consisting of αβγ or αβδ combinations (Fig. 1) [3]. The importance of such molecular diversity is reflected in the complex regulation of gene expression according to the developmental period, brain region, cell types within a given region, membrane location with the cell (axonal, somatic, dendritic), relationship

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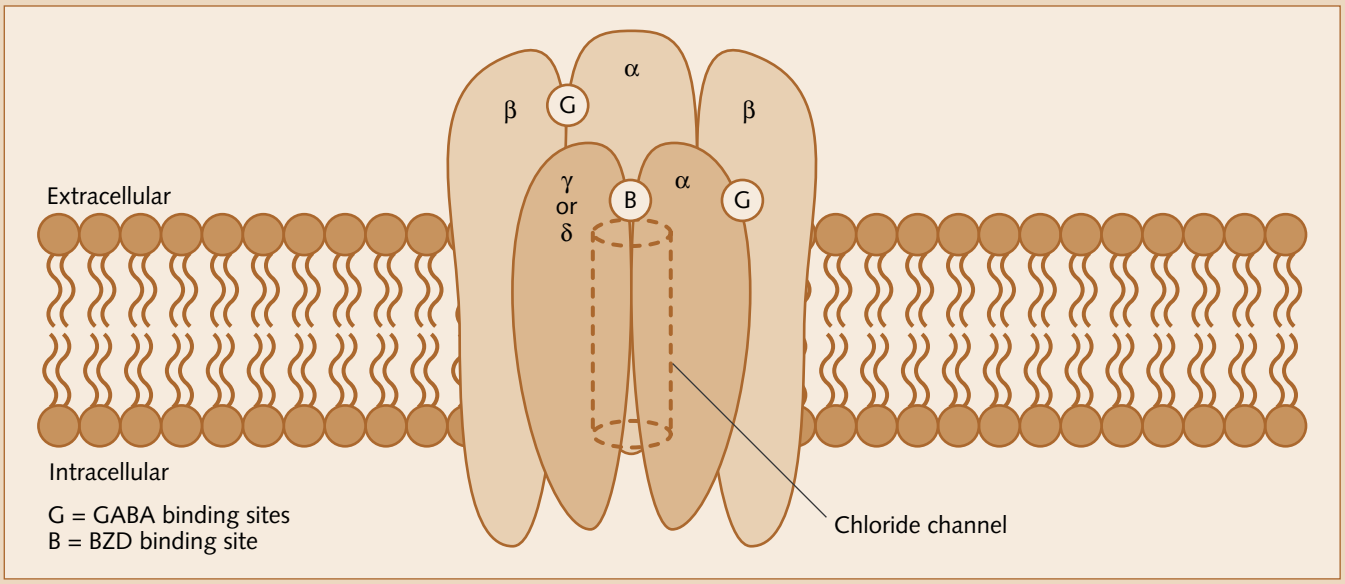
Figure 1. Cartoon of the $GABA_A$ receptor pentamer situated in the membrane. The γ subunit can be replaced by the δ subunit (see text). The GABA binding sites (α–β interfaces) are distinct from the BZD binding site (α–γ interface).



BZD: benzodiazepine; GABA: γ-aminobutyric acid.

to pre-synaptic structures (synaptic or non-synaptic), and even sleep cycle [4–7].

$GABA_A$ receptor pharmacology

Among the numerous endogenous and exogenous agents that are known to interact with $GABA_A$ receptors [4,8], the most clinically relevant are the BZDs, barbiturates, volatile anesthetics, and neurosteroids. The BZDs are commonly used to treat insomnia, and this class of medication acts at specific $GABA_A$ receptor-binding sites formed by adjacent γ and α subunits (in contrast to the pair of GABA binding sites at the α–β interfaces). The γ subunit is usually of the γ2 subtype, and the α subunit must be one of the α1, α2, α3, or α5 subtypes [9]. BZDs enhance receptor function by increasing the receptor affinity for GABA [10], and through this mechanism provides anxiolytic, anticonvulsant, and sedative/hypnotic benefits. The new-generation "non-BZD" hypnotics, such as zolpidem and indiplon, also target the BZD site at the α–γ subunit interface (Fig. 1); however, they are structurally distinct from the classical BZDs such as diazepam.

Barbiturates and neurosteroids enhance $GABA_A$ receptor function at distinct binding sites, and recent evidence suggests that receptors containing the δ subunit are particularly sensitive to modulation by these agents [11–13], and anesthetics [14]. Although neurosteroids are not commonly used clinically for their anesthetic and hypnotic properties, their therapeutic potential is suggested by endogenous concentrations sufficient to enhance $GABA_A$ receptor function [15], and this level can be regulated by stress [16], menstrual cycle [17], and antidepressant use [18]. The depression/antidepressant link to neurosteroids is particularly interesting given the association of depression and sleep disorders [19].

Membrane compartmentalization: synaptic and extrasynaptic $GABA_A$ receptors

The best characterized mechanism of $GABA_A$ receptor signaling occurs at synapses. These specialized neuronal contacts facilitate vesicular release of presynaptic GABA, which binds to post-synaptic $GABA_A$ receptors to trigger chloride-mediated currents that usually, but not always, cause neuronal inhibition. $GABA_A$ receptors comprised of αβγ subtypes typically subserve these intermittent or "phasic" synaptic events, and are targeted to synapses by post-synaptic clustering proteins that depend on the γ subunit [20]. As the BZD binding site is formed by the α–γ interface, synaptic αβγ $GABA_A$ receptors are likely targets for BZD actions, including their hypnotic/sedative effects (Table 1).

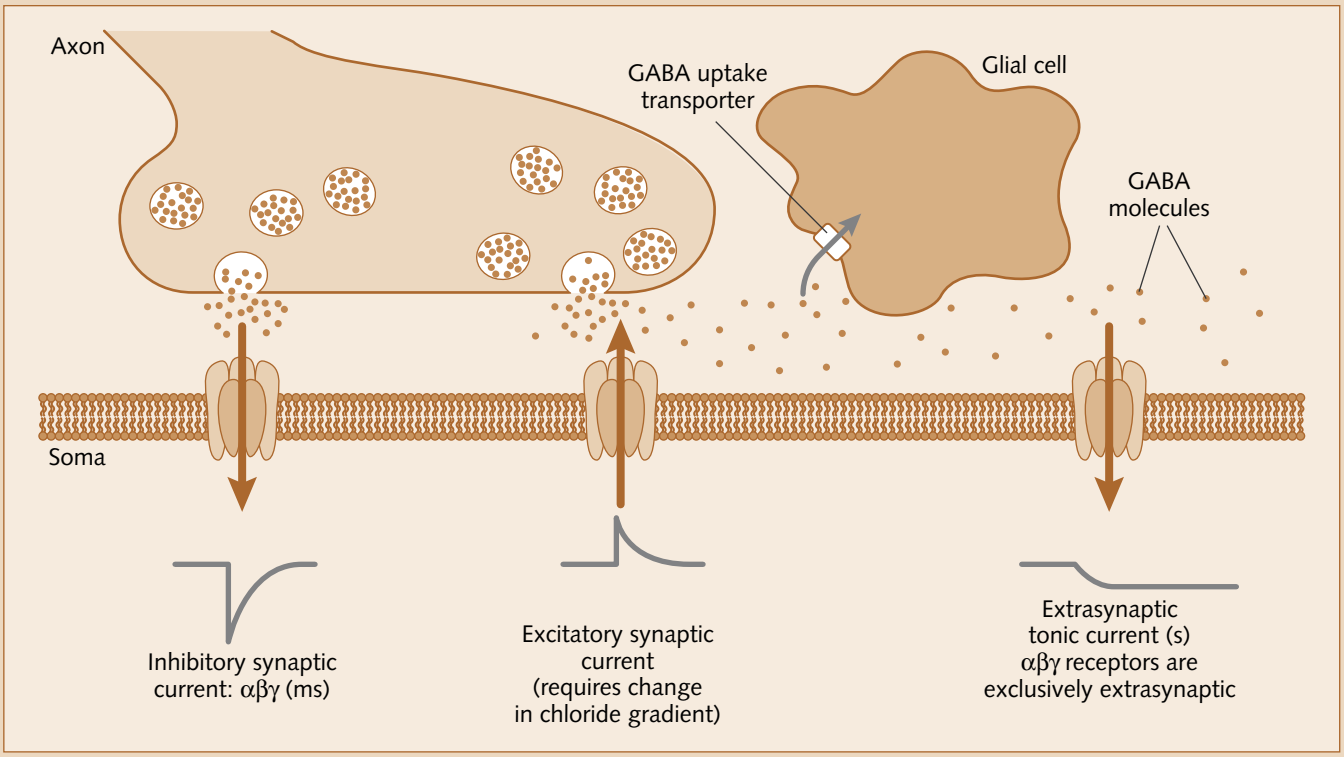
However, recent evidence indicates that many $GABA_A$ receptors are excluded from synapses and, instead, occupy extrasynaptic membrane locations [21]. Although some αβγ receptors do exist outside of synapses [22], αβδ receptors, which contain the BZD-insensitive δ subunit, are exclusively found in extrasynaptic locations as they do not interact with the synaptic clustering machinery. Extrasynaptic αβδ receptors are able to respond to GABA signaling over slower timescales and at lower concentrations than synaptic

Table 1. $GABA_A$ receptor pharmacology.

Drug class	Examples	Preferred receptor target	Type of inhibition	Unique to $GABA_A$ receptors
Classical benzodiazepines	Diazepam, loresepam	*αβγ	Synpatic	Yes
Next-generation hypnotics	Zolpidem, zaleplon, indiplon	α1βγ	Synaptic	Yes
GABA analogue	Gaboxadol	αβδ	Tonic (extrasynaptic)	Yes
Neurosteroids	THDOC, alphaxalone	αβδ	Tonic (extrasynaptic)	No
Alcohols	Ethanol	αβδ	Tonic (extrasynaptic)	No

*Where α=1,2,3, and 5. GABA: γ-aminobutyric acid; THDOC: tetrahydrodeoxycorticosterone.

Figure 2. Mechanisms of $GABA_A$ receptor signaling. Vesicular release of GABA activates synaptic receptors (left), causing fast chloride signaling. Lower concentrations of extracellular GABA contributed by synaptic spillover or glial regulation, causes slow chloride signaling in non-synaptic receptors (right).



GABA: γ-aminobutyric acid.

events (Fig. 2) [23]. This is due to two important properties conferred by the δ subunit: high GABA affinity and minimal desensitization to prolonged GABA exposures [24]. The δ subunit typically assembles with α4 in the thalamus, α5 in the hippocampus, and α6 in the cerebellum, and tonic currents mediated by αβδ receptors have been characterized in each of these regions [24]. Such tonic inhibition can be regulated by anesthetics, neurosteroids, and alcohol [22,25–27], suggesting that this new type of inhibitory signaling may represent an important therapeutic target (Table 1). The extracellular GABA that triggers this GABAergic tone is related to spillover from synapses, GABA transporter activity, glial uptake, and even reversal of glial GABA transporters [28–30], providing multiple potential mechanisms for regulation at the level of extracellular GABA concentration. In fact, the anticonvulsant drug tiagabine may act through blockade of GABA uptake, thus increasing extracellular GABA concentration and tonic inhibition. It is possible that phasic and tonic forms of inhibition have distinct roles in controlling network activity [21,31], and the potential for selective therapeutic manipulation of these two signaling mechanisms is discussed below.

Table 2. Subtype-specific benzodiazepine effects. Adverse effects are less evident with α-subtype selective agents.

Type of effect	Sedative/hypnotic	Anxiolytic	Tolerance	Alcohol synergy
Receptor target	α1βγ	α2,3βγ	α5βγ	α2βγ

$GABA_A$ receptor physiology: beyond simple hyperpolarization

$GABA_A$ receptor activation typically manifests as membrane hyperpolarization and is therefore considered inhibitory. However, multiple electrical consequences are actually possible, including depolarization (Fig. 2), or no change in membrane voltage at all (so-called "shunting" inhibition). GABA-mediated excitation can happen in at least three ways. Firstly, released GABA can inhibit an inhibitory neuron thereby producing disinhibition (i.e. excitation); this form of indirect excitation via sequential inhibitory processes occurs in various sleep circuits [32,33]. Secondly, modulation of the chloride equilibrium potential (e.g. by transmembrane chloride transporters) can switch $GABA_A$ receptor activation from hyperpolarizing to depolarizing [34,35]. The reason for this is that when ion channels open, the membrane voltage is "pulled" towards the reversal potential of the permeating ions (determined by the ion's electrochemical gradient) – this serves as a reminder that there is nothing intrinsically inhibitory about GABA or $GABA_A$ receptors. Interestingly, the suprachiasmatic nucleus may utilize such regulation of chloride gradients to generate a diurnal switch between $GABA_A$ signaling being excitatory or inhibitory [36]. Lastly, certain voltage-gated ion channels are inactivated at voltages near resting potential, such that a $GABA_A$-mediated hyperpolarization enables these inactive channels to recover and produce rebound action potentials (T-type calcium channels [37]). Such a mechanism underlies neuronal activity in the thalamo-cortical system as it pertains to sleep and arousal states [38].

Although hypnotics and sedatives are presumed to act through neuronal inhibition, the relative importance of (direct or indirect) excitatory actions of $GABA_A$ receptor systems relevant to insomnia treatments, or their side effects, remains an area of uncertainty.

Translational research prospects for insomnia and rational drug design

The sedative/hypnotic actions of BZDs effectively treat insomnia, and the anxiolytic effects may have the added benefit of addressing its exacerbation by comorbid anxiety. However, undesirable side effects are a major impetus for developing new agents that can more precisely meet therapeutic goals. If the molecular substrates of BZD action were better understood, the potential for elucidating the therapeutic from the adverse effects could be realized in the treatment of insomnia.

Classical BZDs are considered "nonselective" ligands for the α1, α2, α3, and α5 subtypes as they bind with high affinity and are fully efficacious at receptors containing any of those subtypes. The multiple clinical actions of classical BZDs, including sedative, anxiolytic, muscle relaxant, anticonvulsant (and even adverse effects like abuse and tolerance), likely arise because these subtypes are expressed in multiple brain regions and pathways, and are all activated by the non-selective classical BZDs. The introduction of next-generation non-BZD agonists that are active at the BZD binding site represents successful targeting of a subset of $GABA_A$ receptor systems for clinical advantage. The new hypnotics zolpidem, zaleplon, and indiplon are structurally distinct from BZDs, but are able to interact with the BZD binding site at the α–γ interface. However, they selectively target only those BZD binding sites formed by the α1 subtype, and it is this selectivity that is thought to isolate the hypnotic effects from the other actions of classical BZDs (Table 2).

In the following sections, experimental evidence that supports the potential for isolating the spectrum of BZD actions by linking them to specific $GABA_A$ receptor subtypes is presented. Studies in animal models, using "knock-in" strategies and subtype-selective pharmacology, are unraveling the populations of $GABA_A$ receptors that mediate the various therapeutic effects of BZDs, and those of other agents that may prove clinically useful for insomnia. Knock-in experiments involve engineering mice to harbor a point mutation in a $GABA_A$ receptor subtype gene, which renders the subtype BZD-insensitive [39,40]. This was performed for the four BZD-sensitive α subtypes: α1, α2, α3, and α5. Although it remains to be seen how these discoveries will translate to human studies (to date, there are only two reports of $GABA_A$ receptor mutations associated with insomnia in humans [41]), the potential for translation to rational drug design is encouraged by the clear benefits of the new-generation BZD-site agonists already in use.

α1 subtype is linked to BZD-mediated sedation

Mice harboring the α1 subtype knock-in mutation, rendering that subtype BZD-resistant, were insensitive to BZD-induced sedation, suggesting that neuronal circuits utilizing the α1 subtype mediate the sedative/hypnotic effects of BZDs. Diazepam, which is active at α1, α2, α3, and α5 subtypes,

and zolpidem (α1 selective), both lost their sedative activity in these α1 knock-in mice [42,43]. In contrast, barbiturate- and neurosteroid-mediated sedation was unchanged, confirming specificity for BZD-mediated effects (rather than a generalized resistance to sedation or sleep disruption). The amnestic and anticonvulsant activities of diazepam were also compromised, suggesting that in addition to sedation, the circuits utilizing the α1 subtype mediate other BZD effects (consistent with the mild amnestic effects of next-generation hypnotics). Diazepam retained anxiolytic, muscle relaxant, and ethanol-potentiation effects, suggesting that these are mediated via the other subtypes, namely α2, α3, and/or α5. The involvement of α1 in sedation but not anxiolysis was confirmed by subsequent studies utilizing the knock-in strategy as well as a BZD-site ligand (L-838417) that is selective for α2, α3, and α5 subtypes [44–46]. Diazepam had no effect on behavioral or electroencephalogram (EEG) measurements of sleep in the α1 knock-in mice [47], which is further confirmation that the α1 subtype is critical for the hypnotic effects of BZDs. Additional experimental subtype-selective BZD-site drugs (ocinaplon [48]; TPA023 [49]) have provided further support for the α1 subtype in mediating sedation but not anxiolysis.

The α1 subtype is usually assembled with β and γ subunits, and comprises the majority of $GABA_A$ receptor complexes in the brain. This α1βγ configuration has widespread expression, most notably in the cortex, sub-cortical gray matter including the thalamic relay system, brainstem nuclei, and various interneuron populations (inhibitory neurons interspersed in various circuits) [6]. It remains uncertain which among these regions is most important for the sedation resulting from BZDs interacting with receptors containing the α1 subtype.

α2 and α3 subtypes are linked to BZD-mediated anxiolysis

The studies described above, which linked the α1 subtype with sedation but not anxiolysis, also suggested that the remaining subtypes (α2, α3, and/or α5) mediated the anxiolytic, but not sedative, effect of BZDs. To investigate these possibilities, knock-in experiments were undertaken to target these subtypes and render them BZD-insensitive. α2 subtype knock-in mice demonstrated no anxiolytic effect in response to BZDs, while the anxiolytic effect of barbiturates or ethanol were unaltered [50–52], again confirming that the impact of the mutation was specific for BZD-mediated effects rather than a generalized hyper-anxious state. The importance of understanding the pathways mediating anxiolytic effects is highlighted by the potential for anxiety to cause or exacerbate insomnia symptoms.

In contrast to the results with the α2 subtype knock-in, where the anxiolytic effect of BZDs was abolished, the anxiolytic effect of diazepam was intact in α3 knock-in mice [50,51], suggesting that the α2, but not α3, subtype was the target for BZD-mediated anxiolytic effect. The α3 subtype is expressed in the thalamic reticular nucleus, an area critical for shaping thalamo-cortical network activity, and it therefore was expected that a BZD-resistant α3 subtype might compromise the effects of BZDs on sleep EEG. However, the diazepam-mediated decrease in sleep latency and augmentation of high frequency non-rapid-eye movement (NREM) EEG power were identical in wild-type mice and those harboring the α3 mutation [53]. This may be consistent with the abovementioned connection of sedation and sleep effects specifically with the α1 subtype. Interestingly, despite the exclusion of the α2 subtype in mediating sedative effects, the α2 subtype knock-in abolished diazepam-mediated effects on both REM and NREM EEG activity [54].

In contrast to the knock-in studies linking only the α2 subtype with anxiolytic effects, experiments utilizing selective pharmacological agents have, in addition, suggested a role for the α3 subtype in anxiety. An α3-selective agonist (TP003) was found to be anxiolytic [55], while an α3-selective inverse agonist (α3IA) was anxiogenic [56]. These apparent discrepancies may be related to different animal models of anxiety (many of which depend on locomotion) [57,58], or possibly, to different *in vivo* actions of these drugs, whose subtype-selectivity is necessarily defined using *in vitro* systems that facilitate manipulation of $GABA_A$ receptor subunit/subtype composition.

The α2 subtype is present in a minority of brain $GABA_A$ receptors, and usually co-assembles with β and γ subunits. α2 is expressed in the cortex, amygdala, hypothalamus, and brainstem, and it has been proposed in the studies discussed above that receptors located in the amygdala are the most likely targets for the anxiolytic effects of BZDs, given that the amygdala is known to be involved in processing fear and emotion. Like α2, the α3 subtype contributes a small portion of brain $GABA_A$ receptors, and is expressed in the cortex and, more notably, in the thalamic reticular nucleus, brainstem sleep-related nuclei (such as locus ceruleus and raphe), and in the basal forebrain [6]. Again, it is presently difficult to determine the relative importance of these regions in mediating the anxiolytic effects of BZDs.

α5 subtype is linked to tolerance and cognitive performance

Using mice possessing knock-in mutations in the α1, α2, α3, and α5 subtypes, tolerance to the sedating effects of diazepam (but not the sedation itself) was shown to depend on the α5 subtype [45]. The α1 subtype was again confirmed to be resistant to diazepam-mediated sedation. Interestingly, tolerance was associated with a reduction of hippocampal

α5 subtype expression in these animals. The observation that tolerance required BZD interaction with α5 subtype, which would then be downregulated to manifest tolerance clinically, suggests not only a specific molecular mechanism but also a potential target for intervention – preventing BZD interaction with the α5 subtype.

There is also growing evidence linking the α5 subtype with cognitive performance in animals. Enhanced learning in hippocampal-dependent (but not other) tasks was observed in mice lacking the α5 gene [59], which is mainly expressed in the hippocampus – an extensively studied structure in animal learning and memory. To complement the genetic manipulations, an α5 subtype selective inverse agonist at the BZD site increased hippocampal long-term potentiation (an *in vitro* model of synaptic plasticity), and enhanced hippocampal-dependent cognitive performance in rats [60]. Furthermore, this intervention did not induce epileptiform activity, a risk for any agent that inhibits $GABA_A$ receptor function, especially in the seizure-prone circuits of the hippocampus.

BZD adverse effects: tolerance, abuse, and interaction with ethanol

Despite the widespread clinical utility of BZDs in sleep disorders and anxiety, it is worth noting several limitations of this therapeutic class. For example, when used for insomnia, BZDs may not reproduce physiological sleep; rather, they tend to increase NREM at the expense of REM sleep. In addition, several side effects raise concerns regarding their routine or long-term use, including tolerance and withdrawal, abuse, and interaction with alcohol [61–63]. Alcohol induces behavioral effects similar to those seen with BZDs and is known to enhance $GABA_A$ receptor function by multiple mechanisms [64]. The sustained long-term efficacy of eszopiclone and zolpidem in humans emphasizes the practical importance of understanding the pharmacological mechanisms of insomnia therapeutics.

Again, knock-in studies and subtype-selective drugs are beginning to offer new mechanistic insights into some of these issues. In an animal model of physical dependence, withdrawal seizures were absent in the subtype-selective BZDs, and occurred less with partial BZD agonists (which bind at all α subtypes, but have lower efficacy) compared with their frequent occurrence with traditional BZDs [65], although these experimental paradigms may not reflect typical therapeutic conditions. Similarly, neither tolerance nor dependence was seen with a new compound that has preferential activity at α2 and α3 subtypes [66]. The α1 subtype has been implicated in the abuse potential of BZD in a primate model employing subtype-selective compounds [46]. The potentiating effects of alcohol on BZD-mediated sedation, a clinical complication of co-ingestion, was explored with α1, α2, α3, and α5 knock-in mice. The results implicated the α2 subtype in this synergy [51].

Several other recent studies using experimental BZD site ligands have shown anxiolytic and/or sedative effects without tolerance or sedation, but their molecular selectivity remains to be explored [67,68]. Tracazolate is an experimental anxiolytic with a reduced side-effect profile that was recently shown to preferentially act on αβδ receptors [69], which is a reminder of the potential utility of targeting an entirely different type of inhibition (tonic) mediated by a distinct molecular class of $GABA_A$ receptors (discussed in the next section). The preference for αβδ receptors, together with evidence against its interaction with the BZD site [69], is interesting since it is a pyrazolopyridine compound like zaleplon.

Although these studies are beginning to elucidate the potential molecular mechanisms governing clinical BZD action, there is much overlap between the α subtypes involved regarding the therapeutic and adverse effects. It remains to be seen whether future subtype-selective agents, perhaps targeting non-α subtypes, or subtype-specific antagonists [70] used in combination with existing drugs (e.g. an agent that blocks α5-mediated BZD tolerance) will allow more precise therapeutic options for insomnia.

Modulation of tonic inhibition: neurosteroids and gaboxadol

In parallel to the recent advances in subtype selective BZD pharmacology outlined above, the impact of tonic inhibition on network activity has sparked increased interest in extrasynaptic $GABA_A$ receptors as a target for insomnia treatment. As αβδ receptors are exclusively extrasynaptic, where they mediate tonic inhibition, the pharmacology specified by the δ subunit has been the focus of much attention. Although the precise functions of tonic inhibition remain uncertain, such signaling expands the temporal (seconds to minutes) and spatial (circuit level) influence beyond that available via synaptic communication, which occurs between individual neurons in milliseconds. It is possible that this is relevant to more global processing of mood, anxiety, sleep, or arousal state. Two modulators that target tonic inhibition mediated by αβδ receptors have emerged as potential treatment for insomnia: neurosteroids and gaboxadol.

Gaboxadol (THIP; 4,5,6,7-tetrahydroisoxazolo [5,4-c] pyridin-3-ol) is a GABA analogue that was recently discovered to have selectivity for αβδ receptors [12,71]. Although it can also activate αβγ receptors, its potency for αβδ receptors is much higher, and it is more efficacious than GABA *in vitro*, inducing a current that is greater than that mediated by GABA. In mice lacking the α4 subtype, which normally assembles with δ in the thalamus, tonic inhibition and the hypnotic effects of

gaboxadol were abolished. This suggested both an anatomical and molecular substrate for the hypnotic effect of gaboxadol: thalamic tonic inhibition [72]. $\alpha4\beta\delta$ receptors mediate a tonic current in the thalamus (but not in the thalamic-reticular nucleus), which is selectively modulated by gaboxadol but is BZD-resistant [14,73]. This suggests an alternative pathway to BZDs (even those that are subtype selective), thus broadening the potential therapeutic options for insomnia. In rodents and humans, gaboxadol increased NREM sleep and sleep efficiency without decreasing REM sleep; this is in contrast to BZDs, which decrease REM sleep [74–78]. Based on these studies, it was suggested that gaboxadol may mimic the effect of increased sleep pressure caused by sleep deprivation. Therefore, it is interesting to consider that sleep deprivation may cause an increase in endogenous factors that interact with $\alpha\beta\delta$ receptors, mediating tonic inhibition.

Neurosteroids are a class of endogenous neuromodulators that are known to interact with $GABA_A$ receptors [15] and other ion channels. In contrast to the traditional steroid mechanisms involving altered gene expression, neurosteroids can also reversibly and directly modulate $GABA_A$ receptor function. Mice lacking the δ subunit (knock-outs in which the entire gene has been deleted) were resistant to the hypnotic and anxiolytic effects of neurosteroids, but neither baseline anxiety nor sleep modulation by other agents (etomidate, pentobarbital, midazolam, propofol, or ketamine) was affected [11]. This seminal work was followed by *in vitro* work confirming $\alpha\beta\delta$ receptors as an important target for neurosteroids. Although neurosteroids enhance all known $GABA_A$ receptor configurations, they are similar to gaboxadol in that they favor $\alpha\beta\delta$ receptors, based on data showing increased potency and efficacy *in vitro* [12,72]. These two agents therefore exhibit functional selectivity for $\alpha\beta\delta$ receptors based on subunit-dependent potency and efficacy. Neurosteroids selectively augment $GABA_A$ responses under conditions of low efficacy, such as extrasynaptic $\alpha\beta\delta$ receptors activated by GABA or other endogenous low efficacy agonists (e.g. taurine) [79].

The potential clinical relevance of neurosteroid modulation is suggested by their hypnotic, anxiolytic, and anticonvulsant properties in animal and human studies, and also by the dependence of their synthesis on stress and menstrual cycling [15,17,80]. Similar to the agents discussed above, through targeting a subset of $GABA_A$ receptor inhibition, in this case extrasynaptic $\alpha\beta\delta$ receptors mediating tonic inhibition, neurosteroids or their analogues show exciting promise as agents for the treatment of insomnia.

Endozepines and endogenous somnogens

The concept of endogenous BZDs, or "endozepines", remains a subject of much discussion. The recently described clinical syndrome of recurrent spells of stupor, which could be reversed by the BZD antagonist flumazenil, suggested an etiology of dysregulation, and therefore the existence of, endozepines. This was recently reviewed, along with the subsequent discovery of (covertly administered) serum lorazepam in several of these patients using more accurate toxicity screens [81]. Although a $\gamma2$ subunit mutation associated with human epilepsy was reported to abolish BZD activity, supporting the possibility of the existence of endozepines, the mutant was subsequently shown to reduce surface expression [82,83], providing an alternative pathophysiological explanation to that of blocked endozepine activity. In a human study testing the hypothesis that endogenous BZD activity exacerbated obstructive sleep apnea, there was no effect of the BZD antagonist flumazenil on apnea measurements [84]. Finally, although the general lack of obvious behavioral effect in the BZD-resistant knock-in animals described above argues against a prominent role of endozepines, the $\alpha2$ knock-in mouse did exhibit baseline behavioral excitability [52].

Oleamide is an endogenous somnogen that is also elevated in the setting of hepatic encephalopathy [85]. This fatty acid is known to augment $GABA_A$ receptor activity, and is also implicated in serotonin and cannabinoid systems [86]. The hypnotic effect of oleamide was blocked in mice lacking the $\beta3$ subtype [87], although sleep architecture was not affected by the knock-out of this subunit. It is not known whether oleamide targets synaptic or tonic $GABA_A$ receptors. The $\beta3$ knock-out mice exhibit a high neonatal mortality rate and the phenotype of survivors resemble human Angelman's syndrome, which is characterized by features including mental retardation, seizures (especially related to sleep), and sleep disturbances [88]. These mice also demonstrate thalamic hypersynchrony that is attributable to the loss of $GABA_A$ receptors within the thalamic-reticular system [89]. Additionally, delta EEG activity was altered, and although the BZD-mediated increase in NREM sleep was preserved, it was not accompanied by the typical commensurate decrease in REM sleep [90].

Conclusion

Insomnia is a common problem but only prompts medical attention in a minority of cases. Despite this, the market for prescription insomnia treatment, mainly next-generation BZD-site agonists, is enormous. The significant clinical advantages of these newer hypnotics over traditional BZDs are due, in large part, to increased subtype selectivity at the $GABA_A$ receptor complex, although pharmacokinetic differences contribute to their therapeutic utility [91]. Nevertheless, we have only just begun to take advantage of the enormous body of information available from *in vitro*

and animal studies of $GABA_A$ receptor function over recent decades. As the details of $GABA_A$ receptor-mediated signaling are elucidated, and subtype-specific pharmacology allows more precise targeting of neural circuits for clinical benefit, the basic science of $GABA_A$ receptor function shows increasing promise to provide a rich pipeline of potential new agents for the treatment of insomnia and other disorders.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Christopher L Drake, Andrew Krystal, and Pedram Navab.

INSOMNIA

Interhemispheric EEG asymmetry in patients with insomnia during nocturnal sleep

Kovrov GV, Posokhov SI, Strygin KN.
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The authors of this study investigated electroencephalography (EEG) asymmetry in patients with insomnia. Although these subjects did not display a consistent asymmetry, hemispheric dominance was related to the EEG power spectra of the right hemisphere.

There are few data available on hemispheric electroencephalography (EEG) asymmetry in patients with insomnia. Furthermore, the specific determinants of sleep-related asymmetry and the roles played by each hemisphere are unknown. The authors of this study examined 10 individuals with "neurotic" insomnia. The mean age of the subjects was 39.8 years and the mean duration of insomnia was 4.3 years. The gender distribution was equal. Polysomnographic (PSG) recordings were obtained using two EEG leads (C3 and C4) and other standard PSG channels. Sleep was scored using standard criteria, and EEG spectra were calculated using the fast Fourier transform algorithm. Standard EEG frequency band power was calculated based on segments of data with stable 3-min periods of sleep.

The hemispheric dominance of the EEG spectra varied throughout the night for each subject, with no consistent hemispheric dominance across subjects. The authors found that hemispheric dominance was consistent for all frequency bands, such that when hemispheric dominance occurred for one specific frequency the same hemisphere showed dominance for all other frequency bands assessed. Wakefulness asymmetry was similar to that of stage 1 sleep. In addition, stage 2 and delta sleep showed similar asymmetry in the EEG power spectra. For sigma power during wake and stage 1 sleep, the direction of hemispheric asymmetry depended on right hemisphere power. Specifically, right hemisphere power predominance occurred in conjunction with increased power in the right hemisphere, and left hemisphere power predominance occurred with decreased activity of the right hemisphere. The absolute power was relatively unchanged when looking at activity of the left hemisphere.

These data indicate that hemispheric asymmetry is a dynamic parameter that frequently shifts throughout the sleep period in individuals with chronic insomnia. Future studies may benefit from comparisons with normal sleeping individuals.

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Insomnia, trouble sleeping, and complementary and alternative medicine: analysis of the 2002 National Health Interview survey data

Pearson NJ, Johnson LL, Nahin RL.
Arch Intern Med 2006;**166**:1775–82.

The authors of the current study examined the prevalence of trouble in sleeping, common chronic health conditions, and the use of complementary and alternative medicine (CAM), using the 2002 National Health Interview Survey. The results showed a positive association between reported insomnia and five medical conditions, while 4.5% of patients used some form of CAM therapy as treatment.

The authors of this study used the National Health Interview survey data to analyze the prevalence of difficulty sleeping and complementary and alternative medicine (CAM) use. Five sociodemographic variables associated with CAM and five comorbidities commonly associated with trouble in sleeping were also analyzed. Results showed demographic data similar to that found in previous studies. They also indicated the odds of individuals who report regular difficulty sleeping were significantly higher in those with hypertension, congestive heart failure, anxiety or depression, or a BMI ≥30 kg/m^2. The authors found that 4.5% of individuals who reported difficulty in

sleeping used some type of CAM to treat their condition, most commonly biologically based therapies or mind–body therapies.

This study is interesting in that it provides researchers with a method of investigating the use of alternative methods of treatment that may not otherwise be reported. Evidence presented in this study indicate that individuals who are younger and are educated to a higher level use CAM to treat their conditions. There are useful tools available for individuals who wish to use CAM; specifically, government-provided internet sites often refer people to talk with their primary care physicians prior to and during any additional therapies they are using to treat their condition. The authors of this study showed that 60% of individuals reported telling their primary care physicians about their use of CAM, which is somewhat higher than that shown in previous studies.

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Stress-related sleep disturbance and polysomnographic response to caffeine

Drake CL, Jefferson C, Roehrs T et al.
Sleep Med 2006;**7**:567–72.

There is a widely held belief that certain individuals are more vulnerable to situational insomnia. The current study was performed to investigate the effect of a nighttime low–moderate dose of caffeine in individuals previously hypothesized to be vulnerable to developing insomnia. Results showed that while there was no difference in sleep in the control situation, individuals classed as being more vulnerable to stress-related sleep disturbance displayed a significantly longer latency to persistent sleep after receiving the caffeine dose.

The etiology of insomnia is still unknown; however, recent studies have investigated the susceptibility of subjects to sleep-related disturbances to determine whether a subgroup of individuals is more vulnerable to certain stressors.

The current study included 21 healthy individuals who did not suffer from insomnia and who were classified into two groups, depending on their vulnerability to stress-related sleep disturbances as determined by the Ford Insomnia Response to Stress Test (FIRST). This nine-item, self-report measure evaluates the potential likelihood of an individual experiencing a sleep disturbance following various stressful events/situations, and was designed to assess sleep-related reactivity. The groups had similar demographic characteristics.

Participants visited the sleep laboratory for two overnight visits, a week apart, and standard polysomnographic measurements such as total sleep time, sleep efficiency, sleep stage percentages, and latency to persistent sleep were recorded. Subjects were administered 3 mg/kg caffeine before bed-time on one of these nights while recordings from the alternative night were used as a control.

The results showed that the 3 mg/kg dose of caffeine produced prolonged sleep latency to persistent sleep. Importantly, the findings suggested that this effect was only in the vulnerable group, i.e. those with high FIRST scores. *Post hoc* t-tests showed that the high FIRST scores group responded to caffeine with an increased latency to sleep ($p<0.02$), while the low FIRST scores group did not ($p=0.46$).

The current data demonstrate that those individuals who are vulnerable to stress-induced sleep disturbance also show elevated sleep-related reactivity in terms of their response to the effects of a pharmacological challenge such as 3 mg/kg caffeine. This supports the same group's previous work suggesting that a subject's vulnerability to sleep disturbance may be mediated by their physiological reactivity to stimuli.

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Consequences of comorbid insomnia symptoms and sleep-related breathing disorder in elderly subjects

Gooneratne NS, Gehrman PR, Nkwuo JE et al.
Arch Intern Med 2006;**166**:1732–8.

The present study's design and objectives stemmed from the following questions: How prevalent is sleep-related breathing disorder (SRBD) in elderly patients diagnosed with insomnia? And what are the effects on daytime functioning when these disorders co-occur? In order to address these queries, a group of older adults underwent polysomnography and other objective/subjective assessments. Results showed that SRBD was relatively common in participants with insomnia, resulting in an additive effect on functional impairment.

Although most research studies have investigated the prevalence of insomnia in those diagnosed with a sleep-related breathing disorder (SRBD), most prominently obstructive sleep apnea (OSA), the authors of this study undertook an opposite approach and posed the inverse scenario; the prevalence of SRBD in older adults with insomnia. Furthermore, the authors broached the symptomatology of the two problems when they co-existed in this cohort, hypothesizing their relatively common co-occurrences and, as a result, a greater degree of severity with regard to daytime functioning.

A group of 200 adults (100 cases; 100 controls), aged ≥65 years, were categorized into four groups – those with

and without insomnia and those with and without SRBD – and underwent 2 nights of laboratory polysomnography, a multiple sleep latency test, and neurobehavioral testing, along with the completion of subjective questionnaires. Individuals were categorized as insomniacs if they reported symptoms consistent with that diagnosis, i.e. 3 nights of insomnia per week lasting ≥3 weeks, and excluded if psychiatric symptoms were present. SRBD was classed as an apnea/hypopnea index of ≥5 events/h, as confirmed by polysomnography.

Results revealed that although SRBD was less prevalent in those with insomnia than in those without, it was still relatively common. Furthermore, the co-occurrence of SRBD and insomnia led to greater functional impairments, as relayed by the Functional Outcomes of Sleepiness Questionnaire and Psychomotor Vigilance Tasks.

There are limitations in this study that should be addressed. Participants in the insomnia group did not meet formal criteria for this diagnosis and, as the authors themselves acknowledge, a diagnosis of SRBD by necessity excludes symptoms suggestive of other sleep disorders. Although the authors would like to offer validity for a relatively increased incidence of a SRBD in those with insomnia, this important question was never reasonably broached.

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Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial

Sivertsen B, Omvik S, Pallesen S et al.
JAMA 2006;**295**:2851–8.

The primary objective of this randomized, controlled trial was to gauge the short- and long-term efficacy of cognitive–behavioral therapy (CBT) compared with zopiclone treatment in older adults experiencing chronic primary insomnia. Sleep diaries and data from ambulatory polysomnographies were reviewed, and the results revealed CBT to be more efficacious than zopiclone in the management of insomnia in this subgroup of patients.

Although previous studies in younger adults suffering from chronic, primary insomnia have shown a greater improvement with cognitive–behavioral therapy (CBT) than with pharmacotherapy, this outcome had yet to be replicated in older adults. The current study investigated this comparison from the perspective of adults aged ≥55 years in a randomized, double-blind, placebo-controlled trial that assessed the efficacy of CBT compared with zopiclone, a hypnotic agent with a large market share in Europe.

Polysomnography (PSG) and sleep diaries were utilized at three assessment points (pre-treatment, 6 weeks, and 6 months) to compare the two treatment modalities. Participants fulfilled the criteria for chronic primary insomnia without harboring either a psychiatric or sleep diagnosis, specifically obstructive sleep apnea (OSA) or periodic limb movements in sleep. Forty-six participants were randomized to receive either CBT (n=18), zopiclone (n=16), or placebo (n=12). Ambulatory PSGs were performed at the assessment points, and sleep diaries were completed every morning for 2 weeks at these junctures. The participants undergoing CBT attended six weekly sessions, each lasting approximately 50 min, and those in the zopiclone arm received 7.5 mg/night.

Participants in the study had a mean age of 60.8 years, and did not differ significantly with regard to body mass index, duration of insomnia, and a variety of sleep measures. At 6-week follow-up, participants in the CBT group showed a significant improvement with regard to time spent awake during the night before treatment ($p<0.001$), whereas the zopiclone and placebo groups did not differ significantly from one another. Total sleep time was not significantly different among the various groups; however, slow wave sleep (SWS) improved significantly in the CBT group compared with both the zopiclone ($p=0.002$) and placebo ($p=0.03$) groups. Overall, follow-up at 6 months revealed significant improvements in total wake time, sleep efficiency, and SWS in the CBT group compared with the pharmacologically treated arm.

Based on this study, CBT had greater efficacy than zopiclone in this group of older adults suffering from chronic primary insomnia. However, as only zopiclone was compared with CBT, this limits the present conclusions from being extrapolated to other hypnotics that may prove more efficacious.

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Safety behaviors and dysfunctional beliefs about sleep: testing a cognitive model of the maintenance of insomnia

Woodley J, Smith S.
J Psychosom Res 2006;**60**:551–7.

The current study involved a model of insomnia in which pre-existing dysfunctional beliefs regarding sleep and insomnia severity are predictive of sleep-related safety behaviors. The authors investigated the relationship between insomnia severity, depression, and dysfunctional beliefs about sleep and sleep-related safety behaviors.

Many studies have suggested that individuals with insomnia are more likely to ruminate about their sleep when attempting

to sleep. Insomniac subjects have been shown to have poorer sleep hygiene practices and score higher on dysfunctional belief scales. Significant models exist in which individuals are exposed to an event that disrupts their sleep and subsequent maladaptive behaviors perpetuate this poor sleep. This maintains their insomnia long after the event has passed. Safety behaviors have traditionally been associated with anxiety disorders in which behaviors are learned; these include avoiding and escaping behaviors that are used in order to keep anxiety levels to a minimum.

The study sample was comprised of 40 psychology students (29 women), with a mean age of 19.9 years. Each subject undertook four questionnaires: the Sleep-Related Behaviors Questionnaire (SRBQ), Dysfunctional Beliefs about Sleep (DBAS) scale, Insomnia Severity Index (ISI), Depression, Anxiety, and Stress Scale (DASS-21), and the Pittsburgh Sleep Diary (PghSD). Participants were characterized according to:

- Categorization based on ISI guidelines.
- Mean sleep parameters for each ISI category, which were calculated based on PghSD data.
- DASS-21-assessed levels of depression, anxiety, and stress.

This sample included subjects with and without insomnia, based on ISI guidelines. Internal consistency of the SRBQ was similar to that found in a previous study (Cronbach's α coefficient 0.83) [1]. Multiple regression analysis showed a significant predictive relationship between DBAS score and depression and the use of sleep-related safety behaviors, whereas insomnia severity did not predict safety behaviors. The strongest correlations found in this study were between depression and SRBQ scores. Further analysis found no differences in insomnia severity in patients with depression compared with those with no depression ($p>0.05$). However, those with depression used significantly more sleep-related safety behaviors. Interestingly, insomnia severity did not show a significant relationship with safety behaviors.

When using cognitive behavioral treatments for insomnia it is crucial to identify safety behaviors in order to provide an appropriate and thorough treatment for insomnia. It is important to view these results from the perspective of the study group, which was comprised of young adults who demonstrated the early stages of insomnia.

1. Ree MJ, Harvey AG. Investigating safety behaviours in insomnia: the development of the sleep-related behaviours questionnaire (SRBQ). *Behav Change* 2004;**21**:26–36.

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Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia

Roth T, Seiden D, Sainati S et al.
Sleep Med 2006;**7**:312–8.

Ramelteon is an MT1 and MT2 melatonin receptor agonist that has been approved by the US Food and Drug Administration for the treatment of insomnia. Several papers document the efficacy of this agent in improving sleep onset in adults; however, there have been no published studies of the treatment of elderly insomnia patients. This 5-week placebo-controlled study performed in 829 chronic insomnia patients is the first assessment of ramelteon (4 and 8 mg/night) treatment in older adults (age ≥65 years). The 8 mg/night dosage was found to significantly improve sleep onset latency, as assessed via self-report throughout the 5 study weeks. There was no evidence of rebound insomnia and the medication was well-tolerated. These findings suggest the safety and efficacy of ramelteon (8 mg/night) for reducing sleep onset latency in older adults with chronic insomnia.

The MT1 and MT2 melatonin receptor agonist, ramelteon, is US Food and Drug Administration approved for the treatment of insomnia. Although the efficacy of this agent for improving sleep onset in adults has been documented, the only previous report of the treatment of elderly insomnia patients with ramelteon was a meeting presentation [1]. As the elderly tend to have slower elimination of medications and may be particularly vulnerable to adverse effects, specific studies are needed to determine the risk–benefit profile of insomnia agents in this group.

This placebo-controlled study is the first published assessment of ramelteon treatment for insomnia in older adults. The subjects, 829 chronic insomnia patients aged ≥65 years, were randomized to ramelteon 4 or 8 mg/night or placebo for 5 weeks. Sleep was assessed using self-report, collected via daily morning sleep diary completion.

The authors reported that the 8 mg dosage significantly reduced sleep onset latency compared with placebo in all of the key outcome assessments at weeks 1, 3, and 5. The 4 mg/night dosage improved sleep onset latency compared with placebo at weeks 1 and 5. There was no evidence of withdrawal or rebound insomnia following discontinuation after 5 weeks of nightly treatment and the medication was well-tolerated with no evidence of significant health risks. The most common adverse effects were dizziness (8 mg/night ramelteon 8.4%; placebo 6.6%), myalgia (8 mg/night ramelteon 5.8%; placebo 2.6%), and headache (8 mg/night ramelteon 5.8%; placebo 4.4%).

These findings suggest that ramelteon 8 mg/night is safe and efficacious for improving sleep onset latency in older adults with chronic insomnia.

1. Roth T, Seiden D, Weigand S et al. Phase III study to determine the efficacy of ramelteon in elderly patients with chronic insomnia [abstract]. Proceedings of new clinical drug evaluation unit. June 6–9, 2005, Boca Raton, Fl, USA.

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Altering misperception of sleep in insomnia: behavioral experiment versus verbal feedback

Tang NKY, Harvey AG.

Consult Clin Psychol 2006;**74**:767–76.

A number of studies suggest that insomnia patients often incorrectly report their quantity of sleep, a situation frequently referred to as "misperception" of sleep. This study is based on the premise that it is possible to alter these misperceptions, and that doing so will be therapeutic for insomnia patients. The study authors randomized 42 primary insomnia patients to one of two interventions: providing verbal feedback about their degree of "misperception", or enabling subjects to themselves assess their degree of misperception (behavioral experiment). Self-reported sleep was compared with estimates deriving from actigraphy. They found that the two interventions did not differ in their effects on self-report/actigraphy mismatch; however, those randomized to the behavioral experiment improved in a number of measures of insomnia to a significantly greater degree. These findings reveal a dissociation of therapeutic response and alteration of misperception, and indicate the possible therapeutic utility of behavioral experiment in insomnia patients.

A number of studies suggest that patients suffering insomnia report longer sleep onset latency and shorter total sleep time than is estimated with polysomnography (PSG). This has frequently been referred to as sleep "misperception". This is not a trivial issue in the field of insomnia; 40–50% of individuals who experience difficulty falling or staying asleep, and who suffer associated functional impairment, have no concordant evidence of prolonged sleep onset time or increased wake time on PSG.

The term "misperception" was used in earlier versions of the major diagnostic system for sleep disorders, The International Classification of Sleep Disorders; however, it was eliminated from the newest version. This seems justified on a number of grounds.

At a fundamental level, the term is problematic as it suggests that patients are making an error, while there is no substantive proof that this is the case. There is an implication that there is no real disorder, but that an individual with normal sleep is making a misattribution that their sleep is abnormal. Given that PSG is a superficial and in many ways crude tool to assay brain function, it is not surprising that recent evidence of the so-called "misperception" of sleep appears to reflect alterations in neurophysiology that are not detectable with standard PSG methodology. However, the presence of subgroups of patients with different associated physiological findings raises important questions. It is not clear whether the physiological and phenomenological differences are important in terms of differences in pathophysiology, treatment, or longitudinal course.

The clinical relevance of the "misperception" phenomenon is the subject of this study by Tang and Harvey. They sought to carry out interventions to decrease the PSG/self-report mismatch and to determine if decreasing the mismatch would be therapeutic. A total of 42 primary insomnia patients were randomized to one of two interventions:

- Patients received verbal feedback about their degree of "misperception".
- Patients were shown their actigraphy recordings, and the "misperception" between these recordings and their sleep diaries was highlighted (behavioral experiment).

The authors compared self-reported sleep with estimates derived from actigraphy. While actigraphy has the advantages of ease-of-use and lower cost, it is likely to provide over-estimates of the degree of "misperception" compared with polysomnography, which should be considered when interpreting the results of this study. As the authors note, this method may overestimate the mismatch in insomnia patients in particular.

The results showed the two interventions did not differ in their effects on self-report/actigraphy mismatch; however, those randomized to the behavioral experiment showed a significantly greater degree of improvement in a number of measures of insomnia. These findings do not provide evidence that the PSG/self-report mismatch might be a uniquely important outcome measure or therapy target in the "misperception" subgroup. Instead, they suggest a dissociation of therapeutic response and alteration of "misperception" and indicate the possible therapeutic utility of behavioral experiments in insomnia patients.

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SLEEP-DISORDERED BREATHING

A double-blind, placebo-controlled, crossover study of sildenafil in obstructive sleep apnea

Roizenblatt S, Guilleminault C, Poyares D et al.
Arch Intern Med 2006;**166**:1763–7.

Sildenafil is a medication used to treat erectile dysfunction. In this placebo-controlled study, the effects of a single 50 mg dose of sildenafil on obstructive sleep apnea (OSA) were examined. As erectile dysfunction is frequently a pathophysiological consequence of OSA, it is likely that many individuals with undiagnosed and untreated OSA will receive sildenafil. The finding that sildenafil significantly worsened several indices of OSA suggests it should be used with caution in this patient population, and highlights the need for careful screening of individuals with erectile dysfunction to ensure they do not suffer OSA/hypopnea syndrome prior to initiation of sildenafil therapy. Furthermore, the results support the potential importance of nitric oxide-related mechanisms in OSA and the possible therapeutic utility of inhibitors of this system.

Sildenafil, a drug used to treat erectile dysfunction, relaxes smooth muscle and induces vasodilation by prolonging the action of cyclic monophosphate and nitric oxide by inhibiting phosphodiesterase 5. Phosphodiesterase 5 is present in many tissues in the body and its inhibition in patients treated with sildenafil leads to smooth muscle relaxation and vasodilation in areas other than the sinus of the corpus cavernosum of the penis. A number of these areas, including the mucosa of the nose, the tracheobronchial muscles, and the pulmonary vasculature, are involved in the pathophysiology of obstructive sleep apnea (OSA).

Based on the hypothesis that the smooth muscle relaxation and vasodilation in these structures caused by sildenafil would worsen OSA, the authors of this study examined the effects of a 50 mg dose of sildenafil compared with placebo on disorder severity in 14 men with OSA. This study is of great clinical importance as erectile dysfunction is often a pathophysiological consequence of OSA, and therefore, it is likely that many individuals with undiagnosed OSA will receive sildenafil.

The results confirmed the authors' hypothesis. Sildenafil was found to worsen a number of key indices of OSA severity including the apnea–hypopnea index, the oxygen desaturation index, and mean arterial oxygen saturation. It should therefore be used with caution in this patient population. The findings also argue for careful screening of individuals with erectile dysfunction to ensure that they do not have untreated OSA/hypopnea syndrome prior to the initiation of sildenafil therapy. The potential role of mechanisms related to nitric oxide in OSA is also highlighted, along with the possibility of therapeutic inhibition of this system.

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Obstructive sleep apnoea among HIV patients

Lo Re V 3rd, Schutte-Rodin S, Kostman JR.
Int J STD AIDS 2006;**17**:614–20.

The present study describes a progression of weight gain and lipodystrophy in patients receiving highly active antiretroviral therapy (HAART), which can consequentially lead to sleep disturbances, particularly obstructive sleep apnea (OSA). The medical records of HIV-infected individuals who were diagnosed with OSA were retrospectively analyzed with regard to clinical symptomatology, physical measurements, and polysomnographic evaluation. Of the 12 subjects included in this study, eleven had a body mass index in either the overweight or obese range, lipodystrophy was documented in seven, and nine subjects were receiving HAART at the time of polysomnography.

The authors of the current study aimed to delineate a trend for an increase in weight gain and changes in the distribution of fat (termed lipodystrophy) in HIV-infected patients receiving highly active antiretroviral therapy (HAART). They surmise that these changes may lead to sleep disturbances, particularly obstructive sleep apnea (OSA), as the deposition of fat in susceptible areas can obstruct the airway passage. Twelve patients were identified through retrospective review of the medical records of HIV-infected individuals who were diagnosed with OSA using polysomnography in a 2-year observation period. The demographic, clinical, laboratory, and polysomnographic data of these subjects were collected and analyzed to test the authors' hypothesis.

Subjects had a median age of 47 years and 92% were male. Three patients had a body mass index (BMI) in the overweight range, eight were classed as obese, and lipodystrophy was documented in seven of the subjects' medical records. Nine patients were receiving HAART at the time of polysomnography. Clinical symptomatologies included snoring, fatigue, and excessive daytime sleepiness. Polysomnographic data yielded an average apnea/hypopnea index (AHI) of 14.4 events/h, median oxygen desaturation of 88%, and a periodic limb movement index of >5/h in five of the 12 subjects.

The present study highlights the need to be aware of potential OSA in patients receiving HAART. However, other factors, such as craniofacial abnormalities, were unaccounted for and may also be significant in an individual's risk for OSA. Furthermore, it is unclear as to what degree HAART predisposes to weight gain and lipodystrophy, as other factors associated with HIV infection in general, or the patient's metabolism, may be contributory.

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Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults

Roth T, White D, Schmidt-Nowara W et al.
Clin Ther 2006;**28**:689–706.

The effects of armodafinil in obstructive sleep apnea patients with residual sleepiness were evaluated in this study. Following 12-weeks of treatment, patients were objectively more alert and showed clinical improvement in subjective measures of sleepiness and fatigue.

Untreated obstructive sleep apnea (OSA) is associated with excessive sleepiness, cognitive impairment, and reduced performance. The standard treatment for OSA is nasal continuous positive airway pressure (nCPAP); however, despite appropriate compliance with nCPAP treatment, many patients with OSA continue to experience residual sleepiness. This study was undertaken to determine the effects of armodafinil on measures of residual sleepiness in nCPAP-compliant OSA patients with residual daytime sleepiness.

A total of 392 patients received at least one dose of study drug or placebo (armodafinil 150 mg/day n=131; 250 mg/day n=131; placebo n=130). Patients were required to meet compliance criteria of ≥4 h of nCPAP use per night on 70% of nights during a 2-week screening period. Patients were also required to have an Epworth Sleepiness Scale (ESS) score of ≥10 and an apnea–hypopnea index of ≤10. Individuals with medical or psychiatric conditions were excluded. Patients were instructed to take the study drug prior to 8 AM daily in a fasted state. The primary endpoint was mean latency on the maintenance of wakefulness test (MWT) change from baseline to final visit. A 30-min MWT was performed with a total of six assessments throughout the day. Results of the first four (9 AM, 11 AM, 1 PM, and 3 PM) and last three (3 PM, 5 PM, and 7 PM) MWT assessments were averaged separately to determine earlier and later effects. Additional measures of efficacy were also assessed including the ESS, the Brief Fatigue inventory (BFI), and Cognitive Drug Research (CDR) battery at 0, 4, 8, and 12 weeks.

Results showed that both active treatment groups had significantly reduced sleepiness on the MWT compared with the placebo group at week 12 ($p<0.001$). Similar findings were obtained using the clinical global impression of change, ESS scores, and BFI ($p<0.05$ for both active groups versus placebo). Results using the CDR battery of assessments were less consistent. An investigation of drug tolerability showed that the most frequently reported adverse event was headache, which had a higher incidence rate in the combined active treatment groups compared with placebo (17.6% vs. 8.5%; $p<0.05$). Other adverse events associated with armodafinil included insomnia and dry mouth.

These findings support the use of armodafinil for the treatment of residual sleepiness in individuals with OSA who are nCPAP adherent. Reductions in sleepiness occurred early in treatment and were maintained throughout the 12-week study period.

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A comparison of the long-term outcome and effects of surgery or continuous positive airway pressure on patients with obstructive sleep apnea syndrome

Lin SW, Chen NH, Li HY et al.
Laryngoscope 2006;**116**:1012–6.

Despite high prevalence and morbidity, effective and tolerable long-term therapies for obstructive sleep apnea (OSA) remain a challenge. In this study, the long-term outcome of 84 patients with OSA who had been treated with continuous positive airway pressure (CPAP) was compared with that of 55 OSA patients who underwent a new treatment – extended uvulopalatoplasty surgical therapy. The authors report similar improvements with the two treatments, although the surgical procedure improved snoring and the Epworth sleepiness scale scores to a greater degree. However, a major limiting factor in the utility of this study is the non-random assignation of subjects to the two therapies.

Obstructive sleep apnea (OSA) is a highly prevalent disorder associated with significant morbidity; however, the development of treatments with long-term effectiveness and tolerability remains a challenge. This study explores the use

of a new surgical procedure for the treatment of OSA, extended uvulopalatoplasty (EUPF), and compares the long-term outcome of patients treated with this procedure with those receiving the most common therapy for this condition, continuous positive airway pressure (CPAP).

This investigation included 84 patients with OSA who had been treated with CPAP and 55 OSA patients who had undergone EUPF surgery. Improvements were comparable in the two treatments; however, a greater improvement in snoring and in scores on the Epworth sleepiness scale was seen with EUPF.

A major factor limiting the utility of this study is the non-random assignment of the subjects to the therapies. Patients in the CPAP group were significantly older, more obese, and had significantly more severe OSA in terms of respiratory disturbance index. As a result, it is impossible to draw substantive conclusions about the relative effectiveness of these two treatments, or whether there are individuals with OSA for whom one therapy might be preferred. Additional studies comparing EUPF and CPAP that employ random patient assignment are needed to evaluate the potential clinical utility of this new surgical treatment for OSA.

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Parallel changes in resting muscle sympathetic nerve activity and blood pressure in a hypertensive OSAS patient demonstrate treatment efficacy

Donadio V, Liguori R, Vetrugno R et al.
Clin Auton Res 2006;**16**:235–9.

The increased risk of hypertension observed with obstructive sleep apnea (OSA) is well established. While the mechanisms are incompletely understood, an increase in muscle sympathetic nerve activity (MSNA) is believed to be a contributing factor. This report is consistent with that hypothesis. It documents the treatment of OSA in an individual with continuous positive airway pressure (CPAP), who showed an improvement in hypertension in conjunction with a decrease in MSNA. MSNA did not decrease with uvulopalatopharyngoplasty surgical treatment, and a decrease in blood pressure was not observed. Despite the report being of only one case, it is of interest in terms of the application of MSNA methodology to the study of OSA and suggests the possibility that assessment of treatment outcome and pathological mechanisms should be individualized.

The adverse effects of obstructive sleep apnea (OSA) syndrome on cardiovascular function are well established. One of the most frequent clinically observed cardiovascular pathologies associated with OSA is hypertension. Despite the strength of this association, it is notable that effective treatment for the condition with continuous positive airway pressure (CPAP) therapy inconsistently lowers blood pressure.

The capacity to effectively address the hypertension associated with OSA is limited in that the mechanisms by which OSA causes hypertension are incompletely characterized. There are believed to be a number of mechanisms by which OSA predisposes affected individuals to hypertension and an increase in muscle sympathetic nerve activity (MSNA) is thought to play an important role. The evidence for this is provided by observations from a few studies where CPAP decreased MSNA in conjunction with lowering blood pressure. This case report of the treatment of an individual with OSA-associated hypertension with both CPAP and a common surgical intervention, uvulopalato-pharyngoplasty (UPPP), provides further evidence that MSNA may mediate hypertension in OSA.

The individual had been effectively treated with CPAP but, like many individuals with OSA, he was unable to tolerate sustained CPAP therapy and pursued UPPP. Systematic monitoring of blood pressure and assessment for MSNA via a micro-electrode inserted into the peroneal nerve were carried out with both forms of therapy. CPAP was found to be more effective at reducing nocturnal respiratory-related events and daytime sleepiness than UPPP in this individual. The most interesting observation was that only CPAP improved hypertension, and did so in association with a decrease in MSNA that was not observed with UPPP.

These findings add little to establishing MSNA as mediator of hypertension in individuals with OSA, in that it is a report of a single case and the contribution of other mechanisms to the improvement in hypertension in this patient cannot be ruled out. Nonetheless, it is of interest in terms of the application of MSNA methodology to the study of OSA and suggests the possibility of individualizing the assessment of treatment outcomes and pathological mechanisms.

Given the current hypothesis that hypertension is multi-factorial, it must be considered that some therapies, such as CPAP, are uniquely effective at decreasing MSNA, or that some individuals might have hypertension associated with OSA that is mediated by mechanisms other than MSNA. This may explain why hypertension improves inconsistently with what appears to be an effective therapy.

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RESTLESS LEGS SYNDROME

Efficacy and tolerability of ropinirole in patients with restless legs syndrome and a baseline IRLS total score ≥24 points – data from the ropinirole clinical trial programme

Giorgi L, Ritchie SY, Kirsch JM.
Curr Med Res Opin 2006;**22**:1867–77.

Through compilation of data from four, 12-week studies assessing the efficacy of the dopamine agonist ropinirole in the treatment of restless legs syndrome (RLS), the authors conclude that patients with primary RLS and a total baseline International Restless Legs Scale total score of ≥24 gain clinical benefits with this medication without significant adverse effects.

As a chronic neurological disorder affecting approximately 10% of the population, restless legs syndrome (RLS), symptomatically characterized as the "urge to move the legs", carries a significant burden with regard to a patient's quality of life, primarily signified by disturbed sleep. Although the clear etiology of the disorder remains unknown, it is recognized that, pathophysiologically at least, dopaminergic dysregulation is implicated. To this end, treatment of RLS is usually initiated with a dopamine agonist such as ropinirole, which unlike levodopa therapy, is not associated with augmentation or an earlier occurrence of symptoms.

The present article aims to further analyze *post hoc* data pooled from four 12-week, randomized, double-blind placebo-controlled studies of ropinirole for the treatment of RLS. Patients aged 18–79 years, with a diagnosis of primary RLS and meeting certain inclusion and exclusion criteria, were randomized to receive either ropinirole 0.25–4.0 mg/day (titrated as deemed necessary) or placebo, given once daily 1–3 h before bedtime. Of the four 12-week pivotal studies, three used the International Restless Legs Scale (IRLS), a subjective assessment of the impact of RLS on a patient's daily functioning (total score range 0–40, from benign to severe), to gauge efficacy endpoints. Other questionnaires utilized included the Medical Outcomes Study Sleep Scale, the Johns Hopkins RLS Quality of Life (RLSQoL) questionnaire, and the Short-Form Health Survey.

Further *post hoc* stratification of the four pivotal ropinirole trials identified 454 patients (ropinirole=219; placebo=235) with similar baseline characteristics and demographics, each endorsing an IRLS total score of ≥24. Results of this subgroup of patients revealed benefits of ropinirole not only with regard to symptomatology, but also improvements in global symptoms and sleep measures. Ropinirole was, in general, well tolerated in the study population, although a higher incidence of nausea in the ropinirole-treated group led to the withdrawal of eight patients.

In this study, the authors appear to replicate the results of the four pivotal ropinirole studies in establishing both the efficacy and safety of the agent in patients with RLS, albeit by further stratifying the study population. However, although they promulgate the benefits of ropinirole in patients with a baseline IRLS score of ≥24, the authors do not discuss the agent's efficacy in a population with less severe forms of RLS.

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POSITIVE AIRWAY PRESSURE THERAPY

Continuous positive airway pressure treatment. Good for obstructive sleep apnea syndrome, maybe not for hypertension?

Iellamo F, Montano N.
Chest 2006;**129**:1403–5.

This editorial describes and discusses issues regarding outcomes of previous studies of hypertension effects in conjunction with treatment of obstructive sleep apnea.

Obstructive sleep apnea (OSA) has long been associated with a high risk for cardiovascular disease, as evidenced by multiple studies. The authors of this editorial begin with a description of previous studies, in particular, one conducted by Marin et al. [1], which examined the effects of continuous positive airway pressure (CPAP) treatment of OSA patients on cardiovascular outcomes. The main findings of this study were that, over a 10-year follow-up period, patients with OSA without the use of CPAP had a significant increase in cardiovascular events compared with CPAP users and control subjects. The authors also explore the results of the study by Campos-Rodriguez et al. (reviewed on p.120) [2], which, in contrast to the study of Marin et al., demonstrated no significant changes regarding blood pressure in the two groups of patients with OSA who were being treated for hypertension.

The authors point out that the complex underlying mechanisms of hypertension combined with the progression of the disease state could account for the variation in results between these studies. This editorial highlights the need for further randomized, placebo-controlled trials in the OSA population with newly diagnosed hypertension, based on the results of the study by Campos-Rodriguez et al. It is

widely known that treating OSA with CPAP improves the overall neural cardiovascular regulation, which, in turn, improves arterial hypertension. It will be important to further investigate this relationship in order to fully understand the complex interactions between CPAP use and various other health issues.

1. Marin JM, Carrizo SJ, Vicente E et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;**365**:1046–53.
2. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J et al. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. *Chest* 2006;**129**:1459–67.

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Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial

Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J et al.
Chest 2006;**129**:1459–67.

The authors of the current study investigated the effects of continuous positive airway pressure (CPAP) use on ambulatory blood pressure in patients with obstructive sleep apnea syndrome who were receiving treatment for hypertension. After 4 weeks, CPAP use did not reduce blood pressure compared with the placebo group.

There is a vast number of published studies that have shown a positive relationship between the treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) and the reduction of blood pressure. However, conflicting data also exist. The authors of the current study examined the use of CPAP in individuals with OSA who were being treated for hypertension. A total of 68 individuals were divided into two groups in this parallel, randomized, placebo-controlled trial. Patients were either in the therapeutic CPAP or subtheraputic group. Those individuals in the subtheraputic group received a constant pressure of <2 cmH_2O, which was achieved by setting the CPAP device to the lowest pressure, similar to that of previous studies. Blood pressure was measured using a portable recorder with a cuff fitted on the patient's nondominant arm, which recorded blood pressure every 30 min; the 24-h mean blood pressure was then calculated.

Interestingly, after 4 weeks of treatment, only minor differences in blood pressure were found between study groups (–0.3±6.3 mmHg vs. –1.1±7.9 mmHg; p=0.65), even when controlling for compliance, number of antihypertensive medications, OSA severity, or desaturation index. This study highlights some interesting issues regarding the role of CPAP treatment in patients with hypertension. A compelling editorial by Iellamo and Montano discusses outcomes of the current study and issues including disease state and comorbidity in the hypertensive population [1].

1. Iellamo F, Montano N. Continuous positive airway pressure treatment. Good for obstructive sleep apnea syndrome, maybe not for hypertension? *Chest* 2006;**129**:1403–5.

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NARCOLEPSY

REM alpha rhythm: diagnostic for narcolepsy?

Dyken ME, Wenger EJ, Yamada T.
J Clin Neurophysiol 2006;**23**:254–7.

The perceived need for an unequivocal, universally accepted biomarker for narcolepsy is the basis for this case report by Dyken and co-workers. The subject was a 17-year-old boy with a classic presentation but negative family history for narcolepsy, despite being HLA-DR2/DQ1 positive. His multiple sleep latency test showed a mean sleep latency of 1.1 min and rapid eye movement (REM) onset in all naps. The unusual finding in this case was the electroencephalogram (EEG) pattern occurring during an event of sleep paralysis associated with hallucinations, which consisted of the simultaneous presence of an alpha rhythm that was reactive to eye closure and a REM sleep EEG pattern. The authors propose that this EEG pattern might be useful to aid in the diagnosis of narcolepsy.

Despite recent advances in understanding the pathophysiology of narcolepsy, some uncertainty remains about how to define diagnostic criteria for this disorder. One limitation is the absence of an unequivocal, universally accepted biomarker. It was the perceived need for such a biomarker that led Dyken and co-workers to report this case of a 17-year-old boy with a classic presentation for narcolepsy. He had a history of experiencing cataplexy, hypnogogic hallucinations, and sleep paralysis, as well as 2 years of excessive daytime sleepiness. His family history was negative for narcolepsy, although he was HLA-DR2/DQ1 positive. Multiple sleep latency testing revealed a mean sleep latency of 1.1 min and rapid eye movement (REM) onset in all naps.

The notable observation in this case was the electroencephalogram (EEG) pattern occurring during an event of sleep paralysis associated with hallucinations. This pattern, which had not previously been reported, consisted of the simultaneous presence of an alpha rhythm that was reactive to eye closure, typical of normal waking, and an REM sleep EEG pattern. As the simultaneous occurrence of these

patterns was believed to be unique to this circumstance, the authors propose that this EEG pattern might be useful to aid in the diagnosis of narcolepsy. While the utility of the pattern is likely to be limited by the capacity to reliably capture such events in the laboratory in individuals with narcolepsy, the finding is also of physiological interest. It suggests that during events where there is an intrusion of features of REM, as experienced in this case, enough pathways to the cortex are active to support an alpha rhythm. This observation adds to a growing literature that is eroding the traditional notion that waking and sleep are exclusive, all-or-none states.

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Plasma levels of tumor necrosis factor alpha and soluble tumor necrosis factor receptors in patients with narcolepsy

Himmerich H, Beitinger PA, Fulda S et al.
Arch Intern Med 2006;**166**:1739–43.

Tumor necrosis factor-α (TNF-α) and its soluble receptors play a role in mediating the immune response. There is also evidence that they may be involved in the processes underlying sleepiness and fatigue in pathological states, as well as in the normal regulation of sleep–wake function. The study authors therefore investigated whether alterations in the TNF-α system might occur in narcolepsy. They found that levels of TNF-α and its soluble receptor, TNF-R p75, were significantly elevated in 30 patients with narcolepsy compared with 120 sex- and age-matched controls, and 101 sex-, age-, and body mass index-matched controls. While of great interest, these findings are of uncertain significance. Do they point to an alteration of immune function in narcolepsy, perhaps involved in impaired hypocretin/orexin system function? Are the TNF-α system elevations causes or consequences of altered sleep–wake function in narcolepsy? Further studies are necessary to answer these questions.

Along with the role that tumor necrosis factor-α (TNF-α) and its soluble receptors play in mediating the immune response, evidence suggests their involvement in the processes underlying sleepiness and fatigue in pathological states and in the normal regulation of sleep–wake function. It is therefore possible that alterations in the TNF-α system might occur in narcolepsy.

Prior studies examining TNF-α in narcoleptics found conflicting results. One possible reason is that these investigations did not consistently control for factors that might affect TNF-α levels, including age, gender, and body mass index (BMI). In order to address this issue, the study authors measured TNF-α levels in 30 patients with narcolepsy, 120 sex- and aged-matched controls, and 101 sex-, age-, and BMI-matched controls. In addition, they examined the levels of TNF-α soluble receptors, which are involved in mediating the effects of TNF-α and therefore also of interest, but have not previously been examined in narcolepsy patients.

The results indicated that levels of TNF-α and one of its soluble receptors, TNF-R p75, were significantly elevated in the narcolepsy patients compared with the control subjects.

While of great interest, these findings are of uncertain significance. As the TNF-α system is involved not only in the immune system, but also in regulation of sleep–wake function, it is not clear whether they point to an immune or sleep–wake alteration or both. Furthermore, it is not clear if they reflect cause or consequence of altered sleep–wake function in narcolepsy. As this study does not provide any data that might aid in understanding the relationship between alterations in the TNF-α system and narcolepsy, additional work is necessary to resolve these uncertainties.

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SLEEP SCALES AND MEASURES

Laboratory versus portable sleep studies: a meta-analysis

Ghegan MD, Angelos PC, Stonebraker AC et al.
Laryngoscope 2006;**116**:859–64.

The aim of this meta-analysis was to compare the precision of ambulatory polysomnography with laboratory polysomnography in the diagnosis of obstructive sleep apnea (OSA). Various parameters were evaluated such as respiratory disturbance index (RDI), mean oxygen desaturation, sleep time, quality of the recordings, and cost of the studies. Although the ambulatory polysomnograms were more likely to underestimate the RDI and record a shorter sleep time, their lower costs, as the authors postulate, allow for effective screening for potential OSA.

Although laboratory polysomnography (PSG) remains the gold standard in diagnosing obstructive sleep apnea (OSA), its cost and limited availability do not often justify its use. Ambulatory PSG is therefore used as an alternative diagnostic tool due to its lower cost and greater availability, feasibility, and flexibility. However, these benefits are offset

by the propensity to produce invalid results due to its unattended nature and lack of ability to diagnose other sleep-related disorders. The authors of the present article conducted a meta-analysis of 18 studies that compared the respiratory disturbance index (RDI) score in two groups of patients who underwent either an ambulatory or laboratory PSG. Other parameters, such as mean oxygen desaturation, recorded sleep time, quality of the recordings, and cost, were also analyzed. Of the 18 studies, 14 compared the two methods of diagnosis whereas the remaining four were conducted solely in a laboratory setting.

Despite the fact that not all the studies compared the same parameters, certain trends were evident:

- Ambulatory studies yielded RDI values that were, on average, 10% lower than their counterparts.
- No significant differences in oxygen desaturation were seen.
- An average of 13% longer sleep times was observed in the laboratory settings.
- Poor recording was more likely to occur in the ambulatory studies.
- Ambulatory studies were significantly more cost-effective, at least in short-term analysis.

The authors of this article succinctly conclude that, at least as a screening tool, ambulatory PSG is viable, although it may be marred by poor recording and, hence, inadequate examinations.

Limitations of the study include not only publication bias, as the authors acknowledge, but also the lack of uniformity between the various parameters analyzed. Reproducibility of the various studies also remains problematic, as certain parameters could potentially be altered when repeated. Although a 10% disparity in RDI values may seem significant, it must be remembered that inter-rater reliability could also yield such results without an alteration in clinical decision making.

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Sleep Beliefs Scale (SBS) and circadian typology

Adan A, Fabbri M, Natale V et al.
J Sleep Res 2006;**15**:125–32.

The authors of this study examined sleep hygiene awareness and circadian typology using a revised version of the Sleep Hygiene Awareness Scale. This revised scale, known as the Sleep Beliefs Scale, demonstrates good psychometric properties.

The effective treatment of insomnia is essential in a clinical setting. Utilizing a simple scale to gain a better understanding of a patient's beliefs and attitudes towards sleep is important in keeping healthcare costs down, and for providing more accurate behavioral treatments for individuals who do not wish to take medication for the disorder. In a research setting, it is beneficial to have a simplified scale that is easy to administer. It is also vital that the scales function in a clear and concise manner.

Participants included 510 undergraduate psychology students (182 men and 328 women) aged 18–33 years from Spain (n=264) and Italy (n=246). Each subject completed questionnaires of circadian typology using the reduced Morningness–Eveningness Questionnaire (rMEQ), and sleep notions using the Sleep Beliefs Scale (SBS).

The SBS collects data on an individual's knowledge and beliefs of sleep behaviors, and not the actual behavior in sleep. The scale's measures include beliefs in relation to drug consumption (alcohol, caffeine, nicotine, sleep medication), diurnal behaviors (exercise and naps), and activities and thoughts prior to sleep (eating, studying, relaxing, worries). The SBS adds to the Sleep Hygiene Awareness Scale by including behaviors that affect sleep, for example, going to bed 2 h later than normal. Higher scores represent more accurate sleep beliefs.

The SBS mean score in the entire sample was 13.05 (standard deviation [SD] 3.46), showing a biased distribution towards correct beliefs. Men scored a mean of 12.52 (SD 3.62) while women scored a mean of 13.35 (SD 3.35). Total SBS scores correlated directly with rMEQ scores ($p<0.0001$), where "morning-types" showed a greater tendency towards correct beliefs and "evening-types" had the lowest scores. Significance was also found in a circadian typology by gender interaction ($p<0.01$). Internal consistency for the total sample, estimated using Cronbach's α coefficient, was 0.714, and there was a similar value for both gender groups and country sub-samples. For the circadian typology groups (with one item deleted), values ranged from 0.690–0.718. Factorial analysis found that the 20-item SBS could be separated into three factors, "sleep-incompatible behaviors", "sleep–wake cycle behaviors", and "thoughts and attitudes to sleep".

This scale provides an in-depth approach to the assessment of sleep hygiene. While the SBS needs to be validated with other standard measures of sleep hygiene practice and tested in a broader range of subjects, it is likely that it will prove a useful tool for research purposes and clinical practice.

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Brief and distinct empirical sleepiness and fatigue scales

Bailes S, Libman E, Baltzan M et al.
J Psychosom Res 2006;**60**:605–13.

The authors of the current study collected data on four previously validated and widely used scales in order to create two scales that measure fatigue and sleepiness as separate constructs. Results from the use of these two empirical scales (fatigue and sleepiness) suggest that each scale identifies the two symptoms uniquely.

In both clinical and research settings, there is a need for distinction between fatigue and sleepiness, which are often used interchangeably. The results of this study give both researchers and clinicians useful knowledge regarding the utilization of easily accessed tools, which may be helpful for better understanding of the symptoms of insomnia sufferers. The authors analyzed four well-known sleepiness and fatigue scales, and combined the assessments to create two scales that separate sleepiness and fatigue: the Empirical Sleepiness Scale and the Empirical Fatigue Scale.

Data for a total of 44 individuals were analyzed, 19 with chronic fatigue syndrome (CFS; mean age 44.7 years), 14 with narcolepsy (mean age 36.9 years), and 11 control subjects (mean age 40.6 years). All individuals with CFS were female. Polysomnography showed that several individuals from each group also had apnea–hypopnea syndrome or periodic limb movement disorder; these subjects were included in the analysis. The authors also included a validation sample of older individuals (mean age 64.8 years), all with daytime fatigue, sleepiness, or insomnia. Each subject completed the following: Multiple Sleep Latency Test (MSLT), handgrip fatigue measure, Stanford Sleepiness Scale (SSS), Epworth Sleepiness Scale (ESS), Chalder Fatigue Scale (CFM), and the Fatigue Severity Scale (FSS). All scales were adapted to measure both current and retrospective (past month) levels of fatigue and sleepiness.

The total scores on both sleepiness and fatigue scales were highly correlated, demonstrating the confounded measure of the two constructs. In order to identify factors that were not confounded, the authors assessed only the items that did not significantly correlate with any item on the opposite construct. A total of six Sleepiness and three Fatigue items were used to create the Empirical Sleepiness Scale (six items all taken from the ESS) and the Empirical Fatigue Scale (one item from FSS and two from the CFM). Cronbach's α scores ranged from 0.92–0.95 for the Empirical Sleepiness Scale and from 0.74–0.86 for the Empirical Fatigue Scale. Correlations between the two scales range from 0.06–0.33. These results suggest that both scales have good psychometric properties while the low correlation implies the scales are measuring two different constructs.

The results indicate that the sleepiness scale, which is very similar to previous scales, measures a different construct than the fatigue scale. The fatigue scale measures items from perceived poor physical and psychological functioning to physical tiredness.

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Physical examination: Mallampati score as an independent predictor of obstructive sleep apnea

Nuckton TJ, Glidden DV, Browner WS et al.
Sleep 2006;**29**:903–8.

Although the Mallampati score, a visually simplistic airway-classification system, is one of the many objective variables used to identify those at risk for obstructive sleep apnea (OSA), it has not been subjected to rigorous investigation after adjustment of its confounding variables. Following such adjustments, the present study reveals that the Mallampati score is a practical and useful method for assessing both the presence and severity of OSA in suspected patients.

Craniofacial measurements and descriptive airway terminologies are routinely used for objective determination of suspected obstructive sleep apnea (OSA); however, the former is too complex and the latter too nebulous. The Mallampati score (MS), a derivative of an airway classification system used for endotracheal intubation, has been incorporated as one of the many assessments for individuals at risk for OSA due to its visual simplicity and non-invasive nature. Although previous studies have confirmed an association between the MS and OSA, specific confounding variables, such as (among others) neck circumference and body mass index, were not assessed. The present study used multivariate analysis to account for these variables.

The adult participants suspected of OSA represented a convenience sample over a 6-month period. Subjects underwent routine pre-polysomnographic assessments, including a medical and sleep history, the Epworth Sleepiness Scale, and objective measurements such as neck circumference, body mass index, tonsil size, degree of overjet, and the MS. Subsequently, the 137 participants underwent either an inpatient or ambulatory polysomnography, resulting in a diagnosis of OSA (apnea–hypopnea index [AHI] of ≥5 events/h) in 58%. During multivariate analysis, the MS was identified as an independent risk factor for OSA, with a two-fold odds increase for every 1-point increment

in MS (graded as I–IV). In addition, this 1-point increment also increased the AHI by >5 events/h. Other variables independently associated with an increased risk of OSA included neck circumference, witnessed apneas, and hypertension.

As the authors themselves acknowledge, the MS may not be as robust in a setting where patients have a lower probability of an OSA diagnosis; which is in contrast to this study where subjects were referred to the sleep clinic on suspicion of OSA. In addition, there were no accounts of the craniofacial features of the participants, as these are also identifiable variables for OSA. Nevertheless, the present study underlines the usefulness of the MS, which, in its simplicity, is instrumentally cost-effective and could help in prioritizing patients for polysomnographies.

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MISCELLANEOUS

Objectively measured sleep characteristics among early-middle-aged adults: the CARDIA study

Lauderdale DS, Knutson KL, Yan LL et al.
Am J Epidemiol 2006;**164**:5–16.

The authors of the current study examined 669 participants who were a part of the larger ongoing CARDIA (Coronary Artery Risk Development in Young Adults) study. Data on various sleep parameters were collected using actigraphy and sleep logs over 3 days. Overall, the results showed a mean time in bed of 7.5 h, while the mean sleep duration was only 6.1 h.

Normative data on sleep parameters in the current literature are sparse. This study adds significantly to the literature in terms of the associations between sex, race, various sociodemographic data, and sleep variables. A total of 669 subjects who were enrolled in the CARDIA (Coronary Artery Risk Development in Young Adults) study were grouped by sex and race. Thereafter, various sociodemographic and sleep variables were analyzed. Home-based sleep data were collected by actigraphy and sleep logs over a 3-day period, while sociodemographic data were previously collected through CARDIA.

The results found that the average sleep duration for white women was 6.7 h, the highest of the four groups, and 5.1 h for black men (82 min less sleep per night). Education and income were only weakly associated with time in bed, with a higher income and higher education resulting in less time in bed. Similar to the results of previous studies, individuals with less income showed significantly longer latency to sleep. Analyses of lifestyle factors also produced results similar to previous studies, in which alcohol consumption was associated with a longer time in bed and a decrease in sleep efficiency. Smoking was associated with longer sleep latency, very likely due to the stimulating effects of nicotine, although the time between last cigarette smoked and bedtime was not evaluated. Smoking was also associated with a shorter total sleep time.

Epidemiological data are essential for understanding the sleep habits of the general population. While normal sleepers are often used as controls, little has been published about the general sleep habits of "normal" sleepers. Studies such as this are essential for sleep knowledge and should continue to be performed.

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8th World Congress on Sleep Apnea (WCSA 2006)

Montréal, QC, Canada, September 27–30, 2006

Nelly Huynh[1] and Christian Guilleminault[2]

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The 8th World Congress on Sleep Apnea was held on September 27–30, 2006 in Montreal, QC, Canada. This conference was an opportunity to celebrate both the 50th anniversary of the description of the Pickwickian Syndrome and the 25th anniversary of continuous positive airway pressure (CPAP). The presentations discussed the past, present, and future of sleep-disordered breathing (SDB) and its therapies. This report details what we believe were the key topics at this conference.

History of the Pickwickian Syndrome

The history of sleep apnea was the opening presentation at the conference and featured Professor Peretz Lavie (Technion-Israel Institute of Technology, Haifa, Israel) as an invited speaker. Sleep apnea was first referred to as "Pickwickian Syndrome" due to Charles Dickens' description of a sleepy, overweight character who snored, in his book "The Pickwick Papers" in 1837. However, the pattern of abnormal breathing during sleep in obese patients was reported much before, and in the 19th century Richard Caton gave a very good clinical description of this syndrome, even though he labeled the patients "narcoleptic". Gerardy and colleagues [1] were the first to monitor two Pickwickian patients during sleep, preceding the nap study of Drachman and Gumnit [2] and the work of Jung and Kuhlo [3], and Gastaut and colleagues [4]. The repetitive occurrence of apneic events was associated with a change in heart rate and daytime sleepiness.

The field of sleep apnea in sleep medicine research has grown rapidly, especially during the last two decades. Professor Lavie used the Web of Science database to search for articles containing "sleep", resulting in over 62 000 publications between 1965 and 2006. Among these, >22% are related to SDB. Furthermore, according to Professor Lavie's search, the most cited publication in sleep research is "The occurrence of SDB among middle-aged adults" by Young and colleagues [5], while the leading sleep apnea journals are *Sleep*, *Chest,* and *American Journal of Respiratory and Critical Care Medicine*. Nasal CPAP (nCPAP) therapy and blood pressure, inflammation and oxidative stress, pediatric sleep apnea, and insulin resistance are all promising fields for sleep apnea research.

nCPAP history

The first nCPAP device was designed in 1979 and tested in a dog model, and the arousal and ventilatory responses in airway obstruction during different sleep stages were observed. Similar responses to hypoxia and hypercapnia were later studied in humans, and in June 1980, Colin Sullivan's team (University of Sydney, NSW, Australia) completed the first full night's recording with nCPAP. This device consisted of a pair of clear plastic nasal prongs attached to two tubes. The first tube was wide bore and connected to a flow generator, and the second was constricted at the end to supply resistance. The nasal prongs were held in place with medical-grade rapidly curing elastomer. The upper airway obstruction reversed when the speed of the flow generator was increased, resulting in rebound rapid-eye movement (REM) sleep and short-wave sleep (SWS). After further testing, the first home-use nCPAP treatment was performed in February 1981, in a patient who still uses the device today.

nCPAP reverses upper airway obstruction, and the development of this therapy has allowed a series of experimental studies on sleep apnea pathophysiology and concomitant comorbidities to be carried out. It is now one of the most effective medical treatments for symptom reversal, while producing few comorbidities and side effects. Professor Sullivan's team is currently focusing on SDB in pregnant women as a risk factor for slow fetal growth and metabolic problems during pregnancy. Once again, the nCPAP device will be used to help evaluate these associations and may even result as the treatment of choice in this instance.

Genetics of SDB

Sleep apnea and obesity both have a complex pathogenesis influenced by genetic and environmental factors. Predisposing genetic factors have been suggested to influence the risk of SDB to by up to 40%, while the body mass index hereditability may account for as much as 80%. As leptin, serotonin, insulin resistance, hypertension, and dyslipidemia appear to be involved in the pathogenesis of both sleep apnea and obesity, it is possible that they all share similar genetic susceptibility, i.e. pleiotropic genetic polymorphisms. The accompanying sleep fragmentation, increased sympathetic activity, and intermittent hypoxemia are suggested to influence the genetic factors responsible for the metabolic phenotype of patients with sleep apnea. Identifying these polymorphisms could explain the molecular mechanisms by which obstructive sleep apnea (OSA) syndrome influences metabolic dysfunctions. Thus, genetic factors can influence body fat distribution or metabolism, craniofacial features, upper airway muscles, and sleep regulation.

After reporting a familial link in sleep apnea observed in Icelanders, Thorarinn Gislason (Department of Pulmonary Medicine, Vifilsstadir, Gardabaer, Iceland) and colleagues recruited a total of 4850 Icelanders with OSA, 38% of whom used CPAP [6]. The preliminary results from their ongoing linkage study showed that the highest allele-sharing score was at 20q 13.3. The logarithm of the odds (LOD) score was 3.81 on chromosome 20q, suggesting that these loci are likely to be inherited together as a genetic factor of OSA syndrome. As a result, this region is being further investigated with additional markers and tagging for the *endothelin 3* gene (*EDN3*). It has previously been suggested that a mutation in *EDN3* can cause congenital central hypoventilation; therefore, Dr Gislason et al. hypothesized that *EDN3* on chromosone 20q is a susceptible locus for a potential candidate gene involved in the pathogenesis of OSA. This is now being investigated by Dr Gislason's group using association studies in the Icelandic patients with OSA.

The gene encoding apolipoprotein E, *APOE*, on chromosome 19 has often been studied as a candidate gene involved in sleep apnea. Emma Larkin (Case Western Reserve University, Cleveland, OH, USA) and colleagues performed genotyping, association, and linkage analyses of *APOE* in a cohort of patients with OSA [7]. They suggested that the region surrounding the *APOE* locus on chromosome 19 is susceptible for OSA. However, *APOE* is not directly linked to the pathogenesis of sleep apnea since the inclusion of the *APOE*E2* allele as a covariate decreased the regression coefficient by 18%.

Another consequence associated with OSA syndrome is activation of the inflammatory cascade, with transcription of nuclear factor-κB (NF-κB) involved in the pathogenesis of atherosclerosis. Motoo Yamauchi (Nara Medical University, Nara, Japan) and co-workers observed that a night of CPAP therapy resulted in a decrease of monocyte nuclear p65 and monocyte production of tumor necrosis factor-α (TNF-α) [8], and thus, a reduced risk of developing OSA-associated atherosclerosis.

Hypoxia-inducible factor-1α (HIF-1α) is a transcriptional activator implicated in the carotid body-mediated cardio-respiratory response to chronic intermittent hypoxia. Ying-Jie Peng (Case Western Reserve University, Cleveland, OH, USA) and colleagues demonstrated that this response was associated with an increase in reactive oxygen species in mice [9].

The gene coding for C-reactive protein (*CRP*), a marker for systemic inflammation and a predictor of future development of cardiovascular disease, is also a candidate for OSA. A study by Larkin and colleagues showed that young adolescents without cardiovascular disease but an apnea–hypopnea index (AHI) of ≥5 had higher levels of CRP, predicting an increased risk of developing cardiovascular disease as adults [10]. Thus, while multiple genetic factors are being independently investigated, their involvement in OSA syndrome is probably as complex as OSA itself.

Cardio- and cerebrovascular functions and OSA

The link between hypertension and OSA is well known. Historical studies in the 1970s revealed that daytime hypertension in patients with OSA could be controlled by tracheostomy. These investigations were replicated using nCPAP. As shown by large epidemiological studies, particularly those performed on the Wisconsin Sleep Cohort, OSA is an independent risk factor for hypertension. nCPAP may improve hypertension, but it can lead to the reappearance of the nocturnal physiological "deep" in blood pressure. If hypertension is refractory to drug treatment, the possibility of underlying OSA should be investigated. Similarly, recurrent atrial fibrillation despite appropriate treatment must also raise concerns about an underlying presence of OSA.

If heart rate pacing does not lead to the improvement of OSA as initially expected, the patient may be suffering from Cheyne-Stokes respiration or repetitive central apnea, as is seen with cardiac failure. The large Canadian trial of nCPAP versus sham CPAP was interrupted due to an unexpectedly high mortality rate in the group receiving the active treatment, when using the design planned at the beginning of the study [11]. However, some patients benefited greatly from the nCPAP approach. A better understanding of which patients are likely to respond to the treatment is necessary, along with improved inclusion and exclusion criteria.

Despite a large amount of evidence implying a role for OSA in stroke, there is only one large study indicating OSA as an independent risk factor in first stroke [12]. This investigation requires replication to further support this theory; however, there is already strong data to support a role of untreated OSA as a risk factor for repeat stroke. Acceptance of nCPAP treatment by stroke patients and caregivers varies, and a number of negative factors for approval and treatment compliance have been identified, including cerebral impairment, presence of an initial coma, aphasia, upper limb movement limitation, age of caregiver, and familial and social support.

Brain imaging in OSA syndrome

Deficits in brain function and performance during cognitive tasks have been demonstrated in individuals with OSA. Functional magnetic resonance imaging (fMRI) is a novel approach to studying the effect of the disorder on cognitive performance.

Liat Ayalon (UCSD, San Diego, CA, USA) and colleagues studied 12 OSA patients and 12 matched controls subjects. While the controls demonstrated intact verbal learning and compensatory increased cortical activation, the OSA patients presented with overall increased cortical activation, particularly in the bilateral inferior frontal and middle frontal gyri, cingulated gyrus, areas at the junction of the inferior parietal and superior temporal lobes, thalamus, and cerebellum. Furthermore, Mark S Aloia's team (Brown University Medical School, Providence, RI, USA) used a working memory task during fMRI recordings to image the outcome of effective or withheld CPAP treatment in 10 OSA patients. The results showed an increased activity in the right frontal gyrus with effective treatment, while significant compensatory recruitment was seen in the left middle frontal gyrus when treatment was withheld. These findings seem to suggest that the brain can recruit additional cortical regions to compensate for deficits resulting from OSA or aging in order to maintain performance level. However, a combination of both OSA and aging may decrease the brain's ability to compensate, underlining the importance of early diagnosis and prevention.

It is important to note that characteristics of some sleep apnea patients (e.g. uncontrollable hypertension, obesity) are exclusion criteria for performing an fMRI recording. It is also critical to match OSA patients with control subjects in order to adequately extrapolate conclusions from these fMRI studies. The tasks given during the assessment should be carefully selected and adapted for the specific study environment. Furthermore, it is still unclear whether fMRI recordings, which are dependent on blood oxygenation levels, are accurate when used in OSA patients.

Pediatric sleep apnea

A complete polysomnography is recommended by the American Academy of Pediatrics and the American Thoracic Society to determine if snoring in children is a symptom of OSA, thus helping to identify the correct treatment, with or without adenotonsillectomy. However, a complete polysomnographic recording is expensive and not available to all patients. Robert T Brouillette's group (Montreal Children's Hospital/McGill University, Montreal, QC, Canada) proposed a different diagnostic tool that may be more easily accessible for pediatric patients. A completed physical exam should be performed by the referring physician and sleep history obtained using a computerized questionnaire completed by the parents. This is followed by a two-stage testing procedure: 1) initial testing at home with nocturnal pulse oximetry; and 2) polysomnographic recording if necessary. The initial home test has a high predictive value, with approximately 25% of referred patients diagnosed with OSA. If the early test results are normal, a complete polysomnography may be performed if the referring physician deems it necessary for diagnosis.

It must be remembered that chronic snoring can be associated with poor school performance, inattention, hyperactivity, and parasomnias, as was presided by Christian Guilleminault (Stanford University Medical Center, Stanford University, Palo Alto, CA, USA) in a separate session discussing upper airway resistance syndrome. Diagnosis of this more subtle form of SDB requires polysomnography, often with nasal cannula pressure transducer recording.

In pediatric sleep apnea, the first-line treatment is surgery (e.g. tonsillectomy and adenoidectomy). The "Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea", a risk score based on OSA severity and surgical/anesthetic approach, was recently published by the American Society of Anesthesiologists [13]. It has often been reported that pediatric patients with sleep apnea who suffer from severe oxygen desaturations during sleep have an increased response of respiratory depression to exogenous opioids (46% OSA patients vs. 5% controls with fentanyl). Moreover, these children require less morphine to secure a uniform level of anesthesia. However, as was reported by Kasey Li (Stanford Sleep Disorders Clinic and Research Center), the risk of a respiratory complication increases from 1% to 20% after adenotonsillectomy in pediatric patients with OSA, and this complication may be delayed after surgery.

In a parallel session presided by Carole Marcus (The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA, USA) that discussed the treatment of OSA in children, it was shown that 48% of a group of 200 children treated by adenotonsillectomy still

presented with an AHI of ≥1 – defined as pathological AHI in children – at 3-months post-surgery, highlighting the importance of performing post-surgical evaluation.

In cases where there is underlying medical conditions such as cranio-facial anomalies, muscular dystrophy, or obesity, CPAP can be a trustworthy alternate treatment to adenotonsillectomy. However, compliance is often poor in pediatric patients, although this could be remedied, in part, by adequate parental training and monitoring. CPAP use in younger patients is limited as there are few CPAP devices approved by the US Food and Drug Administration for pediatric use, and due to midfacial deformities. Other possible alternative treatments to alleviate pediatric OSA include intra-oral appliances and rapid maxillary distraction, anti-inflammatory medication (e.g. topical steroids and leukotrine inhibitors), and oxygen therapy; however, these treatments still require further investigation.

Orthodontics and orthognatic surgery

SDB in pediatric patients has been suggested to lead to abnormal cranio-facial growth such as a high hard soft palate, micrognathia, retrognathia, long oval-shape face (longer lower third), and long soft palate. Esthetic orthodontic treatments can have positive effects on OSA by correcting malocclusion and maxillary/madibular equilibrium, thus helping in repositioning the tongue and opening the upper airway. Paola Pirelli's (University of Tor Vergata, Rome, Italy) and colleagues studied 80 children with both adenoid/tonsillar hypertrophy and narrow maxillary complex. Half received rapid maxillary expansion orthodontic treatment and the remainder underwent adenotonsillectomy. Approximately 80% of the children benefited from the orthodontic treatment while 60% improved after adenotonsillectomy. In both groups, 91–96% of those who still showed some signs of OSA achieved complete remission after receiving the alternative treatment (e.g. orthodontics or surgery). Thus, rapid mandibular expansion should be considered part of the therapy protocol when treating a pediatric patient with OSA. Moreover, when both adenoid/tonsillar hypertrophy and a narrow upper jaw are present, the combination of both orthodontic and surgical treatment appears to be the optimal solution. Orthognatic surgery may be used successfully in teenagers who present with a poor response to adenotonsillectomy and with cranio-facial features responsible for a small upper airway. Two procedures can be performed based on these anatomical characteristics: distraction osteogenesis of the mandible associated with maxillary expansion, an extension of previously used orthodontic techniques, and maxillo-mandibular advancement.

Conclusion

The 8th World Congress on Sleep Apnea held in Montreal revealed how far and wide the field of sleep apnea in sleep medicine research has grown, and highlighted the many promising fields of interest that remain to be explored.

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