

Theoretical Review

INSOMNIA CAUSES, CONSEQUENCES, AND THERAPEUTICS: AN OVERVIEW

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There is growing interest in insomnia both from the perspective of recent advances in clinical management as well as research aimed at elucidating its pathophysiology. This theoretical overview of insomnia describes the negative impact, etiological considerations, and pharmacological and behavioral treatments for the disorder, with an emphasis on areas receiving increased research attention. Insomnia, the most prevalent sleep disorder, affects 10–15% of the general population. In population-based studies severe insomnia has been shown to last for a median of 4 years. In addition, insomnia has a significant negative impact on an individual's work, physical, and social performance as well as overall quality of life. Furthermore, the economic cost of insomnia related to lost productivity, work-related accidents, absenteeism, and health-care costs are enormous. There is increasing evidence linking the precipitation of insomnia to stress, and converging evidence from cognitive, endocrine, neurological, and behavioral domains provide clear evidence for hyperarousal in insomnia. However, there remains no consensus regarding the specific etiological mechanisms of this disorder. Although the pathophysiology of primary insomnia remains an enigma, numerous treatments both pharmacological and behavioral have been developed and found to be efficacious in controlled studies. Despite the wide availability of pharmacological treatments and increased knowledge of behavioral interventions, the vast majority of individuals with insomnia do not appear to be receiving adequate treatment. The inadequate treatment of insomnia leads to several important and under-recognized consequences including subsequent development of psychiatric disease and increased substance use. Depression and Anxiety 18:163–176, 2003. © 2003 Wiley-Liss, Inc.

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INTRODUCTION

Insomnia is the experience of inadequate, insufficient, or nonrestorative sleep despite ample time in bed. Insomnia is the most frequent sleep disturbance, with the prevalence of chronic insomnia (>6 months) estimated at between 10 and 15% of the US population [Breslau et al., 1996; Cirignotta et al., 1985; Ohayon, 1996; Ohayon, 1997, 2002; Ohayon et al., 1998; Silva et al., 1996]. Insomnia is an under-recognized and under-treated problem. This theoretical overview of insomnia examines its negative impact and pharmacological and behavioral treatments, with an emphasis on chronic primary insomnia and its associated features. First, diagnostic issues related to the major classifica-

tion systems for insomnia are addressed and an overview of the economic impact that insomnia

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conveys is provided. Second, important considerations regarding polysomnography and other tools used for the assessment of insomnia are discussed along with recent research on the comorbidity of insomnia with major depression and anxiety disorders. Next, a discussion of the three-factor model of insomnia and relationships between stress, arousal, and insomnia will be presented. Finally, an overview of insomnia in the elderly and the major treatments for this disorder are reviewed. Although the present paper is not meant to provide an in-depth critical review, particularly regarding areas related to specific medical diseases, non-therapeutic effects of drugs on sleep (e.g., pro- and anti-inflammatory drugs, adenosine compounds, beta-blockers), or the impact of circadian rhythm disturbances on insomnia, the reader is directed to recent reviews of these important topics [Dagan, 2002; Goh et al., 2000; Guilleminault, 2000; Schweitzer, 2000; Strogatz et al., 1987].

There are three major classification systems used by both clinicians and researchers to diagnose insomnia. Unfortunately, there has been a relative lack of consistency both within (revisions) as well as between diagnostic classification systems and research definitions [Harvey, 2001; Ohayon, 2002; Reynolds et al., 1991]. The Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) classification [APA, 1994], defines primary insomnia as the complaint of difficulty initiating or maintaining sleep, or nonrestorative sleep, persisting for longer than 1 month (pp. 557). This complaint must also be accompanied by clinically significant impairment in daytime function, for which there is no identifiable cause such as another sleep, psychiatric or medical disorder. A second diagnostic system that specifies criteria for an insomnia diagnosis is the International Classification of Sleep Disorders [AASM, 2001]. This system was created and modified by experts in the field of sleep disorders research and is increasingly used by clinicians with specialized sleep training. Finally, the International Classification of Disorders-10 [WHO, 1992] is a third system used to classify insomnia. As opposed to DSM-IV and ICSD, which do not have specific frequency criteria attached, the ICD-10 criteria require a patient to report sleep disturbance that occurs at least 3 nights per week. Other variations across these classification systems are related to considerations of symptom severity (DSM-IV "clinically significant distress or impairment"; ICSD not specified) and duration (specified as 4 weeks in DSM-IV only). Generally, the ICD-10 and DSM-IV attempt to lump insomnia diagnoses together, whereas the ICSD splits them apart.

The nonspecific nature of the insomnia diagnosis in each of the standard diagnostic systems along with the ubiquitous nature of insomnia symptoms (both transient and chronic) have contributed to the difficulty in identifying the etiology of primary insomnia as well as determining an appropriate differential diagnosis.

While insomnia was once thought of exclusively as a symptom rather than as a disorder, primary insomnia and its pathophysiology is beginning to be studied more rigorously with respect to its clinical identification and objectively verified correlates. As a result, primary insomnia is increasingly recognized as a distinct disorder. An important remaining question concerns the specific etiology that may differentiate primary from secondary insomnia and whether there may be common etiological components such as a predisposition to disturbed sleep, negative conditioning, or maladaptive behaviors and cognitions.

NEGATIVE IMPACT

One approach proven useful in determining the negative impact of insomnia includes studies examining the chronicity of this disorder in the general population. In population-based studies, severe insomnia has been shown to last for a median of 4 years [Chevalier et al., 1999] and 88.2% of patients continue to report sleep disturbance 5 years after the onset of the disorder [Mendelson, 1995]. Furthermore, one study found that only 56% of individuals have remission after 10 years [Janson et al., 2001]. In addition to its nocturnal effects, insomnia has a significant negative impact on an individual's quality of life. One study using the Short Form Health Survey 36 (SF-36), a standardized measure of the impact of illness on quality of life, found that insomnia patients report significantly decreased daytime functioning across a large number of areas including emotional, social, and physical domains [Zammit et al., 1999]. Other studies have confirmed these findings, even after controlling for comorbid medical illnesses. Individuals with insomnia report significantly impaired work performance [Leger et al., 2002], lower physical and social functioning [Leger et al., 2001], and an overall lower quality of life comparable to that of individuals with chronic medical conditions [Katz and McHorney, 2002]. Among the most alarming findings in recent years is that insomnia is associated with a subsequent increased risk for major depressive disorder [Breslau et al., 1996; Chang et al., 1997; Ford and Kamerow, 1989]. Depressed patients with sleep difficulties also have higher rates of suicidal behavior in comparison to depressed patients without sleep disturbance [Agargun et al., 1997] and insomnia symptoms predict suicidality in depressed patients [Hall and Platt, 1999]. Additional research is needed to determine the specificity of insomnia consequences in terms of associations with primary insomnia or comorbid diseases.

The large number of individuals affected, along with its chronic nature, cause insomnia to convey a substantial economic burden. Over the past decade a number of studies have investigated the impact of insomnia in terms of its economic burden to society. The economic cost of insomnia related to lost productivity, work-related accidents, and absenteeism

was estimated to be more than \$77 billion per year [Leger, 2000; Walsh and Engelhardt, 1999].

POLYSOMNOGRAPHIC AND CLINICAL ASSESSMENT

Polysomnography (PSG), while helpful [Edinger et al., 1989], is not widely used nor indicated as an initial assessment technique for the diagnosis of insomnia [Chesson et al., 2000; Littner et al., 2003; Vgontzas et al., 1995]. One reason for this is the discrepant findings with respect to subjective reports of sleep disturbance and the degree of objectively verifiable sleep disturbance as determined from PSG [Vgontzas et al., 1994]. Individuals with chronic insomnia symptoms are often found to have PSG sleep that is within clinically accepted normal limits (e.g., <85% sleep efficiency, <30-min sleep latency). It has recently been demonstrated that many insomniacs perceive wakefulness even while they are asleep by PSG criteria [Mercer et al., 2002]. Individuals with such a presentation are regarded as having sleep-state misperception [Salin-Pascual et al., 1992] by ICSID criteria; the DSM-IV makes no distinction. One recent study that assessed memory function near sleep onset in insomniacs and controls gives some support to the possibility that a reduction in the mesograde amnesia of sleep may account for overestimates of sleep latency and underestimates of total sleep time in insomniacs [Perlis et al., 2001b]. While PSG in conjunction with the standardized sleep scoring system [Rechtschaffen and Kales, 1968b] is the "gold standard" for determining sleep-wake states, other scoring methodologies or alterations to the current system may be developed in the future which map more precisely onto the subjective reports of sleep disturbance in the subset of insomnia patients whom overestimate their sleep latency [Bonnet and Arand, 1997].

With regard to the differential diagnosis of insomnia and the prescribing of appropriate treatment strategies, it is important to obtain a detailed account of the patient's medical and psychiatric history as well as recent and historical sleep habits [Nowell et al., 1997]. There are numerous studies documenting the close association between insomnia symptoms and other common disorders including, but not limited to, circadian rhythms disorders related to a misalignment between biological and behavioral rhythms [Morris et al., 1990], other sleep disorders [Edinger et al., 1989], and medical [Ohayon et al., 1998] as well as psychiatric disorders [Benca, 1996; Buysse et al., 1994; McCall, 2001; Schramm et al., 1995; Vollrath et al., 1989]. Although the diagnosis of insomnia relies on a comprehensive medical, psychiatric and sleep history, it remains a challenge to the clinician to determine the relation of comorbid diseases to insomnia symptoms. However, using subjective report to aid the diagnosis of insomnia may be important, as sleep need varies between individuals and is difficult to quantify. There-

fore, shortened PSG sleep given ample time in bed with no evidence for daytime sequelae may indicate a "short sleeper" rather than a clinically significant sleep disturbance. In such cases, relying on purely objective measures may lead to an erroneous diagnosis. Finally, although the reliability of sleep diagnoses are moderately high [Buysse et al., 1994; Schramm et al., 1993], reliability and validity of insomnia diagnoses may be greatly enhanced with the use of standardized diagnostic and assessment tools.

With the increasing recognition of insomnia as an important symptom and in the case of primary insomnia, a disease with a significant impact on daily functioning, a number of standardized questionnaires have been developed to aid in the diagnostic assessment and measurement of morbidity in this disorder. Several of these measures have been demonstrated to have robust psychometric properties and have become widely used in both clinical and research settings. The Pittsburg Sleep Quality Index developed in 1989 by Buysse and colleagues [Buysse et al., 1989] has become an important assessment tool which is helpful in measuring temporal changes in sleep quality or sleep disturbance related to various disease states [Baskett et al., 2003; Buysse et al., 1991; Carpenter and Andrykowski, 1998; Doi et al., 2000; Gentili et al., 1995; Petit et al., 2003; Smyth, 1999]. While similarly validated instruments are available for diagnostic assessment [Douglass et al., 1994; Roth et al., 2002; Schramm et al., 1993] as well as follow-up of insomnia populations [Douglass et al., 1994; Moul et al., 2002; Soldatos et al., 2000, 2003], their use is not as widespread possibly due to their more recent introduction to the field.

Actigraphic assessment is a unique tool that can sometimes be helpful in the differential diagnosis of insomnia [Chambers, 1994; Hauri and Wisbey, 1992]. It involves the nightly use of a movement activated device attached to the wrist or ankle of an individual for a prolonged period of assessment (usually 1–2 weeks). This device can provide both the clinician and patient with objective data documenting the course of sleep disturbance across a specified time period. However, studies using actigraphy for the assessment of insomnia have been equivocal [Chesson et al., 2000]. Just as with the use of PSG as an assessment tool, discrepancies between subjective and objective data can and often do arise [Jean-Louis et al., 1999; Verbeek et al., 2001]. The use of actigraphy is most helpful when there is a desire to have multiple daily assessments, as needed when forming a differential diagnosis between a circadian rhythm disturbance and primary insomnia. Finally, one of the easiest and most economical ways of obtaining reliable information regarding sleep-wake functioning is through the use of a sleep diary/log. Research has shown that this type of assessment may be as accurate as actigraphic assessment, although actigraphy may provide better information regarding night to night variability of sleep in insomniacs [Chambers, 1994].

COMORBIDITY WITH DEPRESSION AND ANXIETY

In order to gain insight into the underlying pathophysiology of insomnia, research has begun to focus on comorbidity. Insomnia is associated with a variety of medical and psychiatric disorders. Among the medical disorders, those associated with dyspnea [Klink et al., 1994; Klink et al., 1992] and with pain conditions [Mahowald and Mahowald, 2000; Mahowald et al., 1989] are the most common. Psychiatric comorbidities are estimated to occur in 40% of chronic insomniacs [Ford and Kamerow, 1989]. The association of insomnia with psychiatric disorders has been demonstrated in both clinic [Buysse et al., 1994; Coleman et al., 1982] as well as population-based samples [Ohayon et al., 1997]. In regards to specific psychiatric disorders, affective disorders are most commonly associated with insomnia. In fact, sleep items are key criteria in diagnosing major depression and are generally included in most depression rating scales. In the past it was assumed that various psychiatric disorders produced the insomnia. Thus, clinical wisdom called for the treatment of the psychiatric disorder in order to alleviate the insomnia. In fact, this was the case when psychiatric disorders were treated with sedating medication (e.g. tricyclic antidepressants, benzodiazepines). However, with the introduction of non-sedating drugs, the insomnia is often found to be refractory to the successful reversal of other depressive symptoms [Stark and Hardison, 1985]. This has led individuals to question the assumption that the insomnia is simply the byproduct of the depressive disorder. Furthermore, given data regarding the chronicity of insomnia [Katz and McHorney, 2002; Mendelson, 1995], it is possible that not only is insomnia refractory to the treatment of depression but it may in fact predate the onset of depression.

In a multinational population-based study carried out in Europe [Ohayon and Roth, 2003], it was found that insomnia predates the onset of the first episode of depression 41% of the time and follows the onset of depression only 28.9% of the time (common onset was reported 29.4% of the time). This effect is even more pronounced in depression relapses, with insomnia predating a relapse of depression 56.2% of the time and following symptom onset only 21.6% of the time (22.1% of the time they reoccur simultaneously). It was found that this relation between insomnia and depression is not generalizable to other psychiatric disorders, as evident from the observation that in anxiety disorders insomnia most typically follows the onset of both the first and relapse episodes of the disorder.

To better understand the relation of the temporal course of insomnia and psychiatric disorders, several longitudinal studies have investigated the evolution of psychiatric disorders in patients diagnosed with insomnia [Breslau et al., 1996; Chang et al., 1997; Ford and Kamerow, 1989]. These studies have utilized a

follow-up period of 1–40 years, with most studies limiting the follow-up to approximately 5 years. In all of these studies, insomnia was found to represent a substantial and statistically significant risk for the development of depressive disorders. Typically the relative risk (RR) was approximately 5 but it ranged from 2 to 40, depending on the particular methodology utilized. Specifically, findings ranged from an RR of 2 in an all male population [Chang et al., 1997], to a study reporting 40, which required insomnia to be present both at the initial interview as well as at the follow-up interview 1 year later. Insomnia was found to be a risk factor for other diagnostic entities such as anxiety and substance abuse disorders in some studies, but these associations have not been consistently found. Finally, in longitudinal studies of depression, those patients whose sleep improved with treatment show a more rapid onset of an antidepressant response and a longer time to relapse than those patients whose insomnia persists after the initiation of treatment [Fava et al., 1990; Perlis et al., 1997a].

Thus far, debate as to whether depression causes insomnia or insomnia causes depression continues. However, another alternative which is gaining increased support, is that the coexistence of these two disorders in the same patients is reflective not of a cause–effect relation, but rather a common pathology. A variety of studies have demonstrated that the presence of insomnia as well as the severity of the sleep disturbance, among insomnia patients is related to hypersecretion of cortisol [Vgontzas et al., 2001; Vgontzas and Chrousos, 2002; Vgontzas et al., 1998]. Similar hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis has also been reported in patients with depression [Hatzinger, 2000; Watson et al., 2002]. Therefore, it is the hypersecretion of cortisol that represents the common risk factor for both insomnia and depression. Thus, the question is not, “which generates the other?” as they both result from a common pathology; rather, “why does insomnia occur first in some depressed patients, second in others, and not at all in some?” Finally, this supports the notion that medications working on the HPA axis (e.g., corticotrophin-releasing hormone antagonists) may be effective for treating both disorders.

THE THREE-FACTOR MODEL OF PRIMARY INSOMNIA

Theoretical models of primary insomnia generally propose a diathesis–stress model. That is, the idea that a precipitating event superimposed upon a premorbid predisposition and subsequent maintaining factors results in the manifestation of the disorder [Spielman et al., 1987]. This model has dominated the field and, although there has been some agreement regarding this general conceptual framework, there has been little consensus regarding the specifics of the separate components. Within this framework, both

physiological and behavioral parameters have been studied in an attempt to elucidate the model elements.

Early theories of insomnia proposed that individuals with clinically significant sleep disruption may be “light” sleepers, thus, more sensitive to sleep-disturbing stimuli [Rechtschaffen, 1968a]. These theories generated several studies testing the possibility that insomniacs are more easily aroused from sleep and slower to return to sleep in comparison to controls. Studies have shown that insomniacs take longer to return to sleep following experimentally induced auditory arousals [Johnson et al., 1979] and the latency to sleep following an arousal is associated with physiological measures indicating increased stress [Haynes et al., 1985]. It has also been shown that auditory awakening threshold is related to the level of pre-sleep arousal (i.e., heart rate) [Haynes et al., 1981]. These results suggested a close link between waking arousal level and vulnerability to experimentally induced sleep disturbance.

In two classic studies of pre-sleep arousal in insomnia, the resting pre-sleep arousal level of insomniacs at baseline was comparable to that of control participants after exercise [reviewed in Rechtschaffen, 1968]. In addition, arousal level in the insomniacs remained high throughout sleep, while in the controls it returned to baseline levels within one hour following termination of the exercise condition. Differences in arousal between insomniacs and controls have also been demonstrated at the cognitive level, as individuals with insomnia more readily perceive themselves as awake while they are physiologically asleep [Perlis et al., 1997b]. These results implicate an intrinsic sleep-related difference in cognitive and physiological arousal between the sleep of insomniacs and controls as well as a failure to return to baseline levels following the discontinuation of the arousing stimulus.

Although the DSM-IV states that “many individuals with primary insomnia have a history of light or easily disturbed sleep prior to the development of more persistent sleep problems” (pp. 553), few studies have focused on individual differences that may predispose one to develop insomnia. Importantly, no studies have demonstrated that experimentally induced sleep disturbance generalizes across different stimuli (i.e., auditory tones, expectancies, pharmacological challenges). Because a concordance across different sleep disruptive challenges has not been confirmed, it is not known whether a general trait vulnerability to sleep disruption exists or whether transient sleep disturbances evolve into chronic insomnia. Thus, vulnerability to particular challenges may simply be related to sensitivity towards a specific type of challenge/stressor rather than a general vulnerability within the individual. This, unidentified predisposition may not only make some individuals more vulnerable to sleep disturbance, but also could potentially delay normalization of sleep following acute disruptions, indicating

a possible pathway for developing chronic insomnia. Although there has been little research in this area, studies are underway in several laboratories to determine the existence of such trait vulnerability and its significance towards the development of chronic primary insomnia [Bonnet and Arand, 2002; Drake et al., 2003].

Another example of an experimental approach within the framework of the three-factor model of insomnia (i.e., predisposing, precipitating, perpetuating components) has been the study of precipitants (triggers) of insomnia. Much research has focused on the effects of sleep disrupting challenges such as the effects of auditory tones [Johnson et al., 1979], viral infection [Drake et al., 2000], pharmacological challenges such as caffeine [Bonnet and Arand, 1992, 1996], shifts in circadian phase [Roehrs et al., 1996], or the effects of traumatic events on sleep [Lavie, 2001]. Not surprisingly, and possibly due to the ubiquitous nature of sleep complaints associated with severe acute or chronic stress, several studies have assessed the relationship between the onset of chronic primary insomnia and stressful life events [Hauri and Olmstead, 1980; Healey et al., 1981; Morin et al., 2003]. Two studies that have specifically addressed the connection between stressful life events and clinical insomnia support the idea that while the onset of stressful life events may be a trigger for insomnia [Healey et al., 1981; Morin et al., 2003], it appears that the *response* to life events rather than their *frequency* that may be the predominant factor driving this association [Morin et al., 2003].

While insomniacs appear to have heightened levels of stress in association with the onset of the disorder in comparison to healthy controls, this difference in stress begins to disappear somewhere within a year after the onset of the sleep disturbance. Importantly, individuals with insomnia continue to have sleep disturbance after the dissipation of the acute stress that may have initially triggered the sleep disturbance (differentiation from adjustment disorder in DSM-IV). They do however retain an elevated responsiveness to stressful life events in comparison to healthy controls [Healey et al., 1981; Morin et al., 2003]. Such elevated responsiveness to stress in insomnia, if replicated in future research, would provide support for the notion that insomnia may be related to an over activation of the stress-response system. Insomnia comorbidity with depression and the commonality with stress in each of these disorders also gives some support for the notion of an abnormality in the stress system (i.e., HPA axis and autonomic nervous system).

Over the past four decades much research has been completed linking insomnia and the broadly defined stress-response system. Physiological studies have identified elevated HPA axis activity as evidenced by measures including cortisol and adrenocorticotrophin releasing hormone (ACTH) [Vgontzas et al., 2001]. With regard to measures related to the autonomic component of the stress-response system, heart rate

[Bonnet and Arand, 1998] and its change in response to a performance task [Stepanski et al., 1988], electromyographic [Haynes et al., 1974], and metabolic variables [Bonnet and Arand, 1995] are all elevated in insomnia patients. Further evidence for hyperarousal in insomnia comes from several studies that have assessed arousal using the multiple sleep latency test (MSLT) [Bonnet and Arand, 2000; Stepanski et al., 1988]. The MSLT assesses physiological sleepiness–alertness and in this respect may be thought of as a generalized measure of arousal [Carskadon and Dement, 1982, 1987; Carskadon et al., 1986; Roehrs and Roth, 1992]. In most studies that have assessed the MSLT in insomnia, patients were found to have elevated scores indicative of general hyperarousal in comparison to controls [Bonnet and Arand, 2000; Stepanski et al., 1988].

While several of the measures noted above point to general hyperarousal in insomnia, more specific autonomic variables such as heart rate variability have also been assessed. Heart rate typically fluctuates corresponding to the inspiratory and expiratory phases of the respiratory cycle; this fluctuation is termed respiratory sinus arrhythmia (RSA) [Berntson et al., 1993; Grossman, 1992]. The magnitude of RSA is a specific index of parasympathetic tone as it has been shown that parasympathetic postganglionic blockers reduce RSA by approximately 99%, whereas sympathetic blockade by either or both β - and α -adrenergic antagonists does not affect RSA amplitude [Berntson et al., 1993]. Using spectral analysis one can measure the magnitude of high frequency heart rate fluctuations centered at the respiratory frequency (HF; ~ 0.16 – 0.5 Hz) and obtain a specific measure of parasympathetic tone. Spectral estimates of lower frequencies (~ 0.02 – 0.16 Hz) are used in conjunction with high frequency measures to determine autonomic balance [Berntson et al., 1993]. In a study by Bonnet and colleagues [Bonnet and Arand, 1998], the ratio of low to high frequency heart rate variability was used as a measure of sympatho-vagal balance and was found to be elevated in insomniacs compared with matched normal sleepers indicating sympathetic autonomic dominance. In addition, high frequency measures were reduced in insomnia patients indicating decreased parasympathetic activity. Evidence suggests that this selective noninvasive measure of *parasympathetic* tone is a sensitive index of stress [Burlison et al., 2003; Porges, 1995, 2003]. Thus, lower RSA (i.e., vagal withdraw) is associated with increased stress.

With respect to cortical activation, both sleep and wake electroencephalographic (EEG) beta frequency (~ 15 – 40 Hz) activity measures have been demonstrated to be elevated in insomnia providing additional support for the conceptualization of insomnia as a disorder of arousal [Freedman, 1986; Lamarche and Ogilvie, 1997; Merica et al., 1998; Merica and Gaillard, 1992; Nofzinger et al., 1999; Perlis et al., 2001a]. Studies of cognitive activity in insomnia have also produced evidence of increased catastrophizing cogni-

tions [Harvey and Greenall, 2003] and demonstrated correlations between intrusive thoughts and subsequent sleep disturbance [Hall et al., 2000; Smith et al., 2001]. However, the magnitude of the relationship is often small and similar associations have not always been reported [Nelson and Harvey, 2003]. Despite increased evidence converging from several domains, hyperarousal theories of insomnia are not without controversy. Indeed, one recent photon emission computed tomography—imaging study found that insomnia patients had significantly lower regional cerebral blood flow during sleep in the basal ganglia, as well as frontal medial, occipital, and parietal cortices compared to a group of healthy controls [Smith et al., 2002a]. At the present time, few neuroimaging studies have been performed in insomnia patients. Thus, additional brain imaging studies are necessary to confirm this finding and to place the results within the context of other arousal-related findings in primary insomnia. Clearly, additional studies are needed to determine the brain areas associated with specific components of hyperarousal across cognitive, behavioral, and physiological domains. Finally, further studies are needed using experimental challenge paradigms (e.g., autonomic blockade, manipulations of cognitive set and attribution, conditioning experiments) to test more specific aspects of the three-factor model. Although such studies may carry greater “risks” in terms of their ability to test and disprove specific hypotheses related to cognitive and physiological arousal in insomnia, they may have the potential for greater explanatory power as well.

INSOMNIA IN THE ELDERLY

Understanding insomnia and disturbed sleep in the elderly offers a unique opportunity to gain insight into the diagnosis and treatment of insomnia. There are many unique aspects of insomnia that are instructional about the nature of diagnosis and treatment of insomnia. With age the prevalence of disturbed sleep, insomnia, and the use of hypnotic medications all increase [Bliwise et al., 1992; Morgan, 1987; Morgan et al., 1989]. Interestingly, the age-related increase in sleep disturbance is more pronounced in men, while the age-related increase in insomnia complaints is more common in women [Morgan, 1987; Rediehs et al., 1990]. As one ages, sleep becomes more fragmented with more frequent awakenings and arousals [Feinburg and Floyd, 1979]. Also, there is a decrease in the “deeper” stages of sleep (i.e. stages 3–4 non-rapid eye movement), and these changes are seen to a greater extent in male subjects [Reynolds et al., 1986]. In contrast, the age-related increase in the prevalence of insomnia is more common among women than men [Morgan, 1987].

These differential age-related changes emphasize the difference between disturbed sleep and insomnia. Insomnia as a disorder is thought to be related to

hyper-arousal and, while associated with disturbed sleep, primary insomnia it is not defined by it. Primary insomnia is associated with consequences such as increased risk of depression, increased rates of absenteeism and decreased productivity. In contrast, the consequences of sleep disturbance, per se, resemble those of sleep deprivation (e.g., sleepiness, impaired performance, memory problems) [Dinges et al., 1997; Drake et al., 2001]. Thus, the first important lesson is that insomnia and disturbed sleep are not synonymous. Second, insomnia can be a primary disorder or secondary to medical, psychiatric, circadian, and primary sleep disorders. In fact, the distribution of diagnoses is different in middle age and the elderly. The elderly show an increased prevalence of insomnia due to medical disorders, circadian rhythm (e.g., phase advance syndrome) and primary sleep disorders (e.g., sleep-related breathing disorders, restless leg syndrome, and periodic limb movement disorder). In contrast, primary insomnia and insomnia secondary to psychiatric disorders do not show age-related increases [Roehrs et al., 1983].

Aside from the diagnosis, the presentation of the insomnia also shows age-related differences. While young and middle aged adults typically complain of difficulty falling asleep or difficulty falling back to sleep after nocturnal awakenings, the elderly more commonly report frequent nocturnal awakening, early morning awakenings, and non-refreshing sleep [Morgan et al., 1988]. These differences in diagnosis seem to parallel the differences in symptom presentation. Thus, psychiatric and behavioral diagnoses often associated with prolonged wakefulness do not increase with age; while medical and primary sleep disorders associated with frequent awakenings and fragmented sleep do increase with age.

There is also a difference in therapeutics associated with age. At a behavioral level certain poor sleep practices (i.e., daytime napping, irregularity of arising times, and an increased time in bed relative to total sleep time) seem to be more common in the elderly [Tune, 1969]. Thus, good sleep practices and behavioral therapies such as stimulus control afford the clinician an opportunity to improve sleep in this population, despite the fact that pharmacological therapies are more commonly used in the elderly. However, it is also important to remember that insomnia complaints also increase with age. Indeed, if you correct for the prevalence of insomnia, medication use does not increase with age. While sleep-promoting medications have been shown to be of benefit in the elderly, there needs to be recognition that their use presents unique challenges. First, the metabolism of these compounds is such that, with one or two exceptions, the elderly will have greater drug exposure relative to their middle age counterparts [Bliwise et al., 1992]. Given a fixed dose of a sleep-promoting agent, the area under the curve of blood levels across time increases with age. Specifically, the maximum drug

concentration, the half-life, or both increases with age. As these components can independently contribute to the increased blood levels of a drug, the duration of action of these medications is longer and the C_{max} is typically higher in elderly patients. As a consequence three potential concerns arise. The first is the increased potential of residual effects given the increased duration of action. Second, the increased chance of falls, given the increased prevalence of nocturia in the elderly and the increased drug blood level during the night. Finally, one has to weigh the potential effects of these compounds on the underlying disorders they are treating.

In summary, insomnia is more prevalent, more complex and is associated with more daytime consequences in elderly patients. Therefore, it provides the clinician with more complex diagnostic and therapeutic challenges. To those who are fortunate, successful treatment of insomnia can have a profound effect on their quality of life.

TREATMENT OF INSOMNIA

PHARMACOTHERAPY

The modern era for the symptomatic treatment of insomnia with sleep-promoting agents began with introduction of the benzodiazepine receptor agonists (BzRAs) in the 1960s. Compounds such as flurazepam and nitrazepam quickly became the drugs of choice throughout the world [Nicholson, 1994]. The switch to the BzRAs from the barbiturates and barbiturate-type compounds was primarily driven by safety. Specifically, the barbiturates had a low effective dose: lethal dose ratio whereas the BzRAs are among the safest compounds in medicine. The other major advantage of the BzRAs is that unlike their predecessors, they did not produce tolerance with nightly use. Since the introduction of the BzRAs two major changes have occurred in the development of new compounds. As early hypnotic medications were associated with residual effects, newer medications were developed that had shorter half-lives. Thus triazolam, midazolam, zolpidem and zaleplon have half-lives of less than five hours and thus are not associated with next day residual effects. The other major change in the evolution of BzRAs has been the development of greater receptor specificity. Using genetic "knock-in" techniques multiple receptor subtypes have been identified at the GABA_A Bz complex. The α -1 subunit has been identified as being responsible for sedative-hypnotic activity [Mohler et al., 2002]. Two non-benzodiazepines (zolpidem and zaleplon) binding at the Bz receptor complex show differential binding to the α 1 subunit.

With the increased awareness of the morbidity and of the chronic nature of insomnia there has been an increase in the search for new insomnia therapies. Currently there are drugs from a variety of classes

being developed. New BzRAs, eszopiclone and indiplone, are currently in clinical trials. The hope is that these compounds will provide a better pharmacokinetic profile than the currently available compounds so as to maximize sleep and minimize residual effects. Aside from new BzRAs, drugs are being developed addressing different transmitter systems. These compounds are aimed at melatonin, γ -aminobutyric acid_a (GABA_a), and serotonin 2c (5HT_{2a}) receptors. These development programs have several things in common as well as some differences. First, they are all hypothesized to have decreased abuse liability and therefore potentially a non-scheduled status with regulatory bodies. Second, it is desired that these compounds will decrease the intensity and frequency of the sedation-related side effects such as amnesia, psychomotor impairment, falls and the interaction with ethanol and other sedating drugs. The GABA_a and the 5HT_{2a} compounds also impact sleep architecture by increasing stage 3–4 sleep and slow wave EEG activity. Though stage 3–4 sleep has been associated with recovery from sleep deprivation, the role of delta sleep in insomnia therapeutics is yet to be defined.

Aside from new molecules, there are two very important challenges for defining the future role of sleep-promoting medications. The first, given the chronic nature of insomnia the challenge for insomnia therapies (regardless of class), is to demonstrate long-term efficacy and safety. The second is to define the benefit of improved sleep on medical and psychiatric disorders. For example, in patients with insomnia and comorbid affective disorders being treated for depression, does augmentation therapy with sleep-promoting medications improve the antidepressant response or prevent relapse? Similarly, does augmentation therapy with hypnotics in insomnia with comorbid pain conditions help alleviate nighttime or even daytime pain? The overall goal of insomnia treatment has to be the long-term improvement in the medical and psychiatric well being of insomnia patients.

BEHAVIORAL TREATMENTS

In addition to pharmacological treatments, behavioral, or “cognitive behavioral” treatments of insomnia as they are often described, include a number of treatment modalities. The range of treatments subsumed under this umbrella indicates that the phrase “behavioral treatment” merely denotes treatments that are not pharmacological rather than a specific behavioral protocol. Indeed, behavioral treatments of insomnia include cognitive, behavioral, and other less specific educational components. Since their inception in the early 1970s, various forms of behavioral treatments have been proposed and tested. Extensive reviews of this literature suggest that several of these behavioral components have considerable efficacy while others are still equivocal [Chesson et al., 1999; Morin et al., 1999b]. A recent meta-analysis comparing the efficacy

of behavioral and pharmacological treatment modalities showed that treatment effects were comparable for most outcome variables except sleep latency, where behavioral treatment may provide some increased benefit [Smith et al., 2002b]. Other studies suggest that behavioral treatments may have a more long-lasting impact in comparison to pharmacological treatments [Morin et al., 1999a].

For a thorough evaluation aimed at identifying mechanisms, behavioral treatments should be viewed independently. When looked at separately, stimulus control therapy, an early technique developed by Bootzin in the 1970s, has received the most support from empirical studies [Bootzin and Perlis, 1992; Morin et al., 1999b]. This specific treatment is predicated on the notion that insomnia is produced by learned associations that are formed between the bedroom environment and some form of hyperarousal within the individual. Although the efficacy of stimulus control procedures has been demonstrated in several studies, [Morin et al., 1999b], there has been surprisingly little research confirming the hypothesized mechanisms responsible for its efficacy, namely the extinction of conditioned associations with the bedroom environment. Some support for the notion of a conditioning effect as a possible mechanism in insomnia might come from studies demonstrating a “reverse” first-night effect in insomnia. Such an effect would include improvement of sleep in insomniacs who sleep away from their usual home environment. However, the studies attempting to demonstrate a reverse first-night effect in insomniacs have been equivocal [Edinger et al., 1997; Edinger et al., 1991; Hauri and Olmstead, 1989; Riedel et al., 2001].

Recent meta-analytic studies and extensive reviews of the behavioral treatment literature suggest that other behavioral techniques such as progressive muscle relaxation and paradoxical intention are also efficacious treatments [Morin et al., 1994; Morin et al., 1999b; Perlis et al., 2003; Smith et al., 2002b]. Progressive muscle relaxation involves the successive relaxation of particular muscle groups until a whole-body state of relaxation is obtained. Initially, the technique may be performed in the clinic setting but patients typically will perform sessions on a daily basis in their home. Such therapy generally lasts for 30–45 minutes and may take several weeks of daily practice to master effectively, especially when considering the elevated levels of arousal present in insomnia. Similar to other forms of behavioral therapy, there has been little research directed at determining the mechanisms responsible for improvements in sleep following a standard 6–8 week trial of relaxation therapy. For instance, the impact of progressive muscle relaxation therapy has not been adequately compared to other methods such as autogenic relaxation, which is less directed and may have differential therapeutic benefits in insomnia.

Considering the cognitive preoccupation regarding sleep in insomnia patients, one might hypothesize that

interventions similar to progressive muscle relaxation, which often redirect patients' thoughts away from sleep or to targets other than sleep onset may also provide benefits. Indeed, such a treatment strategy is thought to be the mechanism behind paradoxical intention [Espie and Lindsay, 1985; Espie et al., 1989; Ladouceur and Gros-Louis, 1986; Morin et al., 1999b; Turner and Ascher, 1979]. In paradoxical intention, a patient is provided with instructions to refrain from forcefully attempting to sleep, thereby lifting the self-imposed performance aspect of the pressure to fall asleep quickly and remain asleep throughout the night that is often seen in patients with insomnia.

Helping a patient to manipulate their negative cognitions is an important aspect related to the benefits seen with techniques of cognitive restructuring of dysfunctional beliefs in insomnia [Edinger et al., 2001; Morin et al., 1993]. Specifically, patients are aided in more fully understanding the specific consequences related to their sleep disturbance and at the same time learn coping mechanisms to actively address specific dysfunctional thoughts such as "I will never get enough sleep tonight in order to be able to perform at work tomorrow." Specifically, cognitive therapy is designed to counter the maladaptive cognitions and inappropriate coping strategies that may serve to perpetuate insomnia beyond the resolution of their acute precipitants [Spielman et al., 1987]. This form of cognitive therapy is tailored to reduce dysfunctional attitudes and beliefs about sleep that are hypothesized to contribute to sleep disturbance in insomnia [Edinger et al., 2001; Harvey et al., 2002; Morin et al., 1993]. Although there have been some studies demonstrating efficacy for this treatment, most of these have undertaken a combined approach incorporating several behavioral treatments making it difficult to determine which specific components are responsible for treatment effects. However, there does appear to be growing support for this approach as insomniacs have been shown to increase catastrophizing cognitions [Harvey and Greenall, 2003]. Other studies have demonstrated that increased anxiety and/or intrusive thoughts in insomnia patients is associated with significant sleep disturbance [Chambers and Kim, 1993; Hall et al., 2000]. In one study, intrusive thoughts were associated with increased beta power in the EEG, indicating a possible link between cognitive activation in insomnia and underlying physiological processes [Hall et al., 2000].

Chronic insomnia patients also tend to attribute their insomnia to cognitive arousal rather than somatic factors [Lichstein and Rosenthal, 1980]. What is not known at present is whether cognitive arousal is a primary component in the pathophysiology of the disorder or is an epiphenomena that is a result of physiological arousal. Longitudinal studies are required to determine the role that maladaptive cognitions may play in the early evolution and maintenance of insomnia irrespective of its causal role in the precipitation of the disorder.

Other treatments for insomnia have produced equivocal results when tested empirically. These include sleep restriction and sleep hygiene education. Although each of these treatments is widely used, few studies have demonstrated their superior efficacy over credible placebo interventions [Friedman et al., 2000; Morin et al., 1999b; Stepanski and Wyatt, 2003]. Studies investigating the role of cognitions in the maintenance of insomnia and on the impact of maladaptive behaviors on the evolution of insomnia are clearly needed.

SELF-MEDICATION WITH ALCOHOL

As previously noted, persistent difficulty falling asleep, maintaining sleep, or nonrestorative sleep is reported by about 10–15% of the general population [Roehrs et al., 2000]. In addition, approximately 30% of persons with persistent insomnia in the general population report having used alcohol to help them sleep in the past year, with 67% of those individuals reporting that it was effective [Ancoli-Israel and Roth, 2000]. Studies of healthy normals sleeping at their usual bedtimes do not adequately represent the hypnotic potential of ethanol in persons with insomnia. In healthy, normal subjects sleep latency and sleep efficiency are already optimal and further improvement is difficult to demonstrate. Ethanol's effects on measures of sleep induction and maintenance in healthy individuals are minimal and inconsistent [Roehrs and Roth, 2001]. Furthermore, the doses used in the healthy normal studies are generally much larger (i.e., BrEC > 0.05%) than insomniacs typically report using (i.e., 1–3 drinks).

A recent study compared the effects of a low dose of ethanol (0.5 g/kg) on the sleep of insomniacs and age-matched healthy individuals [Roehrs et al., 1999]. The sleep of the insomniacs was improved with ethanol relative to placebo and the sleep disruption typically found in healthy individuals during the second half of the night with the higher ethanol doses was not observed. Specifically, slow wave sleep was increased to the level of the age-matched controls. When given an opportunity to choose between either a previously experienced color-coded ethanol or a placebo beverage before sleep, the insomniacs chose ethanol while the healthy individuals chose placebo. The average nightly dose self-administered (≤ 0.06 g/kg was possible) by the insomniacs was 0.045 g/kg, which is similar to the dose that improved the sleep of the insomniacs and that insomniacs most often report using at home.

The preference for ethanol at bedtime by insomniacs compared to non-insomniacs (found in the epidemiological data and in this laboratory study) raises two questions about the risks associated with the use of ethanol as a hypnotic. First, does tolerance to the sedative effects develop in insomniacs as it does in healthy individuals? Second, does the ethanol dose

used escalate over repeated nights and does nighttime use generalize to greater daytime use?

Two recent studies explored the extent to which tolerance to the sleep effects develops and whether the dose self-administered by insomniacs before sleep is increased with previous ethanol exposure. In one study, 0.0, 0.3, 0.45, and 0.6 g/kg ($n = 5/\text{group}$) was administered to insomniacs before sleep for 6 consecutive nights [Roehrs et al., 2003b]. Initially, the ethanol increased sleep efficiency at the 0.45 and 0.6 g/kg doses relative to the placebo dose. These improvements in sleep were lost by the 6th night with sleep efficiency returning to that of the placebo group. In another study, 12 insomniacs were randomly assigned to receive 7 nights of either 0.0 or 0.45 g/kg ethanol before sleep with ethanol and placebo presented in color-coded cups [Roehrs et al., 2003a]. Depending on the group, subjects received ethanol or placebo on the 8th night. During the next 7 nights, the preferred beverage was chosen by cup color (with up to three allowable refills). Ethanol pre-exposed insomniacs chose ethanol 53% of nights and placebo pre-exposed chose ethanol 37% of nights. The ethanol pre-exposed group chose more ethanol refills than the placebo pre-exposed group, but the same number of placebo refills.

These data suggest that the hypnotic use of ethanol by insomniacs may initially be therapy-seeking behavior, an attempt to improve their sleep. However, subsequent studies have suggested that this self-medication is associated with tolerance development to ethanol's hypnotic effects and proceeds to the use of higher ethanol doses. An important question is whether the increased hypnotic use of ethanol extends beyond what could be considered the therapeutic context to modify the insomniacs' social drinking habits.

BEHAVIORAL COSTS OF NOT TREATING INSOMNIA

Although behavioral treatments for insomnia generally require additional resources in comparison to pharmacological treatments in terms of financial costs and staff expertise, there is a growing understanding of behavioral strategies used to manage insomnia. Despite this fact, there is a severe shortage in behaviorally trained personnel required to provide adequate treatment to insomnia patients, not to mention the much larger proportion of insomniacs who do not seek treatment. In response to such needs, the clinical and sleep research community have begun to introduce specific educational and intervention programs, which appears to have increased the appreciation for the importance of recognizing and appropriately treating insomnia and other sleep disorders. Unfortunately, not providing insomniacs with effective treatment has behavioral risks. For instance, insomniacs do pursue self-treatment. As the studies cited above regarding the use of alcohol as a hypnotic by insomniacs indicate, what may initially be effective in improving sleep may

become ineffective as tolerance develops. The data also show that the chosen dose will be escalated consequent to tolerance development. Several critical questions remain including (1) whether the insomniac will continue to increase dose to pursue a desired sleep effect, (2) whether other reinforcing effects (i.e., its mood-altering effects) of alcohol will be discovered, and (3) whether this initial therapy-seeking behavior will then develop into drug-seeking behavior (i.e., alcoholism).

CONCLUSION

Insomnia is the most prevalent sleep disorder affecting 10–15% of the general population. In population-based studies severe insomnia has been shown to last for a median of 4 years, with 44% of individuals continuing to suffer from insomnia 10 years later. In addition to its nocturnal effects, insomnia has a significant negative impact on an individual's daily functioning including impaired work performance, lower physical and social functioning, an overall lower quality of life, and an increased risk for subsequent development of psychiatric disease. The economic cost of insomnia related to lost productivity, work-related accidents, absenteeism, and health-care costs is enormous. There is increasing evidence linking the precipitation of insomnia to stress and converging evidence from cognitive, endocrine, neurological, and behavioral domains providing clear evidence for hyperarousal in insomnia. Despite these facts, a consensus regarding the specific etiological mechanisms of this disorder has yet to be found. Work on a possible early predisposition to insomnia is still in its infancy. Although the pathophysiology of primary insomnia remains an enigma, numerous treatments, both pharmacological and behavioral, have been developed and found to be efficacious in controlled studies. Despite the wide availability of pharmacological treatments and increased knowledge of behavioral interventions, the vast majority of individuals with insomnia do not appear to be receiving adequate treatment. Inadequate treatment of insomnia has several important and under-recognized consequences, including subsequent development of psychiatric disease and increased substance use. As a result, there remains a great need for educational programs regarding insomnia assessment, diagnosis, and treatment from the perspective of both the patient and clinician.

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