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CLINICAL REVIEW

Physiological and medical findings in insomnia: Implications for diagnosis and care☆

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SUMMARY

This review will examine objective physiological abnormalities and medical comorbidities associated with insomnia and assess the need to measure parameters associated with these abnormalities for diagnosis and to monitor treatment outcomes. Findings are used to develop a decision tree for the work-up of insomnia patients. Currently available measures and those with possible future predictive value will be discussed. Costs, advantages, and the development of screening laboratory tests will be presented. It is concluded that there is a need to differentially evaluate insomnia patients based upon their comorbidities and the presence of objectively decreased total sleep time to direct optimal treatment. The development of objective diagnostic criteria and treatment outcome goals beyond subjective symptomatic relief will establish insomnia as a true medical problem and improve patient care.

Introduction

Insomnia is an extremely common disorder. It is well known and easily recognized in the general population but complex and controversial for researchers and clinicians. A number of issues cloud our understanding of insomnia. This paper will explore limitations in our understanding of insomnia and suggest new diagnostic approaches and treatment goals.

Major limitations in understanding and treating insomnia include:

1) Is insomnia a symptom or a disorder? This distinction may seem rhetorical, but it is not, because it determines if treatments are being directed toward symptoms rather than actual pathology. Are there pathologies in insomnia beyond subjective decreases in sleep time, and should treatment be directed toward these pathologies?
2) When the subjective complaint of insomnia does not agree with recorded polysomnogram (PSG) findings, which is correct? Is insomnia a subjective disorder or an objective pathology? How should PSG recordings and other laboratory tests be used in the differential diagnosis of insomnia disorders?
3) If insomnia is treated, what is the appropriate treatment outcome metric? Should treatment decrease or eliminate subjective complaints of patients, or address underlying pathology that produces the complaint? Or are these outcomes the same?

Definition of insomnia

The international classification of sleep disorders second edition[1] defines insomnia as: "A **complaint** of difficulty initiating sleep, difficulty maintaining sleep or waking up too early or sleep that is chronically nonrestorative or poor in quality. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep. At least one of the following forms of daytime impairment related to nighttime sleep difficulty is reported by the patient…". From this definition, it is clear that insomnia is a subjective complaint that the patient must report. There are also subjective defining criteria such as a complaint of increased sleep latency or wake time during sleep of sufficient magnitude for a minimum number of nights. Unfortunately, the diagnostic categories do little more than associate the subjective complaint with possible contributing factors (e.g., insomnia due to mental disorder;

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insomnia due to medical problem) or length of suffering (e.g., lifelong insomnia) rather than identifying unique pathological mechanisms that would point toward specific treatment. The truth is that we know relatively little about insomnia and what is known has rarely been applied to classify patients, to understand the relationship between complaints and underlying physiology, or to treat selectively. As a result, studies look at a hodgepodge of patients who might reflect different underlying pathologies and thus fail to find differences due to large population variability.

As an example of a more complete differential, chest pain patients are not just given a diagnosis of chest pain and universally treated with pain medication. Instead, physicians use a differential diagnosis like that presented in Table 1. None of the items except benign chest wall pain refer back to the subjective complaint. Moreover, the differential diagnosis of chest pain frequently requires objective tests such as an electrocardiogram (ECG) to help confirm an underlying disorder and may lead to other tests. However, the ECG can also be normal in a patient having a heart attack. If an investigator averaged ECGs of all patients referred for chest pain, would ECG be considered a valid means of identifying chest pain or differentiating these patients from normals? Similarly, insomnia, which is associated with more than 40 conditions, is not always associated with an abnormal PSG. As with ECG, PSG may not always be abnormal, but PSG may still be a valuable tool in differentiating pathology in insomnia.

The major goal of this paper is to review physiological findings in insomnia as keys to pathology. It will examine these measures as possible clinical markers and focus on the impact of treatment. It will also examine comorbid medical problems associated with identified pathophysiology and explore evidence to support a differential, i.e., pathology supporting unique treatment options. Finally, the paper will suggest a new clinical guideline for evaluation of insomnia patients. The guideline will provide a checklist of associated risks. Hopefully, a global medical evaluation of insomnia patients will identify important comorbidities and suggest treatment strategies to improve sleep and decrease associated risks. The collection of global screening data will also 1) allow objective placement of insomnia patients into homogenous subgroups based on specific pathology; 2) provide multiple treatment outcome measures; and 3) suggest areas for research.

Physiological markers and risk factors in insomnia

A number of objective tests have been used to compare primary (or idiopathic) insomnia patients and controls. The most commonly used test has been the PSG. Approval of hypnotic medications has been partly based on demonstrating shortened PSG-derived sleep latency and/or time awake after sleep onset in primary insomnia patients who were selected based on increased objective sleep latency or time awake after sleep onset (called objective insomnia in this paper). However, PSG differences were less apparent in studies where patients were selected based on subjective complaint alone. Abnormal PSG results, primarily decreased total sleep time, have been associated with significant clinical pathology and will be discussed in the section on Clinical outcomes associated with insomnia.

Table 1
Differential diagnosis of chest pain.[92]

- Angina
- Heart attack (The electrocardiogram (ECG) is an important and sometimes central tool used to establish the diagnosis of myocardial ischemia or infarction. New abnormalities in the ST segment and T waves represent myocardial ischemia and may be followed by the formation of Q waves. However, the electrocardiogram may be normal or nonspecific in a patient with either ischemia or infarction.)
- Heartburn (gastroesophageal reflux)
- Benign chest wall pain
- Anxiety or panic disorder
- Asthma or other pulmonary condition

Patients with primary insomnia can be also differentiated from controls based on a number of objective physiological measures including beta frequency waves in the electroencephalogram (EEG), cortisol levels, heart rate/sympathetic activation, multiple sleep latency test (MSLT), blood pressure, blood glucose, metabolic rate, inflammation markers, immune system deficits, ghrelin/leptin assays, and levels of gamma-aminobutyric acid (GABA) in the brain.[2] These physiological measures have linked insomnia with increased risk of hypertension, diabetes, depression, pain, chronic obstructive pulmonary disease (COPD), and death.[3–5] Despite these links, most physiological measures have not been used to objectively differentiate types of insomnia patients or as treatment endpoints.

A summary of measures and representative studies is presented in Table 2. A general problem with insomnia research is that different definitions are used to classify insomnia. The definitions used in this paper to classify study populations are listed in Table 2a. Objective insomnia will refer to insomnia defined by PSG sleep time; primary insomnia will refer to international classification of sleep disorders (ICSD) criteria for psychophysiological or idiopathic insomnia; subjective insomnia will refer to the use of questionnaires where patients indicate that they have insomnia; and poor sleep will refer to the use of questionnaires where patients report poor sleep (increased sleep latency, awakenings or wake time during sleep). Studies listed in Table 2 are identified by a grouping marker (A–D) to indicate these groups. In general, higher level grouping such as in objective insomnia (A) includes all of the elements of lower grouped studies (i.e., subjective poor sleep and an insomnia diagnosis). This review will focus on physiological markers and clinical risk factors in insomnia patients rather than exhaustive reviews, and will emphasize treatment studies when available.

Beta activity in the EEG

Beta activity in the EEG was significantly increased in insomnia patients in seven of eight studies (see review in[2]). For example, a study by Perlis[6] in patients with primary insomnia found that beta power was significantly higher in insomnia patients compared with normal controls. The mean difference was about 2.5 times the control standard deviation. A second study using cognitive behavioral therapy (CBT) found that beta power was significantly reduced to less than two standard deviations (a 'normal' range on some lab tests) from the Perlis control value and sleep improved in patients with primary insomnia.[7] While CBT therapy significantly reduced the beta measure, it was still not numerically close to the population mean. Unfortunately, a more recent study in patients with primary insomnia found only a non-significant decrease in beta activity that was numerically less than the decrease seen in a control group.[8] However, the use of an objective measure like beta power can allow assessment of group and individual means and comparison with population values. This example demonstrates how treatment success could be based on a return to a normal range of values.

In practice, it would be easy to obtain beta measures from a standard PSG at little additional cost beyond the PSG, if automated beta analysis were designated as an option in the software. If positive treatment results are replicated in future studies, EEG beta analysis could be developed as a clinical measure or combined with other measures.

Cortisol levels

A recent review found that cortisol levels were significantly increased in six of seven studies that compared insomnia patients