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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

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Table 2
Summary of physiological parameters implicated to be abnormal in restricted sleep and insomnia and results from available treatment studies ("+" is a significant positive treatment response; "0" is no significant difference; and "−" is a negative treatment response).

Parameter	Implicated in normal short sleep	Implicated in insomnia (representative)	Insomnia with CBT treatment	Insomnia with pharmacotherapy
Beta EEG (increased)	No, decreased	Yes [6]B	[7]B + [8]B 0	Benzodiazepines increase[93] B −
Cortisol (increased)	Variable	Yes [10]B, [9]A		Doxepin[11] B +, Triazolam[12] D + Ramelteon[13] B 0
Heart rate or sympathetic activity (increased)	Yes	Yes [15]A	Exercise[22] B-C	Lometazepam[18]B 0 Zopiclone[18] B 0
MSLT (lengthened)	Yes	Yes [2]A		Lorazepam[25] A +
Blood pressure (increased)	Yes	Yes [3]A, [27]B		Zolpidem[28] D +
Glycemic control (abnormal)	Yes	Yes [5]A		Melatonin[32] B +
Metabolic rate (increased)	No, decreased	Yes [33]A, [35]B, [36]B		Lorazepam[25] A + Eszoplicone[37] A +
Inflammation (increased)	Yes	Yes[38]A, [39]B		Etaercept[41] D +
Immunity (decreased)	Yes	Yes[43]B, [42]B		
Ghrelin (decreased)	Yes	Yes [48]A		Eszpiclone[51] A +
GABA (decreased)	No	Yes [52]B, [53]B		

CBT: cognitive behavioral therapy; EEG: electroencephalogram; GABA: gamma-aminobutyric acid; MSLT: multiple sleep latency test.

Table 2a
Patient study classification scheme (letter code appears in Table 2).

A − Objective insomnia: the use of PSG total sleep time to define insomnia
B − Primary insomnia: the use of the ICSD criteria for psychophysiological or idiopathic insomnia. Some studies may also include patients with comorbid insomnia
C − Subjective insomnia: the use of questionnaires where patients classify themselves as having insomnia
D − Poor sleep: the use of questionnaires where patients report poor sleep (increased sleep latency, awakenings or wake time during sleep)

PSG: polysomnogram; ICSD: international classification of sleep disorders.

with controls.[2,9] In one study,[10] hourly blood cortisol levels during sleep were significantly elevated in primary insomnia patients compared with controls. In a second study,[11] patients with primary insomnia treated with doxepin 25 mg showed a significant decrease in cortisol levels measured each hour during the night but did not numerically reach control levels. Elevated cortisol levels in insomnia patients have also been reduced with triazolam and loprazolam with rebound at withdrawal.[12] However, this was not the case with ramelteon.[13] Examination in larger groups of patients or more specific patient selection criteria might improve differentiation but use may be limited if frequent blood sampling is required for reliable measurement. However, refinement of measures such as salivary cortisol[14] with control of extraneous factors such as alcohol use, smoking, food, and exercise could improve clinical use of this measure.

Heart rate/sympathetic activity

Two of three studies have shown significant elevation of heart rate in insomnia patients compared with controls and a meta-analysis of the three studies showed a significant overall 5.7 beats per min difference with a standard deviation of 2.04.[15–17,2] While the mean difference in heart rate was greater than two standard deviations, participants in the positive studies were objective insomnia patients carefully selected and matched. Real world variability in heart rate makes group differentiation more difficult. In addition, one study of lormetazepam and zopiclone did not find changes in heart rate[18] in primary insomnia patients as a function of treatment.

Analysis of all night heart rate variability (HRV) has shown both primary insomnia patients and individuals with PSG-defined situational insomnia have increased low-frequency and decreased high-frequency electrocardiographic spectral power, suggesting increased sympathetic activation and decreased parasympathetic activity compared with good sleepers.[15,19] These results were not replicated in a study with a single afternoon observation or a study with a wide age range.[20,21] Both resting heart rate and sympathetic balance can be significantly influenced by exercise training. A recent review and meta-analysis[22] found that exercise training for 10–16 wk was associated with decreased sleep latency in the combined group of insomnia patients. Although studies have not directly documented changes in resting heart rate or variability, improvement in $\dot{V}O_2$max compared with placebo of about 10%[23] should be accompanied by a decrease in resting heart rate of about ten beats per minute in sedentary individuals.[24] While heart-related measures can be easily obtained from a standard PSG, they do not always clearly differentiate patient groups. However, collection of even simple data like heart rate at sleep onset and sleep offset or mean heart rate across the night could serve as a simple marker for cardiac concern.

Multiple sleep latency test (MSLT)

A meta-analysis of the MSLT found that the average MSLT value for objective insomnia patients in comparison with controls was 16.1 ± 4.4 min (108 patients) vs 13.6 ± 4.8 min (83 controls).[2] It has been suggested that the MSLT actually measures the combined effects of the sleep system (sleep restriction associated with poor sleep) and the arousal system. Therefore, insomnia patients have sufficiently increased arousal system effects to offset the sleep restriction to provide longer than normal MSLT values. The mean difference of 2.5 min is less than one standard deviation and suggests that differentiation of insomnia patients versus normal sleepers by MSLT alone is problematic. However, a study of lorazepam 0.5 mg three times a day (tid)[25] in objective insomnia has shown that a significant decrease in MSLT (from 15.4 min to 13.0 min) was a positive treatment benefit.

Another study looked at sleep restriction in patients with primary insomnia.[26] Primary insomnia patients, who had an average total sleep time of 334 min (sleep efficiency of 71%) on screening had their total sleep time reduced to 265 min for a week. MSLT latencies decreased from 15.6 min at baseline to 11.1 min after a week of restricted sleep showing that sleep restriction successfully reduced the MSLT to a normal value.

Sleep restriction (SR) is a core component of cognitive behavioral therapy for insomnia. However, it is not known whether SR for insomnia provides long term benefits. SR, which 'normalizes' the

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MSLT, may have clinical benefit because it consolidates sleep during limited nocturnal hours. However, one risk associated with SR is that it imposes objective sleep restriction (i.e., decreases clock time in bed) based upon subjective sleep times and could therefore result in significant reduction in total sleep time. The short sleep time may increase risks for hypertension, abnormal blood sugar and other pathology while perhaps masking the underlying problem with sleep deprivation. Research is necessary to understand clinical outcomes associated with sleep restriction in insomnia patients, and additional work is necessary to use long nap latencies as a true clinical marker. The MSLT has the benefit of being a standard clinical test already performed in sleep centers, but it is also a relatively time consuming and expensive test that still needs acceptance as a measure of arousal.

Blood pressure

Lanfranchi et al.[27] documented significantly higher systolic blood pressure and decreased systolic pressure dipping across the night in primary insomnia patients compared with controls. The difference in systolic blood pressure of 9 mmHg was significant but was also less than one standard deviation for both groups. The only significant difference in the groups based on PSG recordings was fewer periodic limb movements in the insomnia group. This suggests it was not differences in EEG sleep, such as increased wake time or arousals, that caused the blood pressure difference. However, it is unknown if nocturnal blood pressure is even more abnormal in objective insomnia patients. In a recent study, Huang et al.[28] showed that patients with poor sleep and controlled hypertension who continued to have a non-dipping blood pressure pattern at night had significantly improved (dipping) nocturnal blood pressure when treated with zolpidem 10 mg at bedtime. Other treatment combinations including zolpidem given to patients with good sleep and placebo administration to patients with poor sleep did not result in significant improvement. Fifty percent of the patients with poor sleep were converted to a normal nocturnal blood pressure profile versus 9% in the placebo group. These data are important because these patients had previously been diagnosed with hypertension, were treated, and were on stable therapy at the time of entry into the study (but were at elevated risk secondary to their lack of blood pressure dip during sleep). The data suggest that hypertensive patients who report insomnia need to have a formal sleep evaluation to rule out sleep apnea along with nocturnal blood pressure measurement to determine if additional sleep-related therapy is necessary.

Unfortunately, the hypertension treatment studies did not include PSG recordings, so the degree of objective sleep disturbance is not known. However, the fact that there was improvement only in patients with poor sleep implies that only the combination of poor sleep and medication produced significant benefit. It is unclear what percent of objective and subjective insomnia patients lack a nocturnal drop in blood pressure that is of sufficient magnitude to benefit from sleep-related therapy and what the most appropriate therapy would be. Treatment with zolpidem was beneficial, but would an arousal-blocking blood pressure medication such as clonidine at bedtime be equally beneficial in improving sleep and controlling nocturnal blood pressure?

Glycemic control

A few studies have examined blood sugar levels in patients with reduced and poor sleep. In one study, patients with subjective insomnia were found to be at increased risk for an abnormal glucose tolerance test.[29] Patients with diabetes and poor sleep were found to have significantly worse levels of glucose and insulin compared with diabetes patients with better sleep,[30] but poor sleep patients without diabetes did not have elevated levels. In a small study of sleep center patients, the incidence of abnormal glucose tolerance test results was not greater in a group of 19 primary insomnia patients versus controls (18% vs 12%).[31] Finally, in a treatment study, 2 mg of prolonged release melatonin given nightly for five months to a group of 36 type 2 diabetes patients with subjective insomnia (as an extension of a double blind crossover treatment versus placebo study)[32] showed significantly improved sleep efficiency and decreased awakenings based on actigraphy and significant improvement in glycemic control as measured by HbA1c.[32] The authors justified the use of prolonged-release melatonin in this clinical setting because of potential relationships between melatonin and insulin production.

Research is needed to understand the exact relationship between insomnia and blood sugar control and diabetes risk reduction associated with treatment of sleep in both diabetes and insomnia patients. It is also important to test whether the beneficial effects of melatonin are secondary to a link with insulin or whether other means of improving sleep efficiency would also have a positive impact on HbA1c.

Metabolic rate

Significant increases in whole body metabolic rate have been shown in patients with primary insomnia selected for both objective insomnia and paradoxical insomnia[33,34] and matched for sex, age, and weight. Relative data for these groups with respect to their individual control groups are shown in Fig. 1 and show greater elevation in whole body metabolic rate in objective insomnia patients compared with paradoxical insomnia patients. The elevated metabolic rate was also found in within-sleep stage comparisons, so the data could not be explained on the basis of increased wake time in the insomnia patients. The average metabolic rate during sleep for normals from these two studies was a $\dot{V}O_2$ of 266 ml/min. In the baseline study with objective primary insomnia patients,[33] the average $\dot{V}O_2$ was 296 ml/min. In a lorazepam treatment study, the placebo value for mean $\dot{V}O_2$ during sleep for the insomnia patients was 299 ml/min.[25] This $\dot{V}O_2$ was significantly reduced with lorazepam at 1.5 mg at bedtime (hs) and 0.5 mg tid compared with placebo to 285 ml/min.[25] In comparison with these values, patients with paradoxical insomnia had a mean of $\dot{V}O_2$ 277 ml/min during a baseline sleep recording that was significantly higher than a control group of good sleepers.[34] As was seen in studies measuring beta EEG and cortisol levels, treatment for insomnia was associated with a reduction in $\dot{V}O_2$ that did not reach the level of controls.

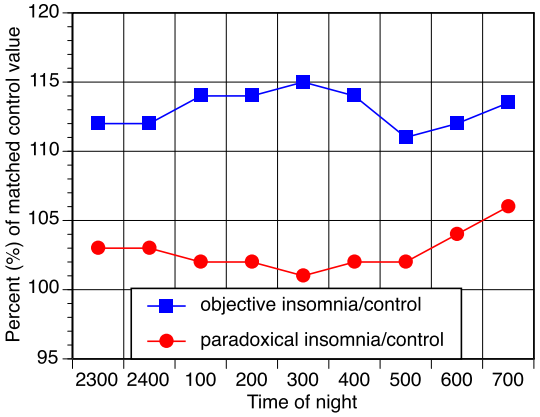

Fig. 1. Whole body metabolic rate percent increase in objective and paradoxical insomnia patients.[33,34]

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Unfortunately, the adequacy of $\dot{V}O_2$ as an insomnia measure cannot be easily evaluated because variability data are not available from any of these studies and oxygen consumption is only rarely measured during sleep tests. However, the availability of screening calorimetry devices has made recording of $\dot{V}O_2$ during sleep possible.

Other insomnia studies have documented increased brain metabolic rate both asleep and awake using functional neuroimaging.[35]Primary insomnia patients had less decline in metabolism during sleep in the reticular system, hypothalamus, thalamus, insular cortex, amygdala, and hippocampus compared with controls. This suggested increased general arousal and increased activity in the "emotional arousal areas" of the brain. In another study,positive correlations between wake time during sleep and brain metabolic rate in areas associated with emotion were found.[36] These differences have not been suggested as clinical measures probably because of expense. However, treatment with eszoplicone in primary insomnia patients reduced non-rapid eye movement (NREM) metabolism in brainstem arousal centers, thalamus, and parietal cortex.[37]

Inflammation markers

Recent studies have begun to document an association between insomnia and inflammation. Proinflammatory cytokines such as interlukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) have been shown to have a significantly different pattern of secretion in objective insomnia patients compared with controls.[38]A study of primary insomnia patients with diabetes showed significantly increased IP-10 (an interferon-inducible protein-10 linked to inflammation) compared with diabetes patients without insomnia.[39]Another study has shown that hemodialysis patients who were poor sleepers based on the Pittsburgh sleep quality index (PSQI) had increased high sensitivity C-reactive protein (hsCRP) compared with better sleeping patients and that PSQI scores showed significant positive correlations with hsCRP, IL-1β, and triglyceride levels.[40]Additional studies of inflammation markers in patients with objective insomnia are greatly needed. One study has examined treatment of rheumatoid arthritis in patients with poor sleep as determined by PSQI with anti-TNF-αmedications and found a significant decrease in wake time during sleep and increased sleep efficiency after two months of treatment.[41]Better controlled studies in well-defined insomnia populations are needed.

Immune function

Reduced sleep impacts the immune system. Two studies have directly examined immunity in primary insomnia patients and controls and have shown significant decreases in the numbers of CD3+, CD4+ and CD8+ T cells[42] and with reduced natural killer cell (NK-cell) responses[43] in patients compared with controls. Other large studies have shown a relationship between poor sleep and infection. A 1997 study in a group of 276 healthy volunteers showed that a subjective sleep efficiency of less than 80% (poor sleep) was independently associated with a greater risk of developing an upper respiratory infection.[44]A prospective study that followed a group of 153 healthy individuals prior to and after a viral challenge found that 88% of the participants became measurably infected.[45]Sleep diaries showed that pre-infection sleep efficiency was again independently associated with risk of infection with 16 possible confounds controlled. Odds ratios were significantly increased for participants with sleep efficiency less than 93% (lower third of sample) and lower than 85% (less than 10% of sample).

A recent study of sleep duration and pneumonia risk attempted to better differentiate types of reduced sleep duration and better control for sleep apnea while evaluating adequacy of sleep.[46]A report of inadequate sleep was related to a 1.44-fold increased risk of pneumonia when controlled for eight confounders including body mass index (BMI), snoring, and hypertension and even with control for habitual sleep duration. Interestingly, risk was not increased in individuals who only reported short (but adequate) sleep. Prather et al.[47] gathered actigraph and sleep diary data from patients obtaining a hepatitis B vaccination. Shorter sleep durations, especially less than 6 h, were associated with decreased likelihood of clinical protection. However, this relationship was with sleep duration rather than sleep efficiency, as in the earlier studies, suggesting that individuals with decreased time in bed as opposed to poor sleep (i.e., suffering from sleep deprivation rather than insomnia) were most at risk. However, no data suggest that insomnia patients with short sleep durations are at less risk for any pathology than normals with short sleep durations. The immunity studies with both primary insomnia patients and poor sleepers suggest significant relationships but additional work including treatment studies showing improved immune function are needed.

Ghrelin and leptin

Studies have shown that sleep deprivation and sleep restriction are associated with abnormalities in ghrelin and leptin, and this suggests that sleep loss could be associated with weight gain. These studies suggest that these two hormones might also be abnormal in insomnia patients. Increased leptin was found in subjective insomnia patients with diabetes as compared with diabetes patients without insomnia.[39] Another experiment found that primary insomnia patients had significantly decreased ghrelin at night compared with age-and-weight-matched normal sleepers.[48] Sleep deprivation studies found decreased ghrelin levels at night with increased ghrelin levels the following day, and these may be associated with appetite and the amount of food intake.[49] The rate of insomnia has been reported as elevated in overweight men, but the potential role of sleep apnea was not controlled.[50] However, one abstract reported significant weight loss in a large group of objective insomnia patients during effective long term treatment with eszopiclone.[51] Weight cannot be used as an indicator for insomnia, but mild weight loss, in association with other clinical changes, might be an indicator of treatment efficacy.

GABA

GABAergic nuclei play a key role in sleep initiation and maintenance. Using proton magnetic resonance spectroscopy to estimate GABA levels in the brain, three studies have shown significant differences in patients with primary insomnia compared with controls.[52–54]

Unfortunately, one of the studies showed significantly increased rather than decreased GABA levels in insomnia patients.[54] However, development of economical tools to measure GABA could provide another means of tracking insomnia and treatment response.

Clinical outcomes associated with insomnia

Clinical studies suggest that insomnia should be a significant risk factor for many medical disorders and all-cause mortality. Implicated disorders will be reviewed by class.

Hypertension and cardiovascular disorders

Many studies have shown an association between insomnia and elevated cardiovascular risk (see meta-analysis by Schwartz et al.[55]). In a large study including PSG recordings, Vgontzas et al.[3] have shown an elevated risk for hypertension in patients with

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insomnia who also slept for 6 h or less on their PSG but not for insomnia patients who slept more than 6 h on their PSG or normal subjects who slept less than 5 h on their PSG (see Table 3). The most significant hypertension risk was in insomnia patients with a PSG sleep time of 5 h or less. All analyses were adjusted for age, race, sex, BMI, diabetes, smoking status, alcohol consumption, depression, and sleep disordered breathing.

These data suggest that hypertension risk increases as PSG total sleep time decreases in patients with insomnia. Patients who complained of poor sleep and slept for less than 5 h on their PSG also had an increased risk for hypertension but much lower than patients with objective insomnia. This study was the first to suggest that medical risk for insomnia patients is dependent upon the severity of the insomnia.[3] It is also one of few studies to classify severity of insomnia based upon an objective measure of total sleep time. These data suggest that patients with objective deficits in total sleep time and a report of insomnia are at much greater risk than patients with only a subjective complaint or patients without insomnia who have a short total sleep time. These data also expose a serious problem in the majority of insomnia studies, which have selected patients based entirely upon subjective report of insomnia. Such studies minimize the power of their results by combining patients with and without objective reduction in total sleep time thereby combining the insomnia risk ratios in Table 3 in an unknown proportion.

The same investigators re-evaluated these patients 7.5 y later and found the risk for development of hypertension during the 7.5-y period was again significantly increased in objective insomnia patients in analyses controlled as in the first study.[56] The level of risk was similar to that seen for patients with sleep apnea.[56] While treatment studies have suggested that improved sleep does improve nocturnal blood pressure, no long-term studies have examined the extent to which treatment for insomnia reduces the risk for development of hypertension or other cardiovascular disorders.

Diabetes

Several studies have shown an association between insomnia and elevated diabetes risk.[57–61] Patients with diabetes and insomnia have elevated insulin, IP-10 and leptin compared with diabetes patients without insomnia.[39] Vgontzas et al. also examined risk ratios in their PSG population for patients with diabetes or elevated blood sugar. Similar to hypertension, patients with objective insomnia who slept 6 h or less were at increased risk for diabetes while patients with insomnia who slept for more than 6 h were not (see Table 3). These data were adjusted for age, race, sex, BMI, smoking status, alcohol consumption, depression, and sleep disordered breathing. Normal sleepers who slept less than 5 h in the lab were not at risk. In contrast with the hypertension data, poor sleepers who slept for less than 5 h in the lab were not at increased risk for diabetes. However, the data consistently suggest that the risk for diabetes or abnormal glycemic control increases as insomnia increases, as measured by complaint and total sleep time reduction, and these are both necessary for the increased risk. Treatment with 2 mg of prolonged release melatonin administered to type 2 diabetes patients with subjective insomnia significantly improved sleep efficiency and glycemic control as measured by HbA1c.[32] Despite the suggestion that improving sleep may improve diabetes markers, no studies have examined whether long-term treatment of insomnia will reduce the risk of development of diabetes.

Depression

Insomnia is known to be a strong predictor for the later development of depression, as shown in a recent meta-analysis.[62] A recent study that included both PSG and subjective data in a sample of 711 patients with depression found that 73% of patients reported insomnia symptoms and concluded that objectively measured prolonged sleep latency and short sleep duration independently or in conjunction with subjective insomnia were risk factors for poor depression treatment outcome.[63] Several studies have also shown that concomitant treatment of insomnia and depression results in both improved sleep and a more rapid clinical response with lower doses of antidepressant medication.[64,65] Interestingly, these latter studies were performed with fluoxetine, an antidepressant that is often associated with insomnia. Whether antidepressant response rates would be better in depressed patients with insomnia given a sedating antidepressant at bedtime or the combination of the sedating antidepressant at bedtime with the hypnotic has not been explored. While treatment of insomnia without concomitant use of an antidepressant has not been shown to adequately treat depression, a large questionnaire study has shown that depressive symptoms were worse in a group with insomnia symptoms using sleep medication and significantly lower in a group without insomnia symptoms using sleep medication.[66] These data have many possible interpretations, but one is that successful treatment of insomnia could reduce the risk of development of depression. In another study, patients with bipolar depression were treated with ramelteon or placebo along with their normal psychiatric medications for 24 wk or until relapse, defined as a depressed or manic event.[67] Patients receiving ramelteon were significantly less likely to relapse and had a significantly longer time until relapse (188 vs 84 days). These results suggest that prior treatment for insomnia may delay or prevent the development of a depressive episode.

Pain

There is no clear surrogate for pain-associated disturbance in the PSG. However, reduced sleep increases pain sensitivity,[68] and this could create a self-perpetuating cycle where pain produces insomnia which exacerbates pain. A 2012 review including 385 studies with sleep and pain outcomes found that medications that produced the worst sleep outcomes were also very likely to produce poor pain outcomes, and the effects were greatest for headache and musculoskeletal pain.[69] In a study of patients after knee surgery, non-insomnia patients treated with zolpidem had improved sleep, reported less pain, and used less pain medication than patients in the control group.[70]Studies using hypnotics

Table 3
Medical condition risk ratios based on PSG recordings.

Patient group	Hypertension risk ratio[3]	Diabetes risk ratio[5]	Male mortality risk ratio[4]	Incident hypertension risk ratio[56]
Insomnia and PSG <5 h	5.12 (2.22–11.79)	2.95 (1.24–7.03)		
Insomnia and PSG 5–6 h	3.53 (1.57–7.91)	2.07 (0.68–6.37)	4.0 (1.14–13.99)	3.78 (1.58–8.95)
Poor sleep and PSG <5 h	2.43 (1.36–4.33)	1.06 (0.53–2.15)		1.34 (0.74–2.41
Insomnia and PSG >6 h	1.31 (0.70–2.46)	1.10 (0.40–3.03)	0.74 (0.7–8.37)	0.85 (0.30–2.40)
Normal and PSG <5 h	1.13 (0.79–1.62)	1.10 (0.68–1.79)	1.34 (0.78–2.28)	0.88 (0.57–1.37)

PSG: polysomnogram.

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(zopiclone, zolpidem, and triazolam) and sodium oxybate in patients with pain associated with fibromyalgia and rheumatoid arthritis found self-reported improvement in sleep and improved pain ratings in one study with triazolam[71] and a large study with sodium oxybate.[72] Four studies used cognitive behavioral therapy for insomnia in groups of insomnia patients with chronic pain and measured both sleep and pain outcomes.[73–76] Two of the four studies found significant improvement in both sleep variables and in pain outcome measures.[75,76] Although it is possible that hypnotic medications have a direct impact on pain that reduces the need for additional pain medication, the success of behavioral therapy for insomnia on pain reduction makes a stronger case that improvement in sleep alone could reduce chronic pain. Research needs to address whether pain is elevated in patients with primary insomnia and especially those with objective insomnia. Treatment of insomnia in individual patients with increased pain sensitivity unrelated to a comorbid diagnosis may also reduce pain, and pain evaluation could be an important component of insomnia consults.

Mortality

Questionnaire studies looking for links between insomnia and mortality have been inconsistent.[77–80] Three recent studies found an increased risk for all-cause death for patients reporting nearly everyday insomnia[81]; decreased survival for patients with insomnia and COPD[82]; and increased mortality within a year of inpatient re-habilitation in relation to Pittsburgh sleep quality index scores.[83] Unfortunately, all studies were limited by inability to actually diagnose insomnia or differentiate it from poor sleep caused by other sleep disorders. A large-scale PSG study that controlled for sleep disordered breathing (and age, race, education, BMI, smoking status, alcohol use, depression, hypertension, and diabetes) showed a significantly increased risk of mortality in males (Table 3) with insomnia who slept for less than 6 h, but not for males with insomnia who slept longer or normal males who slept less than 5 h. Significant risk relationships were not found in females, perhaps because few women in the sample died.

No multi-year PSG studies examining mortality rate in insomnia patients with and without treatment have been published. However, several questionnaire studies have associated general sleeping pill use with increased mortality (see review[84]). Many patients using hypnotic medicine in these studies still report significant insomnia (possibly due to tolerance or inadequate or inappropriate treatment). While these studies statistically control for other medical problems such as cardiovascular disease or depression, it is known that insomnia can also be a strong predictor of the future development of these disorders. Therefore, when studies control for a disorder such as depression by asking about that diagnosis in an initial questionnaire, they miss the fact that depression or other life-limiting disorders may develop later and be responsible for death. One example of such statistical problems replicated the classic finding of increased risk of death for both short and long sleepers, but then split the sample by age and showed that the increased risk associated with both short and long sleep durations disappeared in the younger individuals (aged 32–59 y).[85] It was found that both long and short sleep durations increased greatly in 70 and 80-y-old individuals, but this suggests that changes in sleep duration were common starting only a few years before death and might reflect inflammatory processes or undiagnosed underlying medical or psychiatric problems in low socioeconomic individuals rather than long-term consequences. Short-term treatment studies suggest improvement in risk factors associated with increased mortality, but long-term prospective treatment and outcome studies are essential for understanding the actual course of insomnia and the role of treatment.

Objective versus subjective insomnia

Few studies have looked at differences between patients who have a subjective report of insomnia but relatively normal objective sleep parameters (e.g., paradoxical insomnia) and those patients who have both a subjective report of insomnia and objectively poor PSG-defined sleep. Two studies that examined whole body metabolic rate in these two groups of patients showed that metabolic rate was significantly increased throughout the night in both groups but that the increase was greater (about 13 vs 4%) in patients with objective insomnia.[33,34] These comparative data, plotted in Fig. 1, suggest that objective insomnia may be a more severe type of insomnia as opposed to a different disorder, as suggested by the work by Vgontzas and colleagues.[86] In one analysis, it was suggested that paradoxical insomnia patients could be characterized by having the greatest underestimation of sleep duration and the greatest elevations on anxiety and ego strength (or poor resources for dealing with stress) on the Minnesota multiphasic personality inventory (MMPI). Other studies have shown that patients with objective insomnia are more likely to have other abnormal physiological findings including increased catecholaminergic activity,[43] increased sympathetic or decreased parasympathetic activity,[15,87] increased cortisol,[9] and increased beta EEG during NREM,[88] in addition to hypertension, diabetes and greater mortality.

The several studies that have used PSG measures to quantify insomnia pathology based upon objective total sleep time[3,5,56,86,63] have suggested that medical risk in insomnia increases directly as total sleep time is reduced but is much less strongly related to subjective reports typically used to make the diagnosis of primary insomnia. This split in association is important because it suggests that meager results reported in studies of primary insomnia patients may be related to the mixture of patient groups (i.e., insomnia patients with and without reduced sleep time). Thus future insomnia research needs to consistently split these groups to better understand the dynamics of each.

Insomnia research questions

These studies suggest that the same physiological activation that increases the risk of medical problems also increases the risk for insomnia. Alternatively, insomnia itself could exacerbate these conditions. Insomnia treatments have reduced elevated measures such as beta EEG activity and cortisol level, but, it is not clear whether this improvement is a direct effect of the treatment or if it is secondary to improved sleep. Unfortunately, long-term studies of risks and risk reduction following long-term use of hypnotics have not been done for any of these conditions. The study by Huang et al.[28] showed that treatment with a hypnotic only improved elevated nocturnal blood pressure in patients with poor sleep, again suggesting that improvement in sleep is the major means of risk reduction.

Other important questions include: 1) Is improvement in sleep a general rather than an illness-specific phenomenon (i.e., does improvement of sleep regardless of type of treatment provide universal benefit for all of these disorders or are there specific conditions that are better treated by one modality)?; 2) What are the specific amounts of sleep reduction that predispose to treatment?; and 3) Is there a difference between subjective versus objective insomnia and treatment response? For example, Garfinkel et al.[32] specifically chose a prolonged release melatonin formulation for their diabetes study, based on evidence that nocturnal melatonin may be abnormal in patients with diabetes and that there is a link between melatonin production and insulin. Unfortunately, melatonin was not tested against another therapy to determine if the treatment effect was specific to melatonin or due to the improved sleep associated with melatonin. These questions

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can only be answered empirically and emphasize the need to develop a true neurophysiological understanding of insomnia as it operates with each co-morbidity.

There are many other chronic diseases that are comorbid with insomnia where research must examine sleep interactions. For example, in COPD patients, one study reported adverse COPD outcomes and mortality related to subjective poor sleep and found that poor sleep was associated with cough, dyspnea and a COPD severity score but not force expiratory volume in 1 s (FEV_1).[82] Poor sleep also predicted new COPD exacerbations, respiratory-related emergencies, and decreased survival even after control for FEV_1 and COPD severity score.[82] It is not clear from these data whether insomnia can exacerbate these pulmonary problems or whether patients who are less stable with cough or dyspnea, for example, have associated poor sleep and are also more likely to have exacerbations. Another interacting factor is the role of respiratory medications that are central stimulants in decreasing pulmonary symptoms and perhaps causing poor sleep, which might produce inflammation or in other ways compromise pulmonary status. Studies controlling pulmonary status and measuring both subjective and objective sleep are needed to replicate and better describe the relationship between insomnia and COPD.

Taylor et al.[89] have shown an increased incidence of insomnia in several other medical conditions including cancer, neurologic disease, urinary problems, and gastrointestinal problems. Controlled studies of patients with these medical conditions need to be done to identify increased risks associated with objective insomnia. Directed treatment studies that target sleep and the underlying medical problem, then need to document improvement or reduced risk in those conditions.

To help to clarify the literature, it might be helpful to assess the sensitivity and specificity of the physiological measures to correctly classify insomnia patients from controls. Such classification might also be used to differentiate patients with objective insomnia from those with subjective insomnia or to show increased ability to classify patients with objective insomnia. However, studies have not used this approach.

Development of animal models can also increase our understanding of the relationship of sleep and arousal to clinical issues. To model situational insomnia, rats were placed in a cage previously occupied by a male rat (odor exposure)[90] to produce an acute stress response. Rats exposed to this stress took longer to fall asleep (59 min vs. 32 min in controls) and had increased wakefulness during sleep. The rats were sacrificed 5.5 h later, and Fos expression was found to be significantly elevated in the cerebral cortex, limbic system and parts of the arousal (specifically locus coeruleus) and autonomic systems compared with controls. However, Fos expression was also found in the sleep-promoting areas of the brain. These dual findings suggested that the rats were displaying "simultaneous activation of the sleep and arousal systems".[90, p 10,173] The rats also showed increased high-frequency EEG (gamma) during sleep recordings after the odor stress. Other data showed that lesions in the limbic system or arousal system were associated with improved sleep and normal gamma amounts during sleep after odor exposure. The finding of activation in brain sleep centers is an indicator that the poor sleep was not secondary to reduced drive for sleep but rather to abnormal activation in arousal systems when sleep was attempted. These results also document specific sites of brain activation that could become treatment target sites. While human physiology is different from the rat, this study shows the value of an animal model for understanding both the neurophysiological impact of insomnia and is helpful in directing the development of specific agents to target and inhibit specific brain arousal sites. Such agents would not necessarily be traditional sedatives or hypnotics.

How should insomnia patients be evaluated?

The realization that objective insomnia is related to hyperarousal and medical problems such as hypertension and diabetes while subjective (or paradoxical) insomnia appears to be more associated with psychological issues suggests that insomnia is not a single disorder. PSG can differentiate insomnia patient categories to direct treatment. However, insomnia is a complex problem, and the evaluation of an insomnia patient needs to include a broad range of parameters.

The results of this review have been used to construct an insomnia diagnostic flow sheet, seen in Fig. 2. Several simple, inexpensive measures such as sleep logs, Epworth sleepiness scale (ESS), fatigue scoring scale (FSS), Ford insomnia response to stress test (FIRST), Beck depression inventory, BMI, blood pressure, heart rate, thyroid tests (thyroid stimulating hormone (TSH), T4), complete blood count (CBC) with sed rate, HbA1c, and pain rating scale are suggested at the initial consult to screen for comorbidities and establish baseline levels. Positive findings on these tests may point to treatment of a comorbid condition that also resolves insomnia. Lack of comorbid findings or persistence of insomnia would lead to consideration of more expensive, more involved, or directed tests including screening oximetry; a blood pressure or heart rate log; hsCRP; cardiac evaluation with lipid profile, ECG, cardiac computed tomogram (CT), or echocardiogram; pulmonary function test (PFT); connective tissue disease panel; immune globulins assays, or CD4/CD8. These tests may suggest other pathology such as sleep apnea, hypertension, cardiac problems, pulmonary problems, inflammation, or reduced immunity. Directed therapy for medical problems suggested by these tests may also improve sleep. However, even patients treated for conditions like hypertension may still report insomnia and if so should proceed to the PSG for insomnia (PSGI). PSGI would include the parameters of a classic PSG but with additional directed components. For example, nocturnal or 24-h ambulatory blood pressure monitoring would be added for patients with any history of hypertension or elevated blood pressure to determine nocturnal dipping. HRV and beta power parameters could be derived from the PSG and might be of particular benefit in patients with suspected sympathetic dominance or stress. The PSGI would classify patients as having either paradoxical insomnia, resulting in referral for cognitive behavioral therapy for insomnia (CBTI) therapy[86] or objective insomnia. Patients with objective insomnia would have medical treatment directed at specific abnormalities such as nocturnal non-dipping blood pressure that would include a sleep-related component. Repeated laboratory testing after six months of treatment would document improvement in screening parameters and sleep while also directing further therapy.

For example, consider a patient with chronic insomnia and diabetes with signs of inflammation. This patient would have an HbA1c with other labs at the initial consult and diabetes therapy would be optimized. With a continuing complaint of insomnia, the patient would advance to the next level of evaluation where indicated screens for sleep apnea or other indicated pathology including inflammation would occur. If this patient had positive signs for inflammation despite the previous optimization for therapy for diabetes and a continuing complaint of insomnia, he would pass to the next level of evaluation, which would include PSG, IP-10, and TNF-α. If the patient was found to have a total sleep time of 5 h (objective insomnia), he would receive directed therapy for diabetes associated insomnia, which might include a trial with 2 mg of prolonged release melatonin[32] (and other therapy to reduce IP-10 and TNF-α, if indicated) and follow up to look for improved HbA1c, IP-10, TNF-α, and sleep. If the patient was found to have a total sleep time of 7 h (paradoxical insomnia), he would be referred

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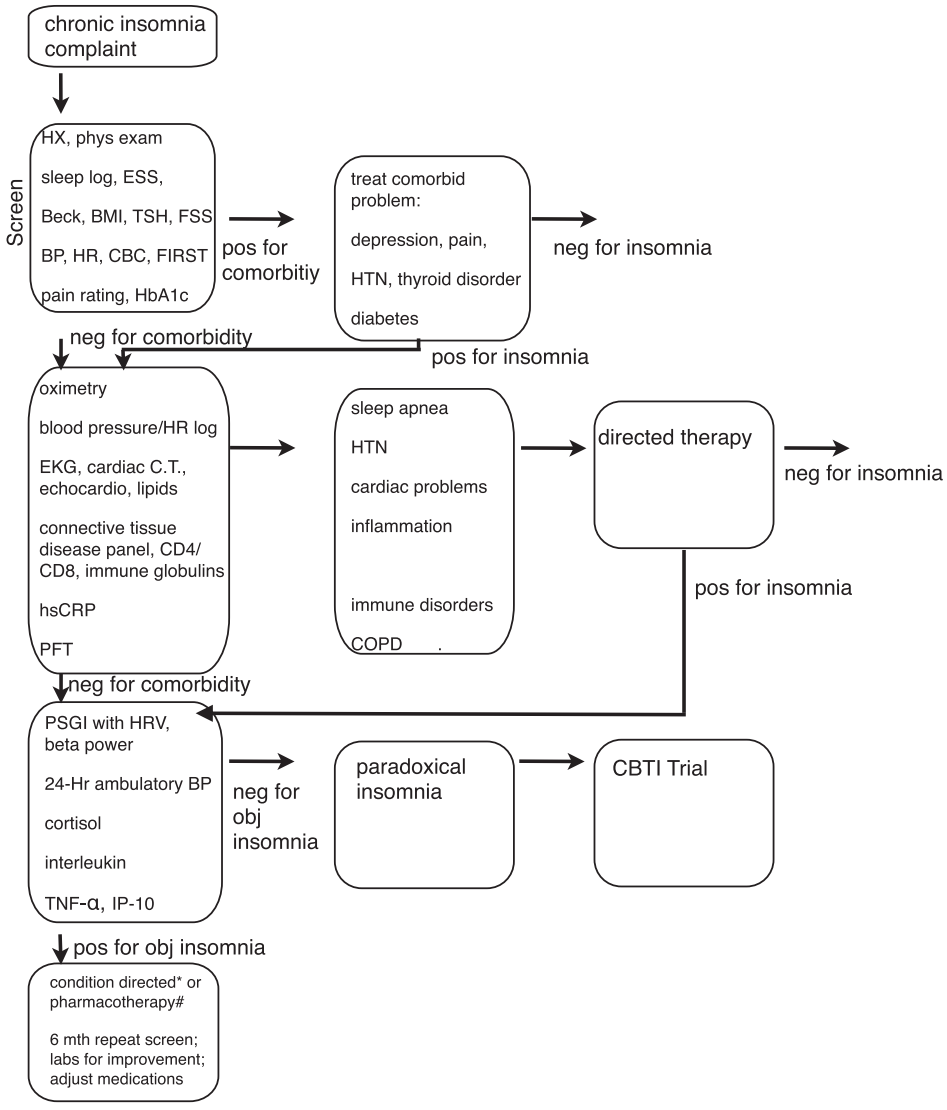

*Might include options such as directed behavioral therapy (for example, blood pressure and insomnia), hypnosis, or exercise
#Might include options such as clonidine (hypertension and insomnia), melatonin (diabetes and insomnia), sedating antidepressants, or hypnotics shown to improve sleep and underlying medical problem

Fig. 2. Proposed insomnia diagnostic flow sheet. *Abbreviations*: BP = blood pressure; BNI = body mass index; CBC = complete blood count; C.T. = computed tomogram; echocardio = echocardiogram; EKG = electrocardiogram; ESS = Epworth sleepiness scale; FIRST = Ford insomnia response to stress test; FSS = fatigue scoring scale; HR = heart rate; HRV = heart rate variability; HTN = hypertension; HX = history; mth = month; neg = negative; obj = objective; PFT = pulmonary function test; Phys = physical; pos = positive; TSH = thyroid stimulating hormone.

for CBTI therapy and returned to his referring physician for continuing care for diabetes and inflammation.

While cost may preclude use of all of these tests in all insomnia patients, costs are minimized by starting with a broad range of inexpensive measures and then narrowing test selection based on preceding results. A broad range of tests will also help in understanding insomnia subgroups. For example, young adults with primary insomnia and reduced sleep time may suffer from an overactive arousal (sympathetic) system that also predisposes them to risk for hypertension and other arousal disorders. These patients may benefit from tests that evaluate sympathetic activity such as heart rate variability or nocturnal metabolic screens and treatments like physical training that reduce sympathetic dominance. In contrast, an elderly adult with more recent development of primary insomnia and reduced sleep time might suffer from decreased activity in the sleep system that might be measured with tests of GABA activity. However, the possibility of multiple types of underlying physiological disorders such as chronic infection or inflammatory diseases implies that complex interactions could occur.

The proposed insomnia diagnostic flow chart is a simplified heuristic device to show movement from the general to the specific in both the scientific and clinical diagnosis and treatment of insomnia by using objective tests to identify, treat, and evaluate patients. However, use of objective tests must be based on an understanding of the pathophysiology of insomnia and requires precise identification of the disorder as a quantitative problem that allows refinement of animal models and use of other correlative brain techniques to identify treatment target sites in the brain.

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Review limitations

A number of considerations are required in the construction of any review. The current review includes a broad range of measures and disorders because insomnia itself is complex. The goal of this presentation was not to provide an evidence-based review of measures of insomnia since there are several recent good reviews and meta-analyses in the area[2,91,62,69] that were used as the basis of discussion. In addition, it became clear that much published research on insomnia has been based on the diagnosis of primary insomnia and that the inclusion of patients without significant reduction of total sleep time has reduced the strength of many results. Therefore, the current paper has relied on studies of objective insomnia where possible and has placed primary emphasis on treatment studies.

The more important goal of the paper has been to try to direct future treatment and research based upon accumulated knowledge. The goal of the diagnostic flow chart is not to denigrate either behavioral or hypnotic therapy but rather to suggest additional therapeutic options and endpoints. There is no rule in medicine that behavioral therapy cannot be used to treat hypertension, and in a similar fashion, there is no reason to believe that CBTI cannot be part of a directed therapy for objective insomnia, especially when there are clear behavioral components such as poor sleep hygiene involved. However, the concept presented here is a differential treatment plan for patients based on *underlying pathology* rather than simply applying the same therapy and endpoint to all patients.

Practice points

1) Insomnia is a complex disorder that requires both a detailed clinical history and laboratory data.
2) Insomnia is associated with significant medical risks that need to be evaluated in a comprehensive fashion, treated as a part of the insomnia complaint, and followed to document reduced risk with treatment.

Research agenda

1) Current research suggests that objective insomnia patients are at increased risk for significant medical disorders including hypertension, diabetes, and depression. However, other current research has shown that restricted sleep by itself is a significant factor in increasing inflammation, decreasing immunity and producing abnormalities in ghrelin and leptin. Controlled studies need to examine these latter conditions more closely in objective insomnia patients and be followed by treatment studies to show improvement in these indices.
2) The interaction of objective insomnia with several other medical conditions including cancer, neurologic disease, breathing problems, urinary problems, and gastrointestinal problems needs to be addressed by controlled studies of patients with these medical conditions and controls to identify increased risks. Treatment studies that target sleep and the underlying medical problem need to follow.
3) Long term treatment studies with follow up for efficacy of treatment for both sleep and comorbid medical conditions need to be done and need to include mortality data to document risk reduction.

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