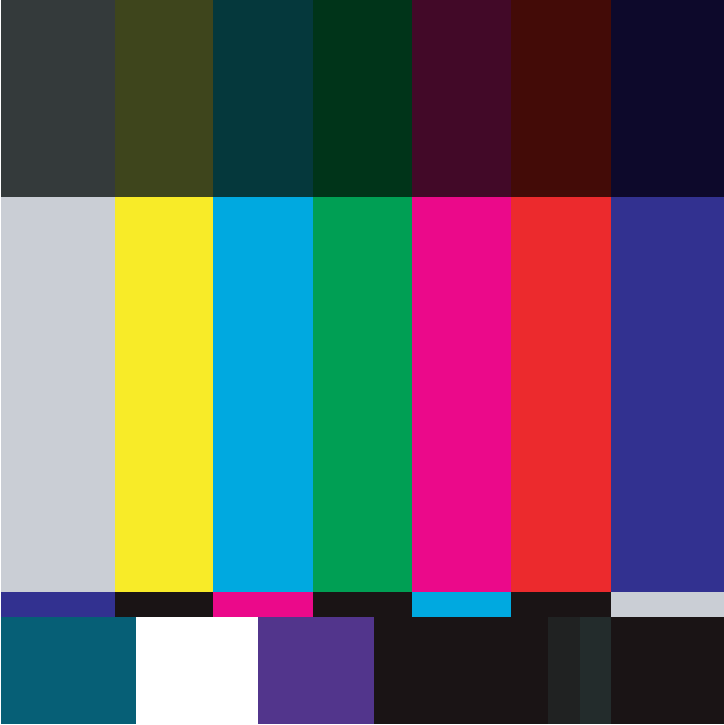


NIH State-of-the-Science Conference Statement on **Manifestations and Management of Chronic Insomnia in Adults**



NIH Consensus and State-of-the-Science Statements

Volume 22, Number 2
June 13–15, 2005

NATIONAL INSTITUTES OF HEALTH
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About the NIH Consensus Development Program

National Institutes of Health (NIH) consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of 1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), 2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, 3) questions and statements from conference attendees during open discussion periods that are part of the public session, and 4) closed deliberations by the panel during the remainder of the second day and the morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the federal government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Reference Information

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The Evidence Report prepared for this conference by the Agency for Healthcare Research and Quality is available on the Web via <http://www.ahrq.gov/clinic/epcsums/insomnsum.htm>. Printed copies may be ordered from the AHRQ Publications Clearinghouse by calling 1-800-358-9295. Requestors should ask for AHRQ Publication No. 05-E021-1.

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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH Consensus and State-of-the-Science panels are reviewed prior to selection to assure that they are not proponents of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

For more information about conference procedures, please see <http://consensus.nih.gov/aboutcdp.htm>.

Archived Conference Webcast

The NIH State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults was webcast live June 13–15, 2005. The webcast is archived and available for viewing free of charge at <http://consensus.nih.gov/previousstatements.htm>.

Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of currently available data on manifestations and management of chronic insomnia in adults.

Participants

A non-DHHS, nonadvocate 12-member panel representing the fields of psychology, psychiatry, neuroscience, anesthesiology, sleep disorders, geriatric medicine, epidemiology, health services research, nursing, and community medicine. In addition, 19 experts from fields related to the subject matter of the conference presented data to the panel and to the conference audience.

Evidence

Presentations by experts and a systematic review of the medical literature prepared by the University of Alberta Evidence-based Practice Center, through the Agency for Healthcare Research and Quality's Evidence-based Practice Centers Program. Scientific evidence was given precedence over clinical anecdotal experience.

Conference Process

Answering pre-determined questions, the panel drafted its statement based on scientific evidence presented in open forum and on the published scientific literature. The draft statement was read in its entirety on the final day of the conference and circulated to the audience for comment. The panel then met in executive session to consider the comments received, and released a revised statement later that day at <http://www.consensus.nih.gov>. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal

Government. This statement and all past statements from the NIH Consensus Development Program are available at the same web address of ***<http://www.consensus.nih.gov>***.

Conclusions

Chronic insomnia is a major public health problem affecting millions of individuals, along with their families and communities. Little is known about the mechanisms, causes, clinical course, comorbidities, and consequences of chronic insomnia. Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder, at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use. Moreover, even for those treatments that have been systematically evaluated, the panel is concerned about the mismatch between the potential lifelong nature of this illness and the longest clinical trials, which have lasted 1 year or less. A substantial public and private research effort is warranted, including developing research tools and conducting longitudinal studies of randomized clinical trials. Finally, there is a major need for educational programs directed at physicians, health care providers, and the public.

Introduction

Insomnia is the most common sleep complaint across all stages of adulthood, and for millions, the problem is chronic. Insomnia often is comorbid with other disorders, particularly depression, as well as some cardiovascular, pulmonary, and gastrointestinal disorders. In the absence of comorbid conditions, insomnia is thought to be a primary disorder in itself. Whether it is the primary disorder or secondary to some other condition, chronic insomnia is often associated with a wide range of adverse conditions, including mood disturbances, difficulties with concentration, and memory. Whether insomnia is the cause or result of associated problems is not always easily determined, but is critical to treatment strategies for individual patients.

A variety of behavioral and pharmacological approaches show promise for managing chronic insomnia symptoms. However, there has been limited guidance for clinicians in choosing the best treatment for chronic insomnia due to the paucity of randomized clinical trials (RCTs) for many widely used treatments. Available treatments include an array of behavioral or nonpharmacologic interventions; hypnotic medications; and antidepressant, antipsychotic, or antihistamine medications.

As pointed out in the recent *2003 National Sleep Disorders Research Plan*, published by the National Center on Sleep Disorders Research at the National Institutes of Health (NIH), there is great need for additional research to better define the nature of chronic insomnia and ways to characterize its detailed expression in diverse patients. Additional systematic research is also greatly needed to provide a more thorough database from which clinicians and patients can make more informed choices about treatment options.

To address these needs, the National Institute of Mental Health and the Office of Medical Applications of Research of the NIH sponsored a State-of-the-Science Conference on the Manifestations and Management of Chronic Insomnia in Adults on June 13–15, 2005, in Bethesda, MD. During the first 2 days of the conference, experts presented the latest scientific knowledge about chronic insomnia and available treatments. After weighing all of the scientific evidence, an independent panel prepared and presented the following state-of-the-science statement. The panel was charged with answering five specific questions:

- How is chronic insomnia defined, diagnosed, and classified, and what is known about its etiology?
- What are the prevalence, natural history, incidence, and risk factors for chronic insomnia?
- What are the consequences, morbidities, comorbidities, and public health burden associated with chronic insomnia?
- What treatments are used for the management of chronic insomnia, and what is the evidence regarding their safety, efficacy, and effectiveness?
- What are important future directions for insomnia-related research?

The conference was intended for health care professionals, researchers, patients and their families, and members of the public interested in the nature of and available treatments for chronic insomnia. The conference included formal expert presentations focusing on the individual conference questions and oral and written input from professionals and members of the lay public. In addition, the independent panel benefited greatly from a comprehensive systematic literature review, prepared by the University of Alberta Evidence-based Practice Center.

1. How is chronic insomnia defined, diagnosed, and classified, and what is known about its etiology?

Definition

Insomnia may be defined as complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep. The disturbance may consist of one or more of three features: (1) difficulty in initiating sleep; (2) difficulty in maintaining sleep; or (3) waking up too early. A fourth characteristic, nonrestorative or poor-quality sleep, has frequently been included in the definition, although there is controversy as to whether individuals with this complaint share similar pathophysiologic mechanisms with the others.

Chronic insomnia should be distinguished from acute insomnia, which may occur in anyone at one time or another (e.g., the night before an important event the next day). While some papers have utilized 6-month duration of the above symptoms to define chronicity, there is evidence to suggest that as few as 30 days of symptoms are clinically important. Accordingly, for the purposes of literature review, we have defined chronic insomnia as 30 days or more of the symptoms described above.

The importance of sleep disruption often rests with its impact on the individual's daytime function. Guidelines incorporating impact on function along with the above features in the definition of insomnia have recently been published in an effort to standardize future insomnia research. However, the impact of sleep disruption goes beyond the insomniac. When children and the elderly (particularly nursing home residents) suffer from insomnia, parents and caregivers also suffer. Employers of those with insomnia suffer when their work performance is affected. Daytime drowsiness may make insomniacs dangerous as drivers.

Most cases of insomnia are comorbid with other conditions. Historically, this has been termed “secondary insomnia.” However, the limited understanding of mechanistic pathways in chronic insomnia precludes drawing firm conclusions about the nature of these associations or the direction of causality. Furthermore, there is concern that the term “secondary insomnia” may promote undertreatment. Therefore, we propose that the term “comorbid insomnia” may be more appropriate. Common comorbidities include psychiatric disorders, particularly depression and substance use disorders; cardiopulmonary disorders; and conditions associated with chronic somatic complaints (i.e., musculoskeletal syndromes such as rheumatoid arthritis or lower back pain) that may disrupt sleep. Other associated sleep disorders can also contribute to insomnia, particularly obstructive sleep apnea, restless legs syndrome, or periodic limb movement disorder. “Primary insomnia” is the term used when no co-existing disorder has been identified.

Diagnosis

Diagnosis is based primarily on patient-derived and family or caregiver complaints, as determined by the clinical interview. However, there has been little research to show how accurately persons reporting sleep problems can judge their own sleep latency or periods of wakefulness during the night. Medical history and physical examination are useful in establishing the presence of comorbid syndromes.

Other tools have been used as an aid to diagnosis, although many are limited in their validation. Sleep diaries can help to document sleep/wake cycles. Various questionnaires have been formulated, but there is a lack of standardization. An actigraph, a wrist-worn device that measures movement to infer sleep and wake cycles, is employed in the evaluation of circadian rhythm disorders, but its use in insomnia has not been fully validated. Multichannel polysomnography, either in-lab or at home, is the most sensitive tool to differentiate wakefulness and sleep. However, polysomnography is expensive and because the numerous monitoring electrodes can

actually disrupt sleep, its use as a diagnostic tool for insomnia should be limited to cases in which other sleep disorders, such as sleep apnea, are suspected.

Classification and Etiology

Insomnia has been classified either based on its specific symptoms (i.e., sleep onset or sleep maintenance) or the duration of the disorder. Etiology-based classification schemes also have been advocated. Evidence supports both psychological and physiological models in the etiology of insomnia. Psychological models include the concepts of conditioning, hyperarousal, stress response, predisposing personality traits, and attitudes and beliefs about sleep. Physiological models have been explored in animals in an effort to identify neural systems that regulate arousal and sleep. The precise relationship between physical illness and changes in brain function that result in insomnia remains uncertain.

2. What are the prevalence, natural history, incidence, and risk factors for chronic insomnia?

Prevalence

Although chronic insomnia is known to be common, studies of its prevalence have yielded variable estimates (i.e., the proportion of persons who have the disorder at a given point in time). Evidence from epidemiologic studies varies depending on the definition of chronic insomnia and the diagnostic and screening methods used. Population-based studies suggest that about 30 percent of the general population complains of sleep disruption, while approximately 10 percent has associated symptoms of daytime functional impairment consistent with the diagnosis of insomnia, though it is unclear what proportion of that 10 percent suffers from *chronic* insomnia. Not surprisingly, higher prevalence rates are found in clinical practices, where about one-half of respondents report symptoms of sleep disruption.

Natural History

Few studies have described the course or duration of insomnia. Unpublished data from a middle-aged population followed over 10 years describe a persistence of symptoms. The limited prospective data on patients with sleep complaints of at least a month's duration showed that in the majority of insomniacs, symptoms are of long duration. The paucity of literature describing the natural course of insomnia underscores the need for large-scale longitudinal studies.

Incidence

Very little is known about chronic insomnia's incidence, which is the number of new cases of the disorder arising in a specific time period, such as a year. Because prevalence may be affected by events occurring after the insomnia is under way, incident cases give the best information about the causes of insomnia's occurrence. Unfortunately, only a few studies have investigated the incidence of chronic insomnia or the circumstances under which it first appears. Increasing the number of studies of the incidence of chronic insomnia is a clear research priority.

Duration

Research on the duration of chronic insomnia is also needed. The disorder can last for relatively short periods of time in some patients and for decades in others. Insomnia can also recur after a period of remission. When studies of chronic insomnia incidence are conducted, the newly ascertained cases can be followed longitudinally to describe the disorder's natural history. In these studies, it will be possible to investigate factors that are suspected of affecting chronic insomnia's duration, remissions, and relapses. It will be particularly important to determine which therapies the treated patients receive and their success in relieving symptoms or preventing relapses.

Risk Factors

Several problems limit the ability to compare and integrate available information from existing observational studies on correlates of insomnia: (1) validated diagnostic instruments have not been applied in large, population-based studies; (2) the many comorbid physical and psychiatric conditions associated with a diagnosis of insomnia may be its cause, its consequence, or share its risk factors. Because most studies have been cross-sectional observations of affected persons rather than prospective studies of persons beginning prior to the onset of insomnia, decisions cannot be made as to which of its correlates are actually causal.

Many studies have found greater prevalence of insomnia among older people, perhaps as a consequence of declining health and/or institutionalization. Whether rates of insomnia increase with age in healthy older people remains unclear. Most observational studies of insomnia have found greater prevalence among women, especially in the postmenopausal years. Current evidence on differences among racial or ethnic groups in prevalence of insomnia within the United States is limited and inconclusive.

Several studies have found higher prevalence of insomnia in divorced, separated, and widowed adults than in married adults. In some studies, lower education and income have been associated with a higher prevalence of insomnia.

Several psychiatric and physical illnesses have strong relationships with insomnia. Insomnia is a symptom of depression, so it is not surprising that a diagnosis of depression is associated with insomnia. Other medical conditions, including arthritis, heart failure, pulmonary and gastrointestinal disorders, Parkinson's disease, stroke, and incontinence, also affect sleep and increase the prevalence of insomnia. The extent to which treatment for these conditions ameliorates insomnia remains unclear.

Cigarette smoking, alcohol and coffee consumption, and consumption of certain prescription drugs also affect sleep and are associated with increased prevalence of insomnia. Although modification of these behaviors might be expected to reduce the prevalence of insomnia, studies have yet to demonstrate the effectiveness of these lifestyle changes as treatment for insomnia.

Future Studies

Validated instruments with known psychometric properties are needed, with attention paid to ease of administration, cross-cultural applicability, and comparability to objective measures of sleep performance, both overall and within important subgroups. Attention is also needed concerning the reliable measurement of the degree of sleep disturbance and the severity of symptoms of insomnia.

Another hypothesis relates to the possible genetic etiology of insomnia. Work is needed to quantify the importance of family history, along with a systematic search for specific genes.

Correlates of insomnia should be explored for their relationships with the development of subsequent insomnia. For example, studies are needed of the impact on incidence of insomnia of divorce, separation and bereavement, polypharmacy, and major chronic diseases.

Longitudinal observational studies are needed to identify factors affecting incidence of and remission from insomnia. An efficient approach would be to add validated questions on chronic insomnia to ongoing observational studies to assess the many potential determinants of insomnia incidence, persistence, and remission.

3. What are the consequences, morbidities, comorbidities, and public health burden associated with chronic insomnia?

Consequences, Morbidities, and Comorbidities

Insomnia appears to be associated with high health care utilization. The direct and indirect costs of chronic insomnia have been estimated at tens of billions of dollars annually. However, these estimates depend on many assumptions. In estimating the economic consequences of insomnia, it is difficult to separate the effects of insomnia from the effects of comorbid conditions. For example, a person with joint pain who has problems sleeping may seek health care for the arthritis rather than for sleep problems, assuming that the pain accounts for the sleep difficulty.

Only a few studies have examined the effects of insomnia on functioning in everyday life. These studies suggest that insomnia reduces quality of life and hinders social functioning. Two studies have identified a relationship between chronic insomnia and work days missed. Other studies indicate that insomnia is related to impaired work performance. There is at least some evidence of a relationship between chronic insomnia and impaired memory and cognitive functioning.

Laboratory studies indicate that sleep loss results in impaired psychomotor and cognitive functioning. There is evidence that chronic insomnia or the drugs used to treat it contribute to the increased number of falls in older adults.

Insomnia usually appears in the presence of at least one other disorder. Particularly common comorbidities are major depression, generalized anxiety, substance abuse, attention deficit/hyperactivity in children, dementia, and a variety of physical problems. The research diagnostic criteria for insomnia recently developed by

the American Academy of Sleep Medicine indeed share many of the criteria of major depressive disorder. Studies to explain these overlaps require determining how often insomnia precedes the disorders with which it is associated and whether it continues to exist if the other disorders go into remission.

Both insomnia and its treatment may adversely affect quality of life. Treatment studies should include measures of undesirable side effects as well as the reduction of symptoms of insomnia. Costs of illness and of treatment should be assessed to allow for an analysis of the cost-effectiveness of treatments. The U.S. Department of Health and Human Services has developed useful guidelines for these assessments, and these should be consulted in the development of evaluation protocols. In addition to measures of sleep symptoms, effects on quality of life should also be measured.

Public Health Burden

The focus of public health is on populations rather than on individuals. The public health consequences of insomnia are difficult to evaluate because the literature is not well developed at this time. Sleep research has focused on basic mechanisms and clinical studies. Relatively little attention has been paid to the public health burden of insomnia. To better understand the public health consequences of insomnia, several lines of research should be considered.

The association of insomnia with premature death has not been studied. Separating the effects of insomnia from the effects of its comorbidities will be a methodological challenge. A start has been made by adding measures of sleep to the National Health and Nutrition Examination Survey; such measures should be added to other major epidemiological studies, including the Behavioral Risk Factor Surveillance Survey.

The effect of insomnia on quality of life has been reported in few studies. Secondary analysis of data from major

population studies that include both measures of sleep and measures of functioning and quality of life should be supported. New studies are needed to determine whether insomnia causes job-related disability. Furthermore, we need to support additional studies to determine whether treatment for insomnia affects job performance and academic performance.

The economic consequences of insomnia are not clearly understood. New studies are needed to estimate the direct and indirect costs of chronic insomnia and the potential societal benefits that might accrue from successful intervention programs. Finally, insomnia has effects beyond individual patients. Families, caregivers, and friends of the sufferers are also affected. More evidence is needed to document these effects.

4. What treatments are used for the management of chronic insomnia, and what is the evidence regarding their safety, efficacy, and effectiveness?

Epidemiological surveys have shown that the most common treatments used by people with chronic insomnia are over-the-counter (OTC) antihistamines, alcohol, and prescription medications. The major forms of psychological treatments that have been systematically evaluated are the cognitive and behavioral therapies. Alternative and complementary treatments include melatonin and herbal remedies, such as valerian.

Assessment of the efficacy of treatments for chronic insomnia is complicated by a number of factors. Studies said to have been carried out on subjects with insomnia often lack consistency in the criteria used to diagnose chronic insomnia, a history of the duration and severity of the insomnia, or agreement on what effects of the treatment are to be evaluated. Further complicating the ability to assess treatments for chronic insomnia is its overlap with many medical and psychiatric conditions, most notably depression. Although there have been RCTs for

several treatments, there is inconsistency in applying rigorous methodology to the assessment of a number of currently used treatments. Additionally, most clinical trials are relatively short term. There is a paucity of information about the long-term effects on sleep, daytime functioning, and quality of life.

Behavioral and Cognitive Therapies

Behavioral and cognitive-behavioral therapies (CBTs) have demonstrated efficacy in moderate to high-quality RCTs. Behavioral methods, which include relaxation training, stimulus control, and sleep restriction, were developed and first tested in the 1970s. More recently, cognitive therapy methods have been added to behavioral methods. Cognitive therapy methods include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. When these cognitive methods have been added to the behavioral methods to compose a CBT package, it has been found to be as effective as prescription medications are for short-term treatment of chronic insomnia. Moreover, there are indications that the beneficial effects of CBT, in contrast to those produced by medications, may last well beyond the termination of active treatment. There is no evidence that such treatment produces adverse effects, but thus far, there has been little, if any, study of this possibility.

It is likely that most CBT is currently delivered by mental health practitioners or physicians with formal sleep medicine training. However, CBT refers to a number of varied nonpharmacologic treatments for insomnia, and a standardized “best practice” model has yet to be formulated and validated. Thus, future research should explore the optimum number and duration of sessions to yield positive results, particularly as delivered in busy primary care practices where the need and impact may be greatest.

Prescription Medications

Prescription medication therapy is intended to relieve symptoms of chronic insomnia only while the medication is being taken. Given this expectation, little or no research has been conducted on persistence or re-appearance of symptoms after prescription medication therapy is discontinued.

This section describes the use of two categories of medications, the benzodiazepine receptor agonists that have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of insomnia and those that the FDA has approved for the treatment of other disorders but which doctors often prescribe to treat insomnia. The latter category is considered “off-label” usage. There are currently eight medications approved by the FDA for treatment of insomnia. Despite the fact that insomnia is often a chronic condition, only one of these medications (eszopiclone) has been approved for use without a specified time limit. The other medications have approved use limited to 35 days or less.

Benzodiazepine Receptor Agonists

Benzodiazepine receptor agonists fall into two broad groups of prescription hypnotics: benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) and the more recently introduced agents that act at benzodiazepine receptors but have a non-benzodiazepine structure (e.g., zaleplon, zolpidem, and eszopiclone). Results from moderate to high-quality RCTs indicate that these eight agents are effective in the short-term management of insomnia. With the exception of eszopiclone, the benefits of these agents for long-term use have not been studied using RCTs. A recent clinical trial of eszopiclone provided evidence of sustained efficacy for 6 months in the treatment of subjects meeting DSM-IV criteria for primary insomnia.

Adverse effects associated with these medications include residual daytime sedation, cognitive impairment, motor incoordination, dependence, and rebound insomnia. These problems appear to be worse in the elderly. The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. The available literature suggests that, in the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study in the general population of insomniacs.

Prescription Drugs Used Without FDA Approval for Insomnia

Antidepressants. Over the past 20 years, there has been a significant change in the use of prescription medications to treat chronic insomnia, with a decrease in the use of benzodiazepine receptor agonists and a substantial increase in the use of antidepressants. Based on recent surveys, the antidepressant trazodone is now the most commonly prescribed medication for the treatment of insomnia in the United States. In short-term use, trazodone is sedating and improves several sleep parameters. These initial effects are known to last for up to 2 weeks. Importantly, there are no studies of long-term use of trazodone for treatment of chronic insomnia. Another antidepressant, doxepin, has been found to have beneficial effects on sleep for up to 4 weeks for individuals with insomnia. Data on other antidepressants (e.g., amitriptyline and mirtazepine) in individuals with chronic insomnia are lacking. All antidepressants have potentially significant adverse effects, raising concerns about the risk–benefit ratio. There is a need to establish dose-response relationships for all of these agents and communicate them to prescribers.

Other Prescription Medications. A number of other sedating medications have been used in the treatment of insomnia. These include barbiturates (e.g., phenobarbital) and antipsychotics (e.g., quetiapine and olanzapine).

Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. Furthermore, all of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended.

Nonprescription Medications (Over-the-Counter)

Antihistamines (H1 receptor antagonists such as diphenhydramine) are the most commonly used OTC treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.

Alcohol

Many insomniacs take an alcoholic drink before bedtime in order to reduce sleep latency. While alcohol does reduce sleep latency, drinking large amounts has been shown to result in poorer quality of sleep and awakening during the night. It is not known whether any impairment of sleep quality occurs when small amounts are used at bedtime. The risk of excess alcohol consumption in persons with alcohol problems makes this an inappropriate treatment for them.

Melatonin

Melatonin is a natural hormone produced by the pineal gland that plays a role in the control of circadian rhythms. Because melatonin is not regulated by the FDA, preparations containing it vary in strength, making comparisons across studies difficult. Although melatonin appears to be effective for the treatment of circadian rhythm disorders (e.g., jet-lag), little evidence exists for efficacy in the treatment of insomnia or its appropriate dosage.

In short-term use, melatonin is thought to be safe, but there is no information about the safety of long-term use.

Valerian

Valerian is derived from the root of the plant species *valeriana* and is thought to promote sleep. Limited evidence shows no benefit compared with placebo. The FDA does not regulate valerian, and thus different preparations vary in valerian content. Safety data are minimal, but there have been case reports of hepatotoxicity in persons taking herbal products containing valerian. Other herbal remedies have also been promoted, but efficacy evidence is lacking.

L-tryptophan

L-tryptophan is an endogenous amino acid that has been used as a hypnotic. Systematic evidence supporting its use in the treatment of insomnia is extremely limited and based on studies with small numbers of subjects. Concerns are also raised about its possible toxic effects, particularly when used in combination with certain psychiatric medications.

Other Treatments

There are a number of alternative activities, including tai chi, yoga, acupuncture, and light therapy, that may be useful in the treatment of insomnia. These treatments have not been adequately evaluated at this time.

Research Recommendations

CBT and benzodiazepine receptor agonists have demonstrated efficacy in the acute management of chronic insomnia. However, full evaluation of the effectiveness of these therapies for chronic insomnia will require trials of longer duration that measure health outcomes—including the ability of treatments to ameliorate the daytime impairment related to sleep difficulty—and also integrate the risks and benefits of treatment.

Other therapies have also demonstrated some promise. However, little is known about the comparative benefits of these treatments, their generalizability, and their effects on understudied features of chronic insomnia.

In order to address this lack of knowledge, RCTs will be required that:

- Are large-scale and multisite.
- Compare at least two effective or promising treatments so that the comparative benefits of effective treatments can be evaluated. This should include comparisons among pharmacological agents, CBT, and combined treatment.
- Evaluate the positive and adverse effects of treatments over longer timeframes, including the period after discontinuation of treatment.
- Incorporate objective and subjective measures of daytime function and quality of life in addition to the traditional parameters of sleep, such as sleep onset latency and total sleep time.
- Systematically evaluate a variety of commonly used OTC and alternative remedies for insomnia that have not been formally evaluated.
- Measure the costs and cost-effectiveness of treatments.

The pharmaceutical industry is called upon to support comparisons of its medications not only with placebo but also with other effective treatments, including CBT.

Studies should be directed to important population subgroups, including children, nursing home residents, postmenopausal women, those with primary chronic insomnia, and those with insomnia comorbid with other conditions.

To overcome reporting bias in clinical trials, in which positive results are published while negative results are not, the development of a central registry for

all insomnia trials is recommended. This registry would allow a systematic synthesis of the available clinical trial data.

As data from RCTs showing efficacy become available, it will be critical to evaluate effectiveness in broader clinical populations in community settings.

RCT study subjects for whom the tested substance appeared to be effective need to be followed over time, with random assignment to varying times at which the drug will be discontinued. These studies will give evidence for the appearance of side effects with long-term use, for the development of tolerance to the drug in time, and for any lasting beneficial effects after discontinuation of the drug.

Repeated surveys of physician prescribing behavior and decision making are recommended to permit an understanding of how their treatment behavior changes as new data on efficacy of insomnia treatments become available. Such studies will show whether substantial re-education programs for physicians should be supported.

5. What are Important Future Directions for Insomnia-Related Research?

Validated instruments are needed to assess chronic insomnia, with attention paid to the ease of administration and cross-cultural applicability. A greater range of outcome measures related to chronic insomnia and its consequences is also needed. Measures of sleep should be added to longitudinal epidemiologic studies that are collecting data on a broad range of items that could turn out to be risk factors for insomnia.

Studies are needed of the possible genetic etiology of chronic insomnia. The neural mechanisms underlying chronic insomnia are poorly understood. Studies aiming to identify neural mechanisms should use animal models and *in vivo* neural imaging approaches in people with insomnia and in individuals with normal sleep. Work is

needed to quantify the importance of family history, along with a systematic search for specific genes.

Longitudinal observational studies are needed to identify factors affecting incidence of, natural history of, and remission from chronic insomnia. An efficient approach would be to add questions about chronic insomnia to ongoing observational studies that assess the many potential determinants of insomnia incidence, persistence, and remission.

The effects of insomnia on quality of life have been reported in few studies. Analyses of data from major population studies that include measures of sleep, measures of functioning, and quality of life should be supported. Studies are needed to determine whether insomnia causes job-related disability and whether treatment for insomnia enhances job performance and academic performance.

Studies are needed to estimate the direct and indirect societal costs of insomnia and the potential societal benefits that might accrue from successful intervention programs. Moreover, because chronic insomnia has effects that go beyond individual patients, more research is needed to quantify effects on families, friends, and caregivers of insomniacs.

CBT and benzodiazepine receptor agonists have been shown to be beneficial in the acute management of chronic insomnia. Other therapies have also demonstrated some promise. However, little is known about the comparative benefits of these treatments, their combination, and their effects on understudied features of chronic insomnia. To address this lack of knowledge, RCTs will be required that are large scale and multisite and compare at least two effective or promising treatments. This should include comparisons between pharmacological agents as well as between those agents and CBT. The pharmaceutical industry is called upon to compare its medications not only with placebo but also with other effective treatments, including CBT. Trials should include measures of cost and cost-effectiveness.

To overcome potential problems with reporting bias in clinical trials, the development of a central registry for all clinical trials is recommended. This registry would allow a systematic synthesis of the available clinical trial data.

As comparative efficacy data become available, it will be critical to conduct effectiveness studies to determine generalizability to broader clinical populations in community settings.

Studies should be directed to important population subgroups, including children, nursing home residents, postmenopausal women, those with primary chronic insomnia, and those with insomnia comorbid with other conditions.

Conclusions

Chronic insomnia is a major public health problem affecting millions of individuals, along with their families and communities. Little is known about the mechanisms, causes, clinical course, comorbidities, and consequences of chronic insomnia. Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder, at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use. Moreover, even for those treatments that have been systematically evaluated, the panel is concerned about the mismatch between the potential lifelong nature of this illness and the longest clinical trials, which have lasted 1 year or less. A substantial public and private research effort is warranted, including developing research tools and conducting longitudinal studies of randomized clinical trials. Finally, there is a major need for educational programs directed at physicians, health care providers, and the public.

State-of-the-Science Panel

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