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Manifestations and Management of Chronic Insomnia in Adults

Summary

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Prevalence of Insomnia

Insomnia, or inability to sleep, is the most commonly reported sleep problem in the industrialized world.[1] Estimates suggest that between 40 and 70 million Americans are affected by either intermittent or chronic sleep problems, representing approximately 20 percent of the population.[2] The Sleep in America Poll, conducted by the National Sleep Foundation, revealed that almost 50 percent of people surveyed had complaints of frequent insomnia, but only 6 percent were formally diagnosed.[3] Moreover, approximately, 30 to 35 percent of respondents complained of nightly insomnia.[3] The most prevalent symptoms of insomnia, experienced at least a few nights a week by people with insomnia, include waking up feeling unrefreshed (34 percent) and being awake often during the night (32 percent).[3] The symptoms of difficulty falling asleep and waking up too early are less common, but still experienced at least a few nights a week by about one-fourth of adults with insomnia (23 to 24 percent).[3]

Risk Factors for Insomnia

Although some risk factors and etiologies of insomnia have been identified, the nature of the relationships has not been fully elucidated. Some risk factors for insomnia that have emerged from data related to insomnia include female gender[3] and old age.[4] Additional risks factors include less education, unemployment, separation or divorce, and medical illness.[1] Insomnia may be primary or secondary to other sleep problems and may be associated with a number of co-morbidities. An association has been found between insomnia and psychiatric (depression and anxiety) and psychological disorders.[4] There is increasing evidence that chronic insomnia may predispose individuals to the development of psychiatric disorders.[5-6] Persistent insomnia increases the risk of depression, substance abuse, and anxiety disorders. Environmental factors such as irregular sleep schedules, use of caffeine or other stimulants, co-morbid medical conditions, and/or shift work may also predispose vulnerable individuals to insomnia.

Consequences of Insomnia

Insomnia has significant direct and indirect effects on the health and wellness of affected individuals. Insomnia has been correlated with frequent use of medical services,[7-8] chronic health problems, [9-10] increased drug use,[7-8] and perceived poor health,[11] and has been associated with medical problems including heart disease,[12] hypertension,[13] and musculoskeletal problems.[12] The daytime consequences of chronic insomnia often include increased healthcare utilization, increased risk of depression,[14] poor memory, reduced concentration, poor work performance, and perceived or real risk of failure at work.[15] The economic implications of insomnia and

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associated morbidity have been described.[7,3] The direct costs of insomnia (insomnia treatments, healthcare services, hospital and nursing home care) are estimated to be nearly $14 billion.[16-17] The indirect costs of insomnia, such as time lost from work and loss of productivity, are estimated to be nearly $28 billion. A National Sleep Foundation survey found that lost productivity from insomnia alone was over $18 billion.

Management of Insomnia

Management of acute insomnia has traditionally involved pharmacotherapy. The use of such agents is common practice for both acute and chronic insomnia, despite the fact that the Food and Drug Administration (FDA) has approved none of them for chronic insomnia. Another medication, eszopiclone (Lunesta), was recently approved by the FDA for treatment of insomnia, but the duration of use is not explicitly stated. An estimated 0.5 percent of the population takes sedative medications for insomnia for more than 1 year.[3] More than 1 in 10 people (11 percent) report using prescription (6 percent) and/or over-the-counter (OTC) medications (6 percent), at least a few nights a month, to help them sleep, according to a Sleep in America Poll.[3] Individuals reporting symptoms of medical conditions are more likely to take sleep aids, both prescription and OTC medications. For example, 14 percent of people with symptoms of depression report using prescription medication, and 12 percent of people with symptoms of depression report using OTC sleep aids.[3] Medications commonly used to treat insomnia include sedating antidepressants,[18] antihistamines, anticholinergics, benzodiazepines, and non-benzodiazepine hypnotics. A side effect of all hypnotics is to reduce slow wave sleep. Other side effects of concern are possible daytime residual effects related to sedation, rebound insomnia, and tolerance, along with minor side effects specific to each drug class. Many questions and challenges related to pharmacological therapy for chronic insomnia remains, such as the appropriate treatment for different types of primary and secondary insomnia, and the long-term side effects and daytime consequences of pharmacotherapy. The evidence for management of chronic insomnia with pharmacotherapy has not been systematically evaluated.

Cognitive/behavioral therapy has been recognized as a valid and successful treatment approach for insomnia. Cognitive/behavioral therapy can include any combination of sleep restriction, sleep hygiene, stimulus control, paradoxical intention, and cognitive restructuring. Many of these commonly used clinical tools have not undergone rigorous testing to determine their efficacy and long-term safety. The efficacy of these treatments has been evaluated in some studies,[4,19] but differences in the definition of insomnia and outcome measures make it difficult to compare study results.

In summary, insomnia is a common complaint with significant consequences. Significant advancements have been made in sleep research over the past three decades, yet many questions related to the treatment of chronic insomnia remain. Our goal was to review the evidence and state of research in the area of chronic insomnia.

Objectives

The objectives of this report are to conduct a systematic review of (1) the prevalence, natural history, incidence, risk factors, and consequences of chronic insomnia in adults and (2) the efficacy and safety of treatments used in the management of chronic insomnia in adults. A population was considered to suffer from chronic insomnia if the sleep disturbance persisted for at least 4 weeks, regardless of severity of symptoms.

Methods

Literature Search

The research librarian, in collaboration with the TEP (Technical Expert Panel), developed and implemented search strategies designed to identify relevant evidence for key questions of the review. A systematic search of 21 electronic databases was conducted. We searched MEDLINE®, EMBASE, CINAHL®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid OLDMEDLINE®, PsycINFO®, EBM Reviews-Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts, AMED (Allied and Complementary Medicine) , HealthSTAR/Ovid Healthstar, EBM Reviews-Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club (ACPJC), Database of Abstracts of Reviews of Effects (DARE), Science Citation Index Expanded™, Biological Abstracts, Cochrane Complementary Medicine Field Registry, CAB Abstracts, SIGLE, OCLC Proceedings First, Dissertation Abstracts, Alt HealthWatch, NLM Gateway, and PubMed®. Most of the searches were limited to humans, and no age restrictions were applied to any of the searches.

For Question 1, which relates to the definition, classification, diagnosis, and aetiology of chronic insomnia in adults, we searched for narrative and systematic reviews, book

chapters, diagnostic manuals and standards of practice parameters, and applied English-language restrictions. For Question 2, which relates to the prevalence, natural history, incidence, and risk factors for chronic insomnia in adults, and Question 3, which relates to the consequences, morbidities, co-morbidities and public health burden associated with chronic insomnia in adults, we searched for observational studies, encompassing a range of designs including cross-sectional, case-control, and cohort studies, and applied English-language restrictions. For Question 4, which relates to the treatments for chronic insomnia in adults, and the evidence regarding their safety, efficacy, and effectiveness, we searched for randomized controlled trials, and no language restrictions were applied.

Inclusion Criteria

We did not develop formal inclusion criteria for the question pertaining to the definition, classification, diagnosis, and etiology of chronic insomnia (Question 1), nor for the question pertaining to the future direction of insomnia-related research (Question 5). The former question was answered by providing an overview of the literature, and the latter question was answered by assessing the limitations in the evidence for the other questions of the review.

Inclusion criteria were developed for three questions of the review (Questions 2-4). Question-specific inclusion criteria appear below. In the interest of clarity, questions 2 and 3 will be referred to as the questions on manifestations of chronic insomnia, while question 4 will be referred to as the question on management of chronic insomnia.

2. **What are the prevalence, natural history, incidence, and risk factors for chronic insomnia?** Specific risk factors of interest include age, gender, race/ethnicity, psychiatric illness and psychological problems, medical disease, socioeconomic status, and shift work.

A study was considered to be relevant to the portion of Question 2 pertaining to the prevalence, natural history, and incidence of chronic insomnia, if it met the following criteria:

- The report was written in English
- Participants were at least 15 years old
- It examined chronic insomnia
- It had a cross-sectional or cohort design
- It assessed the prevalence, natural history, or incidence of chronic insomnia

A study was considered to be relevant to the portion of Question 2 pertaining to risk factors for chronic insomnia, *if it met the first three criteria listed above* as well as the following:

- It had a cohort, case-control, or cross-sectional design
- It assessed one of the risk factors of interest

3. **What are the consequences, morbidities, co-morbidities, and public health burden associated with chronic insomnia?** Specific outcomes of interest include healthcare utilization, psychiatric illness, absenteeism, work performance, accidents, falls in the elderly, quality of life and social relationships, memory, cognitive function, mood, and direct and indirect costs.

A study was considered to be relevant to this question of the review, *if it met the first three criteria outlined for Question 2* as well as the following:

- It had a cohort or cross-sectional design
- It assessed one of the consequences of interest

For Questions 2 and 3, a study was considered to examine chronic insomnia if this condition was defined as a sleep disturbance of four weeks or more or the report explicitly mentioned that chronic sleep disturbance was examined.

4. **What treatments are used for the management of chronic insomnia and what is the evidence regarding their safety, efficacy, and effectiveness?** Specific treatments of interest include prescription medication, over-the-counter medication, alcohol, behavioral therapy, combination therapy, and complementary and alternative care.

A study was considered to be relevant to this question of the review, if it met the following criteria:

- The report was written in English
- Participants were at least 15 years old, and the majority were at least 18 years old
- Participants suffered from chronic insomnia
- Participants were randomized to intervention or placebo
- Participants and assessors were blind to treatment received
- It assessed at least one of the following outcomes, listed in order of importance in deriving conclusions of the review:
  - sleep onset latency
  - wakefulness after sleep onset
  - sleep efficiency
  - total sleep time

- sleep quality
- quality of life

Sleep onset latency was defined as the amount of time between the participant laying down to sleep and the onset of sleep; wakefulness after sleep onset was defined as the amount of time spent awake in bed following the attainment of sleep; sleep efficiency was defined as the amount of time spent asleep as a percentage of the total time spent in bed; and total sleep time was defined as the total time spent asleep while in bed. Sleep onset latency and wakefulness after sleep onset were given the highest priority in deriving conclusions from the review, since they were considered the best indices of sleep initiation and sleep maintenance, respectively. However, subgroup analyses were conducted only on data relevant to sleep onset latency, since this outcome was the most highly reported outcome across studies.

If the majority of participants met one of the following criteria, the study population was considered to suffer from chronic insomnia:

- Participants suffered from a sleep disturbance of four weeks or more.
- Participants were described as having a chronic/long-standing/persistent sleep disturbance.
- Participants were selected from a sleep disorders clinic.

In the case of combination therapy, the combined treatment could be compared to either placebo or single treatment.

We acknowledged the fact that double-blinding is often not feasible in studies of psychological treatments by not requiring double-blinding in these studies for inclusion in the review. The placebo treatment for relaxation therapy and cognitive/behavioral therapy was minimal treatment, such as sleep hygiene recommendations or minimal instruction. We required that the placebo resemble the intervention of the study except that it was known to produce either no effect or only a minimal effect.

Study Selection

In the first stage of study selection, two reviewers screened the titles and abstracts of all potentially relevant articles, independently. Each reviewer noted the titles and abstracts that were potentially relevant to the review, and these articles were retrieved. In the second stage of study selection, two reviewers appraised the potentially relevant articles, independently, using pre-determined, question-specific, inclusion criteria. Disagreements between reviewers were resolved by discussion and consensus. The rate of disagreement between reviewers and the primary reason for exclusion of potentially relevant articles were noted.

Data Extraction

Data relevant to study design, population, interventions, and outcomes were extracted from studies, as appropriate, using standardized data extraction forms. A trained reviewer extracted relevant data, and a second reviewer verified the data extracted for accuracy and completeness.

Assessment of Study Quality

The quality of studies relevant to the questions on manifestations of chronic insomnia was assessed using one of three instruments; studies on prevalence and incidence were assessed using a scale designed specifically for this purpose.[20] All other studies relevant to manifestations of chronic insomnia were assessed using one of two Newcastle-Ottawa scales (unpublished), each scale specific to either cohort or case-control studies.

The quality of studies relevant to management of chronic insomnia was assessed using the Jadad scale.[21] The concealment of allocation of participants to treatment groups was also assessed.[22]

Data Analysis

Data relevant to manifestations of chronic insomnia were analyzed qualitatively, while data relevant to management of chronic insomnia were analyzed quantitatively.

Manifestations of Chronic Insomnia

For the questions on prevalence, natural history, incidence, risk factors, and consequences of chronic insomnia, data relevant to each variable were analyzed separately, except for data relevant to potential risk factors and potential consequences of chronic insomnia, which were analyzed together as associated factors of chronic insomnia. The data were synthesized to provide a description of the methods and results of the studies relevant to a given variable.

Management of Chronic Insomnia

For continuous outcomes (e.g., sleep onset latency and sleep efficiency), studies were combined using a mean difference (MD), with the exception of sleep quality and quality of life, where studies were combined using a standardized mean difference (SMD). Dichotomous outcomes (i.e., safety outcomes) were combined using a risk difference (RD). A

number needed to harm (NNH) was also reported for any safety outcomes that were found to be statistically significant. The Inverse Variance Method[23] was used to weight the studies. An efficacy estimate, with corresponding 95% confidence interval, was computed for each outcome. All meta-analyses were performed using a Random Effects Model.[24]

For some outcomes (sleep onset latency and number of adverse events), treatment categories were compared indirectly, via their relationship to placebo. Differences of differences with 95% confidence intervals (CI) were computed.

All estimates of efficacy were assessed for heterogeneity using the I-squared statistic.[25] For our primary outcome (sleep onset latency), heterogeneity was explored in subgroup and sensitivity analyses using a number of variables (treatment, presence/absence of psychiatric illness, length of treatment, age, gender and study quality). Deeks' chi-square statistic[26] was used to test for significant heterogeneity reduction in partitioned subgroups.

We tested for publication bias visually using the Funnel Plot[27] and quantitatively using the Rank Correlation Test,[28] the Graphical Test,[29] and the Trim and Fill Method.[30]

Main Results

Prevalence of Chronic Insomnia

In general populations: Interquartile Range (IQR): 8.5-24.3 percent. There was evidence of an association between female gender and chronic insomnia.

- In clinical populations: IQR: 27.8-43.0 percent.
- In outpatients of general practice: IQR: 19.8-53.7 percent.
- The majority of studies were either of moderate or high quality.

Natural History of Chronic Insomnia

- Only one study provided evidence on natural history of chronic insomnia: the remission rate was 13.1 percent after a 4-month followup period in a population suffering from insomnia for 1 month or more.
- The study was of moderate quality.

Incidence of Chronic Insomnia

- No studies were identified that provided evidence on incidence of chronic insomnia.

Factors Associated with Chronic Insomnia

Potential Risk Factors

- **Age.** Eleven studies found evidence of an association between age and chronic insomnia, whereas seven studies found no evidence of an association between these variables. Of the studies that found an association, all, except one,[31] found evidence that chronic insomnia is associated with older age.
- **Gender.** Eleven studies found evidence of an association between gender and chronic insomnia, while seven studies found no evidence of an association between these variables. All of the studies that found evidence of an association between gender and chronic insomnia, found evidence that chronic insomnia is associated with female gender.
- **Race/ethnicity.** Two studies found evidence of an association between ethnicity and chronic insomnia,[32-33] while one study found no evidence of an association between these variables.[34] Bixler et al. found evidence that chronic insomnia is associated with being a non-Caucasian minority, and Riedel et al. found evidence that chronic insomnia is associated with being White.
- **Psychiatric illness and psychological problems.** Thirty-eight studies found evidence of an association between present or past psychiatric illness or psychological problems and chronic insomnia. Seven studies did not find evidence of an association between these variables.
- **Medical conditions.** Twelve studies found evidence of an association between medical conditions or poor general health and chronic insomnia, while one study[35] did not find evidence of an association between these variables.
- **Socioeconomic status.** Six studies found evidence of an association between socioeconomic status and chronic insomnia. Nine studies did not find evidence of an association between these variables.
- **Shift work.** Only 2 studies provided evidence regarding the relationship between shift-work and chronic insomnia.[31,36] The study by Kageyama et al. provided evidence that chronic insomnia is associated with three or less night shifts per month within the preceding three months in hospital nurses. The study by Martikainen et al. found no evidence of an association between shift work and chronic insomnia.

Potential Consequences

- **Healthcare utilization.** Five studies provided evidence of an association between increased healthcare utilization and chronic insomnia. One study did not find evidence of an association between chronic insomnia and undergoing medical treatment in hospital nurses.[31]
- **Absenteeism and work performance.** Only two studies provided evidence regarding the relationship between work performance or absenteeism and chronic insomnia;[37-38] both studies found evidence of an association between chronic insomnia and absenteeism. The study by Zammit et al. also found evidence of an association between chronic insomnia and impaired work performance.
- **Quality of life and quality of social relationships.** Five studies examined the relationship between either quality of life (from a global perspective) or quality of social relationships and chronic insomnia. All studies found evidence of an association between chronic insomnia and either lower quality of life or lower quality of social relationships; one of these studies found evidence that both quality of life and quality of social relationships are impaired in chronic insomniacs.[39]
- **Memory, cognitive function, and mood.** Fifteen studies found evidence of an association between decrements in memory, mood or cognitive function and chronic insomnia. One study[40] found evidence of increased recall of presentations made just before sleep onset in chronic insomniacs. Eleven studies found no evidence of an association between mood, memory, or cognitive function and chronic insomnia.

We did not identify any studies that provided data relevant to the relationship between accidents or falls in the elderly and chronic insomnia or direct and indirect costs of the disorder.

The majority of studies were of either moderate or high quality.

Efficacy and Safety of the Six Main Categories of Interventions Identified in the Literature

The efficacy estimates are provided as mean differences (MDs) in the effect of intervention and placebo on sleep onset latency (SOL) or wakefulness after sleep onset (WASO). The safety estimates are provided as risk differences (RDs) between intervention and placebo.

- **Benzodiazepines.** MD (SOL): -16.5, 95% CI: (-20.5, -12.5); MD (WASO): -23.1, 95% CI: (-35.7, -10.5); RD: 0.15, 95% CI: (0.10, 0.20); number needed to harm was eight.
- **Non-benzodiazepines.** MD (SOL): -18.1, 95% CI: (-22.5, -13.7); MD (WASO): -12.6, 95% CI: (-23.0, -2.3); RD: 0.05, 95% CI: (0.01, 0.09); number needed to harm was 20.
- **Antidepressants.** MD (SOL): -7.4, 95% CI (-10.5, -4.4); MD (WASO): -11.4, 95% CI: (-16.2, -6.6); RD: 0.09, 95% CI (0.01, 0.18); number needed to harm was 12.
- **L-Tryptophan.** MD (SOL): -11.0, 95% CI: (-33.0, 11.1)
- **Melatonin.** MD (SOL): -8.3, 95% CI: (-14.5, -2.0); MD (WASO): -9.7, 95% CI: (-33.6, 14.3); RD: 0.09, 95% CI: (-0.11, 0.29)
- **Valerian.** MD (SOL): -1.3, 95% CI: (-21.4, 18.9); MD (WASO): -8.4, 95% CI: (-15.9, -1.0); RD: -0.06, 95% CI: (-0.48, 0.35)
- **Relaxation therapy**. MD (SOL): -14.6, 95% CI: (-29.3, 0.2); MD (WASO): -1.6, 95% CI: (-14.1, 10.8). No adverse event data was provided.
- **Cognitive/behavioral therapy.** MD (SOL): -4.6, 95% CI: (-9.8, 0.6); MD (WASO): -18.2, 95% CI: (-30.4, -6.0). No adverse event data was provided.

Most studies were of moderate or high quality.

Discussion

Prevalence, Natural History, Incidence, and Factors Associated with Chronic Insomnia

The interquartile range of prevalence varied from 8.5-24.3 percent across high-quality studies of general populations, to 19.8-53.7 percent across moderate-quality studies of outpatient populations, to 27.8-43.0 percent across moderate-quality studies of clinical populations. Therefore, the prevalence estimates for chronic insomnia in outpatient and clinical populations appear to be significantly higher than those for the general population, a finding that is consistent with evidence of an association between chronic insomnia and

medical conditions, poor general health, and increased healthcare utilization.

Only one study provided data on the natural history of chronic insomnia; the remission rate was 13.1 percent after a 4-month followup. More research is necessary to determine the course of chronic insomnia in various populations. We did not identify any studies that provided evidence regarding the incidence of chronic insomnia; more research is needed in this area as well.

We found evidence to suggest that chronic insomnia is associated with older age, female gender, present or past psychiatric illness and psychological problems, medical conditions and poor general health, increased healthcare utilization, lower quality of life and social relationships, socioeconomic status (marital separation, unemployment, poorer working conditions, and lower social status), and decrements in memory, mood, and cognitive function. Some of the factors that are thought to contribute to insomnia in the elderly include multiple medical problems, polypharmacy, and environmental factors such as absence of zeitgebers (time/schedule cues).[11,41] Similarly, factors such as stress, pregnancy, menopause, medical conditions, and complex home life may explain the higher prevalence of insomnia in females.

Efficacy and Safety of Treatments for Chronic Insomnia

The interventions for chronic insomnia that were investigated in included studies may be categorized as either benzodiazepines, non-benzodiazepines, antidepressants, complementary and alternative care (L-tryptophan, melatonin and valerian), relaxation therapy, cognitive/behavioral therapy, barbiturates, hormone therapy, alcohol, low energy emission therapy, and combination therapy. The majority of studies were classified under the first six categories of the preceding list.

The review provides evidence that benzodiazepines and non-benzodiazepines are effective treatments for chronic insomnia. There is some evidence that antidepressants are effective treatments for chronic insomnia, although more research is required in this area. The review provides some evidence that melatonin is effective in subsets of the chronic insomnia population; however, more research is required in this area. There is also evidence that relaxation therapy and cognitive/behavioral therapy are effective treatments in subsets of the chronic insomnia population. There were too few studies of L-tryptophan and valerian to draw conclusions regarding the efficacy of these treatments in the management of chronic insomnia: additional large-scale, randomized trials are needed. Additional large-scale, randomized trials are also needed in the area of relaxation therapy and cognitive/behavioral therapy in the management of chronic insomnia to determine the efficacy of these interventions across subsets of the chronic insomnia population. The reduction in sleep onset latency by benzodiazepines and non-benzodiazepines was significantly greater than that for antidepressants and melatonin, based on indirect comparisons. However, it should be noted that there were significantly fewer studies of antidepressants and melatonin compared to benzodiazepines and non-benzodiazepines, and additional large-scale, randomized trials of the former interventions are needed before firm conclusions can be drawn regarding the relative efficacy of these interventions.

The benzodiazepines, non-benzodiazepines, and antidepressants had a significantly greater risk of harm than placebo, while melatonin did not. There were too few studies of L-tryptophan to draw conclusions regarding the safety of this intervention. Although there was no evidence that valerian poses a risk of harm, this result was based on only three studies of relatively small sample size. Therefore, more studies are needed before firm conclusions can be drawn regarding the safety of valerian. The risk for benzodiazepines was significantly greater than for non-benzodiazepines, based on indirect comparisons. Indeed, benzodiazepine use has been shown to increase the risk of injury in the elderly,[42] and there is pharmacologic evidence that the non-benzodiazepines have a better side-effect profile than the benzodiazepines.[43-44] Studies of relaxation therapy and cognitive/behavioral therapy did not provide adverse event data.

There was substantial heterogeneity in the pooled estimate for SOL for benzodiazepines, non-benzodiazepines, L-tryptophan, valerian, and relaxation therapy. Similarly, there was substantial heterogeneity in the pooled estimate for WASO for benzodiazepines, non-benzodiazepines, melatonin, and cognitive/behavioral therapy. The heterogeneity was often due to differences in the magnitude of the point estimate and confidence interval across studies, rather than differences in the directionality of the effect. The exceptions are for estimates of the efficacy of relaxation therapy with respect to SOL and the efficacy of melatonin with respect to WASO. The heterogeneity in the pooled estimates for SOL was explored in

sensitivity and sub-group analyses. The results indicate that heterogeneity in the pooled estimate for SOL for relaxation therapy is at least partially due to type of relaxation therapy, length of treatment, age and gender distribution of the study population, and study quality.

There was strong evidence of publication bias in the pooled estimates for SOL for the benzodiazepine and non-benzodiazepine categories of intervention. This finding suggests that the true estimate of efficacy is lower than the estimate calculated in the current analysis.

We identified a small sample of studies examining the efficacy of combination treatments in the management of chronic insomnia; some of these studies compared a combination of treatments with placebo, while others compared them with single treatment. Many comparisons did not have data for our primary outcome, sleep onset latency, and the majority of results were non-significant. The latter finding may reflect the low power of these analyses. None of the studies provided data on adverse events. We identified only one study that compared the efficacy of a combined pharmacological and psychological treatment with these treatments administered sequentially. The research agenda for the management of chronic insomnia should include an evaluation of the efficacy and safety of combination treatments and sequential treatments.

Our results relating to relaxation therapy and cognitive/behavioral therapy are somewhat at odds with three meta-analyses reviewing the efficacy of psychological treatments in the management of chronic insomnia.[45-47] The difference in the findings may relate to key differences in the conduct of the reviews. First, we restricted our meta-analysis to a review of placebo-controlled, randomized trials and accounted for placebo effects in our estimations of efficacy. Other meta-analyses have included non-controlled studies, and for these studies, have not accounted for placebo/control effects in their estimation of efficacy. Second, we used clearly defined criteria for chronic insomnia; however, for some studies the criteria for insomnia was not clear. Third, we separated predominantly cognitive/behavioral approaches from predominantly relaxation approaches in management of insomnia, resulting in distinct meta-analyses for each category of intervention. These interventions have been grouped under the broader heading of psychological/non-pharmacological treatments in other reviews.

Conclusions

- There is evidence that the prevalence of chronic insomnia in outpatient and clinical populations is larger than in the general population.
- There is evidence that chronic insomnia is associated with older age, female gender, present or past psychiatric illness and psychological problems, medical conditions and poor general health, increased healthcare utilization, lower quality of life and social relationships, socioeconomic status (marital separation, unemployment, poorer working conditions and lower social status), and decrements in memory, mood, and cognitive function.
- Additional studies are needed to determine the incidence and natural history of chronic insomnia in adults. Similarly, additional studies are needed to explore the relationship between chronic insomnia and race/ethnicity, shift work, absenteeism, work performance, accidents, falls in the elderly, and the direct and indirect costs of the disorder. It is necessary that longitudinal studies be undertaken to explore the risk factors and consequences of chronic insomnia.
- There is evidence that benzodiazepines and non-benzodiazepines are effective in the management of chronic insomnia. There is some evidence that antidepressants are effective in the management of chronic insomnia: more research is required in this area. There is evidence that benzodiazepines, non-benzodiazepines, and antidepressants pose a risk of harm.
- There is some evidence that melatonin is effective in the management of chronic insomnia in subsets of the chronic insomnia population, and there is no evidence that melatonin poses a risk of harm. However, more research is required in this area given that the results are based on a small number of studies. Similarly, additional large-scale, randomized trials are needed to determine the efficacy of melatonin across subsets of the chronic insomnia population. There is insufficient evidence to conclude on the efficacy and safety of L-tryptophan and valerian in the management of chronic insomnia. Additional large-scale, randomized trials are needed in these areas.
- There is evidence that relaxation therapy and cognitive/behavioral therapy are effective in the management of chronic insomnia in subsets of the

chronic insomnia population. Additional large-scale, randomized trials are needed to determine their efficacy across subsets of the chronic insomnia population.

- There is evidence that benzodiazepines have a greater risk of harm than non-benzodiazepines.
- There is insufficient evidence to conclude whether there are differences between the short- and long-term efficacy and safety of the various categories of interventions in the management of chronic insomnia; additional long-term studies are needed.
- There is insufficient evidence regarding the efficacy and safety of combined treatments of pharmacological and psychological interventions, and sequential treatments, in the management of chronic insomnia; additional studies are needed in these areas.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Alberta Evidence-based Practice Center, under Contract No. C400000021. It is expected to be available in June 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 125, *Manifestations and Management of Chronic Insomnia in Adults.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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