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DO HERBAL AGENTS HAVE A PLACE IN THE TREATMENT OF SLEEP PROBLEMS IN LONG-TERM CARE?

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Abstract

Sleep disruption is common in the long-term care setting. This paper discusses the available literature on two herbal approaches to sleep problems in long-term care. The largest body of evidence exists for the use of the dietary/herbal supplements valerian and melatonin. While these agents appear to have a modest positive effect on sleep quality among older adults, most studies were small in size and included only subjective assessments of sleep quality. In addition, it is unclear whether these agents pose risks to long-term care residents due to potential drug interactions. Additional research is needed prior to making conclusive recommendations about the use of these interventions for sleep in the long-term care setting.

Keywords

alternative therapies; elderly; insomnia; sleep

PROBLEM

Sleep disruption among long-term care residents

Sleep disorders are prevalent in the elderly population, and numerous age-related changes in sleep, including an increase in arousals and awakenings from sleep, increased sleep latency, decreased sleep efficiency and total sleep time, more daytime napping, and earlier bedtime and morning rise times contribute to more complaints about sleep among older compared to younger individuals.[1;2] Sleep architecture changes with age as well. Sleep architecture refers to the underlying characteristics of sleep, which is divided into rapid eye movement (REM) and non-REM sleep. REM sleep has been implicated in memory and learning and is the period of sleep during which most dreaming occurs. Non-REM sleep is comprised of four stages (stages 1–4), which roughly parallel a “depth of sleep” continuum. Stage 1 is the lightest stage of sleep, and stage 4 is the deepest. Together, stages 3 and 4 are referred to as slow-wave sleep due to the characteristics of the EEG during these deeper stages of sleep. Slow-wave sleep has been implicated in physiological restoration and is the part of sleep during which growth

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hormone secretions are highest. Older adults experience significantly less slow-wave sleep, slightly less REM sleep and more stages 1 and 2 sleep compared to younger adults.[2;3] The age-related reduction in SWS and increase in Stage 1 sleep are much more pronounced in men than in women.[3;4] In addition, older people experience a greater number of brief arousals during sleep (again, more pronounced in men compared to women); however, many of the arousals from sleep appear related to breathing related sleep disorders (e.g., sleep apnea). While the implications of these changes are not fully understood, these changes may be related to neuroendocrine and/or neurotransmitter changes that occur with aging.

Studies examining rates of sleep disorders in the long-term care setting suggest that sleep disorders and sleep disruption are common in this setting as well. Martin et al.[5] have found that 69% of long-term care residents hade objective evidence of excessive daytime sleeping (defined as asleep >15% of the day from 9am to 5pm), 60% of whom also had objective evidence of disrupted nighttime sleep (defined as <80% nighttime sleep from 10pm to 6am). By contrast, Voyer et al.[6] found that, among a cohort of Canadian long-term care residents, only 6.2% met full diagnostic criteria for primary insomnia (i.e., difficulty initiating or maintaining sleep or non-restorative sleep that cannot be accounted for by medical or psychiatric disorders or by other sleep disorders) and 17.4% had at least one insomnia symptom based upon nursing staff interview and medical record review. The difference in rates of disrupted sleep between these two studies likely results from the very different methods used and differences in the definitions of “sleep problem.” Taken together, these studies suggest that the majority of sleep problems among nursing home patients are likely related to other medical or psychiatric conditions or to other sleep disorders (which were excluded in the Voyer et al. study).

Older adults use prescribed and over-the-counter sleep aids more often than young adults,[7] and there is some evidence to suggest that community-dwelling older adults may use complementary and alternative therapies for sleep at a higher rate as well, although no systematic data have been collected.[8;9]

The lack of standardization and quality control for dietary/herbal supplements is an area of concern. Under the Dietary Supplement and Education Act of 1994, these products are not required to undergo testing for safety and efficacy. Also, since there is a lack of standardization within the herbal industry, it is difficult to assess whether retail products actually contain the ingredients as advertised. In particular, one investigation conducted by ComsumerLab.com in 2004, found that four out of 17 valerian products tested had no detectable valerian content, another four only had half the amount listed, and one was contaminated with cadmium.[10] Additionally, herbal supplements may interact with prescription medications. This is a particular concern among long-term care residents who typically take multiple prescription medications.

SIGNIFICANCE OF THE PROBLEM

What are the limitations of current therapies, and what is the role for herbal remedies?

Management of sleep problems in long-term care is challenging, and with the exception of one study,[11] available data suggest that pharmacotherapy appears to contribute to negative health outcomes.[12–14] In addition, while there are a number of efficacy studies conducted with healthy older adults in the community, there are no controlled trials documenting the effectiveness of medications for sleep in the long-term care setting. Several studies have demonstrated that non-pharmacological interventions may be somewhat effective, although research personnel typically deliver the interventions, and strategies for incorporating these interventions into routine care have not been developed.

In the US, there is a growing interest in the use of Complementary and Alternative Medicine (CAM) interventions for sleep.[15] The NIH defines CAM as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine--that is, medicine as practiced by holders of MD (medical doctor) or DO (doctor of osteopathy) degrees and their allied health professionals."[15] In CAM, *complementary* medicine is used *together with* conventional medicine, and *alternative* medicine is used *in place of* conventional medicine." In the United States, 36% of adults are using some form of CAM. When megavitamin therapy and prayer specifically for health reasons are included in the definition of CAM, that number rises to 62%. Overall, Americans spend about $5 billion out-of-pocket on herbal products, with sleeping problems accounting for about 2% of natural product use.[15]

Here we review available evidence for the use of two CAM interventions for sleep: valerian and melatonin. Data from available randomized controlled trials are reviewed. We discuss the potential utility of these agents in the long-term care setting specifically, and we highlight limitations of the available literature. Information on both agents is summarized in Table 1.

Valerian

Valerian (*Valeriana officinalis*) is a perennial plant native to Europe and Asia and naturalized in North America. Preparations of valerian marketed as dietary supplements are made from its roots, rhizomes (underground stems), and stolons (horizontal stems). There is no scientific agreement as to the active constituents of valerian, and its activity may result from interactions among multiple constituents rather than any one compound or class of compounds. Valerian has been used as a medicinal herb since at least the time of ancient Greece and Rome. Its therapeutic uses were described by Hippocrates, and, in the 2nd century, Galen prescribed valerian for insomnia. It was listed as an anxiolytic and hypnotic in the US National Formulary until the 1940s, when more potent pharmacologic agents became available.[16]

There is currently no uniform agreement on the mechanism of valerian's pharmacological activity. One proposal suggests GABA agonistic activity.[17] Other more recent studies have found possible effect on adenosine and 5HT-5a receptors.[18;19] 5HT-5a receptors are expressed in the suprachiasmic nucleus, the intergeniculate leaflet, the dorsal raphe nucleus and the medial raphe nucleus, which are involved in the body's circadian (24-hour) timekeeping system.[19]

Few studies have examined the impact of valerian on sleep among older adults, and none have been conducted in the long-term care setting. Nine randomized, placebo-controlled, double blinded clinical trials published through 1999 were evaluated in a systematic review by Stevinson and Ernst.[20] Two of these trials were focused on elderly poor sleepers. These two studies and one additional study of younger adults were the only ones that evaluated valerian administration for more than seven days. The first by Kamm-Kohl et al. evaluated 80 chronically ill patients in geriatric hospitals who received valerian or placebo for 14 days. Assessment was performed by two validated questionnaires and a sleep rating scale. Improvement in sleep latency (i.e., how long it takes to fall asleep after going to bed) and sleep duration with valerian compared to placebo was noted. A pilot study by Schulz et al. utilizing polysomnography (the gold standard method for sleep assessment) on 14 elderly female poor sleepers found, after eight days of valerian, significant increases in slow wave sleep (i.e., deep sleep) and decreases in stage 1 sleep (i.e., the lightest stage of sleep) compared to placebo, suggesting valerian improved overall sleep quality.[21] The third study by Vorbach et al. monitored 128 individuals (across age groups) with sleep difficulty who received valerian or placebo for 28 days, following treatment response with questionnaires. Valerian resulted in improvement in sleep quality, less difficulty falling asleep, and fewer nighttime awakenings.[22] The remaining six trials studied short-term administration (3–5 days) and/or included people

with no sleep complaints. Three found acute improvement, and three found no significant differences between valerian and placebo. Overall, significant differences were noted more frequently in studies with more prolonged administration and in individuals with prior sleep complaints. Two randomized double blind comparative studies have been performed comparing valerian to oxazepam for insomnia.[23;24] These studies included some elderly patients but had a wide age range. Both utilized sleep questionnaires and followed patients for either four or six weeks. No significant differences were noted between the two treatments, as they were comparable in improved sleep parameters.

Two other studies of valerian measuring changes in polysomnography have been performed in the last six years, since the publication of the review discussed above. The first was a randomized, double-blind, placebo controlled, cross over study that evaluated short term (1 dose) and long term (14 doses) use in 16 non-elderly patients with insomnia.[25] No short-term differences were noted, but there was a long-term decrease in slow-wave-sleep latency (i.e., the time from initially falling asleep to entering slow wave sleep) and increased percentage of time spent in slow-wave-sleep. Interestingly, both valerian and placebo showed decreased stage 1 sleep percentage (i.e., less time in the lightest stages of sleep) and increase in REM sleep (i.e., the period of sleep during which most dreams occur).

One interesting study investigated the usefulness of valerian in patients discontinuing benzodiazepine use.[26] Nineteen non-elderly chronic benzodiazepine users were followed with polysomnography and questionnaires. There was a 14-day tapering period, followed by a 2-day washout, then 15 days of valerian or placebo. Both groups showed increased slow wave sleep and decreased stage 1–2 sleep, which were thought to show physiological recovery after washout. The valerian patients had decreased wake time after sleep onset (WASO) compared with placebo, which appeared to correlate with reports of improved sleep compared to placebo.

Historically, Valerian has been consumed in the form of a tea, (1.5 to 3 grams root steeped for 5 to 10 minutes in 150 milliliters boiling water); however, this formulation has not been studied for insomnia. Studies of insomnia have included a broad range of doses (400–900mg) taken 30–60 minutes before bedtime as an aqueous solution or in tablet form. While no consensus exists on precise dosing, a 600mg dose one hour before bedtime has been most widely studied.[27]

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring neurohormone primarily produced by the pineal gland. Its secretion is timed by the oscillation of the endogenous circadian pacemaker.[28] Since its discovery in 1958 there have been descriptions of its use as a hypnotic.[29] It has been proposed that melatonin acts on receptors of the suprachiasmatic nucleus (SCN), causing adjustments in the timing of the circadian pacemaker, and possibly attenuating a daytime alerting process emanating from the SCN.[28]

Some studies have examined the impact of melatonin on sleep among older adults, but none have been conducted in the long-term care setting. A systematic review of treatment of elderly insomnia patients with melatonin was performed by Rikkert.[30] Six double blind randomized crossover trials were evaluated, with measurements in these studies done with polysomnography or wrist actigraphy. In five of six studies, melatonin improved either sleep latency (time to fall sleep) or sleep efficiency (time asleep out of the total time in bed) compared to placebo. One study found even more striking improvements in patients who were prior benzodiazepine users. The review did note that there did not appear to be a simple causal relationship between low melatonin levels (measured in urine, serum or saliva) and insomnia in the elderly. No changes were noted in subjective sleep improvement, and slow wave sleep

(i.e., deep sleep) was not increased. The studies reviewed all had small sample sizes, ranging from 10 to 26 participants.

A more recent study with elderly subjects was done by Zhdanova.[31] In a double blind, placebo-controlled study, patients were monitored with polysomnography and given three different doses of melatonin with washout periods in-between. At all doses, sleep efficiency in the middle and latter third of the night was improved. No other differences were noted on other objective parameters. Percentage of slow wave sleep was unchanged. As in the other studies, no correlation was seen between serum melatonin levels resulting from exogenous melatonin administration and sleep quality. Singer et al.[32] studied the efficacy of melatonin on insomnia in Alzheimer's patients. This was a randomized, placebo controlled trial of 157 patients, who were treated for a 2-month period. No significant differences in objective sleep measures were noted.

In 2005, Brzezinski et al. performed a meta-analysis of the effects of exogenous melatonin on sleep across age groups.[33] This meta-analysis only included trials that were randomized, double-blind, placebo controlled and used objective measures of sleep evaluation (actigraphy or polysomnography). Overall, the authors concluded that melatonin caused statistically significant decreases in sleep onset latency, increases in sleep efficiency, and increases in total sleep duration; however, only changes in sleep efficiency and duration were clinically significant. Sleep architecture was not significantly affected, and no next-day "hang over" effects were noted with melatonin, as may occur with some benzodiazepines used to treat insomnia.

Administration of melatonin requires consideration of the natural activity of the hormone. Melatonin can have both sleep inducing and chronobiologic (i.e., circadian rhythm) effects. Studies have typically tried to capitalize on the sleep-inducing effects with administration at or near the desired bedtime. To capitalize on the chronobiologic effects, timing of administration must be linked to biological markers of the circadian clock. Clock timing is typically determined in a laboratory setting in which natural melatonin levels and/or body temperature rhythms are measured.[34] Natural melatonin levels typically peak several hours after habitual sleep onset time. To shift the timing of sleep earlier, melatonin should be given before natural melatonin levels peak, and to shift the timing of sleep later, melatonin should be given after natural melatonin levels peak. In the nursing home setting, one typically wishes to shift sleep to a later time (to improve evening alertness and reduce early morning awakenings). Melatonin should then be given in the early morning. Melatonin has not been studied in this way in the nursing home. While early studies of melatonin used super-physiologic doses (5–10mg), more recent studies have found that very low doses (0.1–0.25mg) are generally more effective, perhaps because these doses more closely mimic physiological melatonin levels.[30;35]

Although not an herbal supplement, one recently-approved prescription sleep aide acts on melatonin receptors MT1 and MT2.[36] A double-blind, placebo controlled crossover study was done by Zelman et al. in 2005,[37] using Beta-Methyl-6-Chloromelatonin (ramelteon), a melatonin receptor agonist that does not cause hyopothermia, as high doses of melatonin occasionally can. This choice was designed to eliminate hypothermia as a possible mediator of melatonin's soporific effect. The study included 40 patients who used three different doses of the melatonin agonist with washout periods between dose changes. Sleep latency was significantly reduced with an escalating dose effect. Other objective sleep parameters including sleep efficiency, sleep architecture, and total sleep were not significantly changed. There were no significant differences in serious side effects across groups.

In a large study (n=829) of the effects of ramelteon on subjective sleep quality among older adults with chronic insomnia, Roth et al.[38] found that 4 or 8 mg of ramelteon led to improved sleep latency (i.e., participants fell asleep more quickly) compared to placebo. They also found no evidence of negative consequences with discontinuation of the agent after 5 weeks.

Ramelteon (Rozerem™) was recently approved by the FDA for use as a sleep aide. The adult dose is typically 8mg, taken at bedtime for sleep onset insomnia. The effectiveness and safety of this agent has not been fully evaluated in the frail elderly, however, and additional research is needed.

DISCUSSION

Given the widespread nature of sleep problems among older adults, the limitations of available pharmacological treatments and difficulties incorporating most nonpharmacological interventions into routine clinical care, CAM interventions are appealing. However, data to support the effectiveness of many CAM interventions for sleep are lacking, and at times, results are conflicting (refer to Table 1). In our review of the literature on valerian, we found that several RCTs have been conducted; however, only two studies focused on the elderly, only one of which involved long-term care residents. The study by Kamm-Kohl et al. on institutionalized elders did reveal improvements in sleep latency and duration and included 80 patients; however, it did not utilize objective measurements of sleep, relying solely on questionnaires.[39] While the pilot study by Shultz et al. employed objective measures of sleep (polysomnography) and showed an increase in slow wave sleep among older adults, this study was limited by small sample size.

Data for melatonin did not include primary studies in long-term care, but we did identify three studies of elderly participants. The systematic review by Rikkert et al. reported improvements in various sleep parameters in five out of six randomized trials utilizing objective measures of sleep (wrist actigraphy or polysomnography), although study sizes were small. The study by Zhdanova et al. showed improvements in sleep with melatonin, but this study was also limited by small study size. Singer et al. studied a group of Alzheimer's patients and did not find improvements in sleep with melatonin. Across studies of melatonin, sleep architecture did not appear to be significantly affected (positively or negatively). Studies with ramelteon (a melatonin receptor agonist) do show promise in terms of improved sleep among older persons with insomnia, although studies have not been conducted in long-term care settings. Together these findings leave some question regarding the utility of melatonin in the long-term care setting, and more work is needed in this area.

Other alternative/complementary therapies are less well studied, and at this point, there is insufficient data to evaluate the utility of the majority of alternative/complementary therapies for sleep among older adults, including those in long-term care settings. The availability of systematic research on safety, effectiveness and efficacy of CAM therapies is somewhat limited making a complete evaluation challenging. First, some peer-reviewed papers are published in scientific journals that are not available in university or medical libraries and/or in languages that are not widely read. Second, information available online is difficult to evaluate for quality and accuracy, and many CAM websites require fees to access information.[10;40]

Other limitations of the available research literature include the fact that there are still relatively few studies of CAM interventions in long-term care, and community studies have often focused on healthier elderly patients, excluding those with significant chronic disease or limited mobility.

CONCLUSIONS

The majority of studies of herbal agents to treat sleep disorders did not include elderly subjects in long-term care, the total number of available studies was small and most studies had small sample sizes. It appears, however, that valerian and melatonin may have some utility in the long-term care setting. Nonetheless, more research is needed. It is not yet clear whether these agents would be any more effective than current therapies or whether they may negatively interact with prescription medications. Overall, evaluation of CAM interventions in the long-term care setting needs further research before recommendations can be made regarding their use.

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Table 1

Valerian and Melatonin use in the long-term care setting

Agent	Mechanism of action	Dosing/administration time	RCTs with community-dwelling older adults	RCTs with older adults in instutional settings
Valerian	Unclear. Possibly GABA agonistic[17] or 5HT-5a receptor[18;19] activity	600mg one hour before bedtime	2 RCTs -Schulz et al., 1995[21] -Vorbach et al., 1996[22*]	1 RCT -Kamm-Kohl et al., 1984[39]
Melatonin	Melatonin receptors in the suprachiasmatic nucleus and other areas	0.1–0.25mg at bedtime OR 0.1–0.25mg after the midpoint of the sleep period for phase shifting	2 RCTs -Zhdanova et al., 2001[31] -Singer et al., 2003[32**]	None

* This study included participants across age groups, including older adults.

** This study included only participants with Alzheimer's disease.

RCT = randomized, controlled trial.