The Effectiveness of Melatonin for Insomnia in Older Adults:

A Systematic Review

By

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A Master's Paper submitted to the faculty of
The University of North Carolina at Chapel Hill
In partial fulfillment of the requirements for
The degree of Master of Public Health in
The Public Health Leadership Program.

Chapel Hill

2004

Advisor

Second Reader

4/29/04

Date

Abstract

Background: Age-related insomnia is a condition affecting over 50% of those aged 65 years and older, and is characterized by difficulties in sleep onset and maintenance. Poor sleep is associated with cognitive impairment, daytime sleepiness, injuries, and decreased quality of life. Common insomnia pharmacologic therapies often result in side effects and the development of tolerance.

Purpose: To review the evidence of the effectiveness of melatonin (MLT) for insomnia in adults 65 years and older?

Methods: A priori study inclusion criteria included: study subjects aged 65 or older, male or female; randomized, placebo-controlled trial; objective outcome measures to include either sleep log or diary, actigraphy and/or overnight polysomnography. To identify relevant studies, articles published from 1966 to March 2004 were retrieved from the online databases: MEDLINE, CINAHL, PsychInfo, DARE, Cochrane, and EBM Reviews. MEDLINE (via PubMed) was searched using Medical Subject Headings (MeSH terms) "Sleep Initiation and Maintenance Disorders" and "Melatonin." A total of 121 English language journal articles were identified using this search strategy. All but 4 of these were excluded due to lack of randomization, inclusions of subjects less than 65 years, or failure to include objective data regarding sleep parameters.

Results: Four crossover-designed studies of melatonin included 74 insomniacs aged 65 years or older. In three of four randomized, placebo-controlled trials, sleep efficiency was significantly improved compared to placebo, while sleep latency was significantly improved in two, with a trend toward significance in a third. In two others, total sleep time improved significantly. Further, in all but one of the included studies, melatonin significantly improved at least one actigraphic measure of sleep quality.

Discussion: The results of this systematic review suggest that melatonin may be effective in improving two objective measures of insomnia, sleep efficiency and sleep latency. Although melatonin may be a safe alternative to standard hypnotic therapy, its use will be limited until more information is available regarding appropriate patient selection and dosing, especially when effective therapies exist (e.g., cognitive behavioral, standard hypnotics). This information will need to be obtained from much larger, well-designed, randomized controlled trials.

Burden of Suffering from Insomnia

Definition of Insomnia

Insomnia is a disorder characterized by a difficulty initiating or maintaining sleep and results in daytime dysfunction.[1] The definition of insomnia can be either primary or secondary depending on cause. To distinguish, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) advises using the term primary insomnia when there is not an additional medical or psychiatric disorder that could be precipitating the sleep disturbance. The International Classification of Sleep Disorders (ICSD), however, does not use the term primary insomnia but differentiates three subtypes of insomnia (psychophysiological, sleep state misperception, and idiopathic).[1]

For the purposes of this review, the term primary insomnia from the DSM-IV (which encompasses the three subcategories of the ICSD) will be used. Since insomnia directly related to neurodegenerative disorders, depression, medical comorbidities may be different from primary insomnia; they will be excluded from this review. Further, since there is no specific definition for "age-related insomnia," the complaints most research authors have used as the definition of insomnia will be used in this review. These complaints include one or more sleep disturbances that are associated with daytime consequences, occur three or more time per week and last a minimum of six months.

Etiology and Pathophysiology

The basic classification of insomnia is based on the duration of complaints, whether acute or chronic.[2] The exact duration of sleep complaints that justifies one diagnosis over another varies among authors and sources. Transient insomnia is referred to when sleep problems and complaints last less than two to four weeks. Chronic insomnia generally is regarded as complaints that persist longer than one month.[1,3]

Acute or transient insomnia often is closely related to a variety of precipitants. Examples of precipitants seen in older adults include environmental alterations, grief or bereavement, and/or medical illness.[1] Interestingly, sleep of older adults without medical or psychiatric illness may be more similar to those of younger persons.[4]

Chronic insomnia patients may have many factors contributing to their condition and a specific precipitant may be less obvious or absent.[1] The exact physiologic mechanism of primary or chronic insomnia, unrelated to those associated with transient insomnia noted above, is unclear. Some have suggested that chronic insomniacs may be over-stimulated and hyper-aroused. Many of these patients have been noted to exhibit increased metabolic rates and body temperatures compared with healthy controls.[1]

Among the elderly, age-related changes in the circadian rhythm also may lead to poor sleep.[5] The circadian pacemaker (or clock), located in the suprachiasmatic nucleus (SCN) of the hypothalamus, regulates many physiologic functions and the sleep/wake cycle. Abnormalities of this

system may lead to poor sleep.[6,7,8] The concept that sleep may be disturbed by alterations in the circadian system of older persons is supported by decreased circadian rhythm amplitude and an advance phase-shifted rhythm, manifested clinically by earlier sleep onset and wake times.[9] Disturbances of sleep quality and duration also may be related to the fact that older adults generally have more abnormalities of sleep initiation (i.e., the time it takes to fall asleep), sleep maintenance (i.e., the ability to stay asleep), sleep efficiency (i.e., the time asleep/time in bed), sleep duration and nocturnal awakenings or arousals.[10] Although any of these sleep parameters may be altered in the elderly, larger disturbances have been reported in sleep duration and the ability to maintain sleep, as opposed to sleep initiation.[11] Consequently, older persons often have more fragmented sleep and daytime napping than younger controls.[8]

Prevalence of Insomnia

Age-related insomnia is a common complaint of the elderly. In a large sample of greater than 6,000 subjects, the National Institute on Aging found that 28 percent of older adults reported problems falling asleep (sleep initiation), and 42 percent reported problems with both falling asleep and staying asleep (sleep maintenance).[2] In a telephone survey conducted by the National Sleep Foundation (NSF) in 2003, 1506 community-dwelling subjects between the ages of 55 and 84 were interviewed about their sleep. Overall, nearly one-half (48 percent) of

older adults reported having one or more symptoms of insomnia at least a few nights per week.[12] Further, although the prevalence of insomnia among primary care patients has been estimated to be greater than 50 percent, less than one-third of these patients report their complaints, and much less receive treatment.[13,14,15]

Morbidity from Insomnia

Insomnia among older adults causes significant morbidity. In the above recent NSF survey, 38 percent of persons who reported excellent or very good quality of overall health were less likely to have symptoms of insomnia more than a few nights a week. That compares with 71 percent of those reporting fair or poor quality of health. Similarly, 42 percent of those reporting excellent or very good memory were less likely to have symptoms of insomnia compared to 68 percent for those with fair or poor memory.[12] Sleep abnormalities often cause significant daytime sleepiness that results in slower reaction times, impaired mental abilities, increased rates of injuries, gait and balance instability and a decreased self-reported health status.[16]

There is some evidence that insomniacs also have greater rates of healthcare utilization due to an increased rate of accidents. After adjustments for age, gender, BMI and study site, 6,440 participants from the Sleep Heart Health Study (SHHS), reported that those with self-reported insomnia were noted to have an increased Chronic Disease Score (CDS). Although the increases in CDS were modest, due to the high

prevalence rates of insomnia in the general population, these increases may be associated with a cost burden for the U.S. healthcare system. A potential limitation of this study may include a selection bias. This cohort consisted of subjects already involved in epidemiologic research and thus may have more healthcare contact than the general population. Another problem may have been a measurement bias, since the authors did not measure direct health costs, but a surrogate marker, CDS score. [17]

Furthermore, patients suffering from insomnia may be at a higher risk of developing an affective disorder, such as depression or anxiety. Traditionally, insomnia has been considered secondary to depression. This may not necessarily be the case in all circumstances. [18] In a large European population-based telephone study of 14,915 subjects, aged 15 to 100 years, 40 percent of those with affective disorders reported insomnia appearing before any mood disorder symptoms. In 38 percent of the cases, insomnia appeared at the same time as the anxiety disorder and in 34 percent, after the anxiety disorder.[19] Other longitudinal studies have reported that insomnia is a risk factor for the development of depression,[20] but whether depression causes insomnia – or vice versa – is unclear.[18]

Dependency of older insomnia patients on alcohol and hypnotic medications also is a concern since this dependency may precipitate sleep abnormalities, lead to tolerance and addiction, cause cognitive difficulties, and worsen other comorbidities.[22] Alcohol often is used as a sleep aide for patients suffering from insomnia. While it is true that alcohol consumption may initially lessen sleep latency, as it is metabolized, it

typically causes more sleep fragmentation and nighttime arousals. Due to a prolonged metabolism in the elderly, alcohol becomes a much more potent hypnotic but with increased side effects.[16]

The use of over-the-counter sedating agents (e.g., antihistamines) and prescription sedative hypnotics (e.g., benzodiazepines) also is problematic in the elderly. These agents may have significant side effects; probably most important of these is gait abnormalities and subsequent falls. The etiology of falls in older adults is usually multifactorial and not related to one cause.[23] In a recent large study, benzodiazepines were shown to be associated with a significantly increased risk of falls in women aged 65 years of age and older.[24] However, the true association of hip fracture and benzodiazepine has been less clear.[25,26,27]

In a case-controlled study by Pierfitte and coworkers, 245 persons older than 65 years presenting to a university emergency department with hip fracture were compared against 817 controls. Benzodiazepines use was determined from medical records, questionnaires, or plasma samples at admission. Benzodiazepine use, except for lorazepam, was not associated with increased odds of hip fracture (OR 0.9, 95% CI 0.5, 1.5). Since controls were selected from other hospital admissions, their drug use (including benzodiazepines) may be higher than a healthy control population, and the association between benzodiazepine usage and hip fracture may have been lessened.[28] In the prospective cohort study of 8,127 older women, Ensrud and associates found no statistically significant increase in risk of hip fracture among women taking

benzodiazepines after adjustment for multiple risk factors (Adj. RR 1.20, 95% CI 0.72, 2.00). Additionally, no association was found between those taking long- or short-acting preparations and hip fractures.[27] In contrast to these reports, a 2003 review of benzodiazepine use and hip fracture, Cumming and Couteur identified 11 primary epidemiologic studies. After excluding four hospital-based, case-controlled studies (due to difficulties finding appropriate controls), and one other comprised only of institutionalized subjects, the authors reported an increased risk of hip fracture of less than 50 percent among the remaining six high-quality studies.[29]

Benzodiazepines also may be associated with increased rates of motor vehicle crashes. In a case-controlled study of 19,386 UK drivers between Aug 1, 1992, and June 30, 1995, 235 drivers taking a benzodiazepine were involved in a traffic accident and had an increased odds of accidents compared to controls (OR 1.62, 95% CI 1.24,2.12).[30] In another case-controlled designed study of 224,734 elderly Canadian drivers, 5,579 injurious automobile crash were reported. The use of long-acting benzodiazepine medications but not short-acting ones, were associated with an increased odds of automobile accidents (1.45, 95% CI 1.04,2.03).[31]

Treatments for Insomnia

There are several therapeutic strategies available for older adults suffering from insomnia. Most common strategies include cognitive-

behavioral techniques, environmental modifications and as mentioned above, pharmacotherapy.

Non-pharmacologic

Cognitive behavioral therapies usually include efforts to improve sleep hygiene, and often include: 1) limiting daytime napping, 2) limiting stimulant consumption (e.g., caffeine and nicotine), 3) using the bed for sleeping and sex only and 4) keeping a regular sleep schedule or routine.[2] Other effective methods might include sleep restriction and stimulus control.[32,33,34,35] Environmental modifications for age-related insomnia often include stimulus control and bright-light therapy for those suffering from phase-shift disorders, in an attempt to delay, or phase-shift their circadian rhythms and consolidate sleep time. [36, 37, 38, 39, 40]

In a recent meta-analysis comparing the efficacy of pharmacologic and cognitive behavioral therapies (stimulus control and/or sleep restriction) revealed comparable treatment effects in most outcome variables studied (total sleep time, nighttime awakenings and sleep latency) except in regards to sleep latency, which was significantly reduced in the behavioral trials compared to those using pharmaceuticals. Due to wide confidence intervals between mean treatment differences and the timing of benzodiazepine administration in many trials (often just before bedtime) which more than likely effected sleep maintenance, the true difference of sleep latency may be somewhat more modest.[13]

A major limitation of cognitive behavioral therapies for those patients with transient insomnia is cost. Hypnotic agents used for 30 days are much less expensive than multiple behavioral education sessions.[13] In terms of chronic insomnia, these cost differences may be minimal, especially when other studies suggest that behavioral therapies may provide more long-lasting improvement in sleep outcomes. In a 1999 review of nonpharmacologic treatment for chronic insomnia, Morin and colleagues reported that a majority of patients achieved good outcomes with a variety of behavioral therapies. Despite these findings, the authors found limited evidence that improved sleep in these studies resulted in improved daytime function.[41]

Pharmacologic

Pharmacotherapy for insomnia usually involves benzodiazepine hypnotics. Due to the serious side effects associated with hypnotics in this population, as mentioned above, newer short-acting, non-benzodiazepine agents (e.g., zolpidem and zaleplon) have been increasingly prescribed. Although these agents generally are considered safer than other hypnotics, current recommendations suggest that they be used infrequently and for short periods for transient insomnias. Chronic use of any hypnotic is generally discouraged, due to side effects and difficulties with withdrawal.[22] Further, these agents slow metabolism and thus increase drug concentrations as well as interactions with other medications taken by elderly patients.[42]

Nonprescription, or "over-the-counter," sleep aides are frequently used by older insomniacs. Sedating antihistamines, alcohol, and melatonin are some of the more common agents. Sedating antihistamines often are successful at promoting sleep onset or decreasing sleep latency, but the development of tolerance, anticholinergic side effects and morning drowsiness, limit their usefulness. Alcohol is another popular substance used by older patients for the promotion of sleep initiation. Notwithstanding the other significant adverse consequences of alcohol in this population, [43] the limitation of alcohol as a sedative hypnotic includes increased sleep disruption, particularly during the later sleep period when alcohol levels decrease due to metabolism, and the development of dependence.[22]

Melatonin

Melatonin is a derivative of tryptophan, which is produced and secreted from the pineal gland. The secretion of melatonin is regulated by light and dark periods. During daylight hours, light impulses sent from the retina to the suprachiasmatic nucleus of the hypothalamus, inhibit beta-adrenergic sympathetic outflow and thereby decrease melatonin secretion. Dark periods have the opposite effect, stimulating sympathetic flow to the pineal gland and promoting melatonin secretion. Correspondingly, serum levels of melatonin have been shown to peak during evening hours but remain low during daytime. Melatonin

suppression occurs only with ocular light but not with extraocular light, such as light directed toward the popliteal fossa, or constant dim light.[44, 45]

Melatonin, as opposed to sedative hypnotics, has a low side effect profile. In a study to determine adverse effects associated with 28 days of therapy with 10mg of melatonin, multiple laboratory outcome measures were assessed. Results indicated no toxicologic effects of melatonin over this one-month period.[46] In another study, however, endogenous melatonin secretion, reflected by a drop in core body temperature, was associated with decreased cognitive processing.[47] There also is some preliminary evidence that melatonin may have a negative impact on orthostatic tolerance in the general population. [48] In attempt to evaluate the potential effects of melatonin premedication for preoperative anxiolysis, melatonin was found to be associated with anxiolysis and sedation without cognitive or pyschomotor side effects. It was not, importantly, found to decrease recovery.[49] One potential limitation of melatonin is a concern over orthostatic hypotension.

Discovered in 1958 by Lerner et al, the hypnotic effects of melatonin have been shown in healthy persons. Melatonin administered to a group of healthy young men was associated with a significant correlation between salivary melatonin levels and the timing of increased subjective sleepiness.[50]

Melatonin has been used to promote sleep in a variety of conditions, circumstances and populations. In conditions such as jet lag and some circadian rhythm sleep problems, melatonin has been shown to

be somewhat effective.[51] In patients with schizophrenia, melatonin was found to improve sleep efficiency in those whose sleep quality was poor.[52] In medically ill patients with transient insomnia, melatonin was found to significantly decrease sleep latency, increase sleep duration and improve sleep depth without causing daytime dysfunction.[53] Melatonin also has been recently shown to improve circadian rhythms in some blind patients.[54] The effectiveness of melatonin in older adults with insomnia has been less studied.

The available literature regarding endogenous melatonin's ability to initiate and promote sleep maintenance[55] and reports suggesting that decreased serum levels of melatonin are associated with sleep disorders,[56] has prompted studies to evaluate melatonin supplementation. This, coupled with evidence suggesting that there are age-related declines in melatonin circulating levels,[57, 58, 59, 60] and even lower levels in primary insomniac patients compared with normal sleepers (45 v. 60 pg/ml, respectively),[61] have led researchers to hypothesize that exogenous melatonin may be useful in the treatment of insomnia in older adults.[58] In addition, not only do older adults produce less melatonin, they may also have more difficulty responding to the hormone that is secreted. This supports the theory that there may be a lessened response to the hypothermic effects of melatonin in elders.[62, 63] The purpose of this review is to examine the available evidence for melatonin supplementation in older insomniacs and – based on these findings – whether melatonin should be recommended as a therapy for this population.

Methods

To identify relevant articles, articles published from 1966 to March 2004 were retrieved from the online databases: MEDLINE, CINAHL, PsychInfo, DARE, Cochrane and EBM databases. MEDLINE (via PubMed) was searched using Medical Subject Headings (MeSH terms) "Sleep Initiation and Maintenance Disorders" and "Melatonin." A research librarian was consulted to assist in this systematic search.

Articles and abstracts were reviewed by the author for appropriateness and all potentially relevant articles identified by the search were evaluated for inclusion in the analysis. To be included, studies must have 1) a randomized placebo-controlled design, 2) included only subjects 65 years of age and older (male or female), 3) provided information concerning participant-oriented outcomes (sleep efficiency, duration, maintenance, and/or awakenings) and described the objective instruments used (i.e., sleep log, sleep diary, actigraphic and/or overnight polysomnographic) and 4) included results for both treatment and control groups.

A summary of included articles, describing design, subjects, intervention evaluated, outcomes measures, and methological quality, is presented in Table 1. Any article that failed to meet any of the stated inclusion criteria was excluded from further analysis. Exclusion criteria included study designs other than randomized placebo-controlled (i.e., case-controlled, case reports, case series, animal studies, and observational studies), non-English language articles, subjects with other

primary sleep disorders (i.e., obstructive or central sleep apnea, restless legs syndrome, or periodic leg movements of sleep), other comorbidities that affect sleep, specifically dementia and/or depression.

Each article was assigned a grade of "pass" or "fail" for each of the stated inclusion/exclusion criteria. The author graded articles and assessed methodologic quality of each included trial using modified criteria of Khan and associates.[64] The criteria components included: 1) specified eligibility criteria, 2) concealment of allocation, 3) similarity of groups at baseline, 4) randomization of treatment groups, 5) blinding to allocation, patient, and provider, 6) point estimates for the primary outcome measures, and 7) intent-to-treat analysis. Studies were rated as "good," "fair," or "poor." A "good" rating suggested that the study adequately addressed all quality criteria; a "fair" rating suggested the trial did not adequately all quality indicators; and a "poor" rating was assessed if the trial contained a fatal flaw that invalidated the study results.

Results

A total of 121 English language journal articles were identified using this search strategy, of which four randomized, placebo- controlled trials were identified and met the inclusion criteria for this review. All of the trials were of a crossover design (Haimov et al., 1995; Garfinkel et al., 1995; Garfinkel et al., 1997; Baskett et al., 2003).[65, 66, 67, 68] Six reports did not meet inclusion criteria due to design, and included: abstract, research

letter, retrospective case study and three open-label studies. Twelve randomized, placebo-controlled trials of melatonin were excluded because subjects did not have insomnia or were younger than age 65 years of age. Six other randomized, placebo-controlled trials were further excluded, even though they included subjects older than 65 years, because no subgroup analyses by age was performed. The majority of other reports were excluded due to inclusion of subjects with cognitive impairment, bipolar disorder or depression.

Outcome Measures

Each included study reported actigraphic measures of sleep quality effects of melatonin in older insomniacs. The measurements that were calculated and reported in each of the four studies include: sleep latency (time in minutes to fall asleep) and sleep efficiency (calculated by dividing time asleep over total sleep period, and reported as a percent). The following actigraphic outcome measures were not consistently reported, and include: activity level during sleep period (the mean sum of actigraphic movements recorded during sleep divided by sleep duration) (Haimov et al., 1995), number of awakenings (Garfinkel et al., 1997; Baskett et al., 2003), awake after sleep onset (Garfinkel et al., 1995; Garfinkel et al., 1997) and total sleep time (Garfinkel et al., 1995; Garfinkel et al., 1997; Baskett et al., 2003). Empirical data of self-reported sleep quality, based on the Pittsburgh Sleep Quality Index (PSQI) score, was reported only in the study by Baskett, et al., 2003. All studies measured

continuous actigraphy outcome endpoints repeatedly over consecutive nights (ranging from 3 to 7) in order to decrease intra-patient variability and thus increase statistical power. A summary of results is presented in Table 2.

An actigraph is a wrist-worn device that uses an accelerometer to record wrist movements and automatically differentiates between sleep and wake states. It has been used in clinical trials to discriminate between sleep and wake episodes and correlates highly with polysomnographic measures.[69] More importantly, actigraphy has been shown to be sufficiently sensitive to detect the effects of insomnia treatments in elderly subjects.[70] It has the additional benefit of the ability to assess sleep for longer durations in more natural circumstances and environments (i.e., subjects are at home and in their own beds).[71]

Summary of Studies

Haimov et al., 1995

Hiamov and colleagues recruited (n=26) patients with reported sleep problems on at least three evenings per week if those problems were present for at least six months. (An elderly group without insomnia was included in the baseline but was not included in any of the treatment arms). The subjects with insomnia were either community-dwelling (n=8), or institutionalized (n=18). None of the subjects suffered from dementia on Mini-Mental Status Exam (MMSE), or depression on the Hamilton rating scale, however, no specific criteria were reported in the

text regarding cut-offs. The potential subjects were then interviewed by an experienced physician to rule out other medical reasons for sleep problems or other primary sleep disorders. Since a priori hypothesis of this study was that elderly insomniacs classified as melatonin-deficient, peak secretions of melatonin were evaluated and found to be lower in the both insomnia groups.

After a placebo run-in period of one week, both groups of insomnia subjects received 2mg of fast-release, slow-release or placebo during three experimental periods (including a two-week wash-out period between each period). To determine if tolerance or side effects developed, a two-month period of either 1mg melatonin or placebo was used. Actigraphic measurements recorded activity during all treatment periods, except for the last two-month period when recording was monitored only during the last week of therapy. To limit intra-subject night-to-night variability, actigraphic measures for each subject were averaged over the week. Outcome analysis included all 26 subjects for sleep efficiency and activity but due to institutional bedtimes, institutionalized subjects were not included in sleep latency analysis.

In this study, the 2mg slow-release formulation of melatonin revealed a significant improvement in sleep efficiency (80.4 v. 77.4%, p=0.008) and sleep latency (37 v. 54, p=0.05). Sleep latency also significantly improved with a 2mg fast-release melatonin formulation as compared to placebo (32 v. 54 minutes, p=0.05). There was also statistical improvements in sleep latency (14 v. 54, p=0.05), sleep efficiency (84.3 v.

77.4, p<0.001) and activity levels (18.6 v. 26.9, p<0.001) in the open-label, two-month trial 1mg sustained–released melatonin, but conclusions from this treatment arm may be more problematic due to lack of blinding of treatment groups.

How and where the subjects were recruited was not clearly identified in the article. Although eligibility criteria were clearly specified, there may be selection bias since both institutionalized and community-dwelling subjects were included in the insomnia group and it is unclear if subjects were truly similar at baseline. Subject randomization was reported but details of assignment and method of concealment were not described. Although the study was reportedly conducted in a double-blind manner, the allocation process was not described in the paper. Only three subjects withdrew from the study but reasons for withdrawal were not described and there was no mention of intent-to-treat analysis reported. There was no sample size calculations reported in the article. The continuous variables of actigraphic outcome measures were analyzed using paired t-tests, reporting means, standard deviations, and significance levels of <0.05.

Garfinkel et al., 1995

Elderly insomniacs (n=12) were included in the randomized, double-blind, crossover study by Garfinkel and colleagues (1995) of controlled-release melatonin on sleep quality indicators among elderly insomniacs. The subjects were recruited after a sleep disorders lecture at

senior center. All were independently living and three out of the initial 15 were excluded because of dementia or limited compliance. All subjects were taking at least one type of sleep medication (types not reported). Melatonin (2mg slow-release) or placebo was administered to subjects over three weeks, and then, after a one-week washout period, were given the other preparation.

After each three-week treatment period, nighttime sleep was assessed with actigraphy over three consecutive nights. Each of the sleep variables was averaged for each subject. Urinary 6-suphatoxymelatonin (6-SMT), the metabolite from melatonin, and a surrogate for serum levels, were measured from each participant prior to treatment periods to estimate peak overnight secretion.

Garfinkel et al., 1995, however, did report a statistically significant change in sleep efficiency between melatonin group and placebo groups (83% v. 75%, $p < 0.001$) and in wake after sleep onset (in minutes) (73 v. 49, $p < 0.001$). There was a trend towards significance among groups in terms of sleep latency ($p < 0.088$), but not in total sleep time.

Eligibility criteria were used to limit confounding by excluding known conditions that affect sleep and were clearly specified in the article. Due to the crossover study design, the control and intervention groups were similar at baseline. Subjects were randomized and the pharmacist preparing the containers knew randomization codes. Treatment codes were broken only after study results were obtained. During the treatment periods, investigators and subjects were blinded to intervention. All

randomized subjects completed the study and no data was reported missing. No references to power calculations were reported. The continuous variables of actigraphic outcome measures were collected equally among groups and analyzed using two-tailed t-tests, reporting standard errors and significance levels of <0.05.

Garfinkel et al., 1997

In 1997, a new study by Garfinkel, Laudon, and Zisapel enrolled (n=21) elderly subjects who complained of long-term insomnia and who also were currently using a benzodiazepine. Study design mirrored the protocol of the previous study by Garfinkel et al., 1995, described above. Recruitment was in a similar manner to the previous study by the author. Similar measurements of urinary 6-MT were collected and reported.

Garfinkel et al., 1997, in contrast to their previous study, showed a significantly higher percent of sleep efficiency among those taking melatonin as compared to placebo, 83 percent v. 75 percent ($p<0.001$), respectively. Melatonin treatment also had a significant effect compared to placebo on decreasing sleep latency (19 v. 33 minutes, $p=0.007$) and also significantly shortened the amount of time spent awake after sleep onset (49 v. 73 minutes, $p<0.001$). Total sleep time or sleep duration also was significantly improved with melatonin treatment compare to placebo (360 v. 365 minutes, $p=0.027$) and the number of awakenings was lower in the melatonin group, 11.4 v. 16.2, $p=0.004$) Further, reported side effects

included only two cases of pruritis, one in the treatment and one in the control group.

Eligibility criteria were clearly specified in the article and due to the crossover study design the control and intervention groups were similar at baseline. Randomization and blinding were similar to the study by Garfinkel, et al., 1995, reported above. All 21 randomized subjects completed the study and no data was reported missing. A priori sample size estimates were not reported in the article. The continuous variables of actigraphic outcome measures were analyzed using two-tailed t-tests, reporting standard deviations and significance levels of <0.05.

Baskett et al., 2003

More recently, Baskett and colleagues (2003) studied the effects of melatonin in elderly insomniacs (n=20). Subjects were recruited from advertising and screened with a questionnaire (Pittsburgh Sleep Quality Index) by mail. Exclusion criteria were determined during a clinical interview and were the most stringent of all the included studies. Subjects were excluded for advanced or delayed sleep phase syndrome, poor sleep hygiene, changes in medications during the study, use of hypnosedatives, low creatinine clearance and medical conditions significantly interfering with sleep. Subjects with a MMSE below 26 (out of 30) points or a score of six or more on the Geriatric Depression Scale (GDS) were also excluded from enrollment. The 20 subjects were randomly chosen from 60 problem-sleeping persons who met inclusion criteria for enrollment.

During the trial, five of these subjects withdrew (two due to poor health, two due to adverse reaction and one changed their mind), leaving 15 for analysis.

Subjects were given 5mg of fast-release melatonin or placebo to be taken prior to retiring to bed. Melatonin or placebo was each taken for four weeks, separated by a washout period. Actigraphic watches were worn on the subject's non-dominant wrist for five consecutive nights during the last week of each trial period. Baskett et al., 2003, reported no significant changes among any of the actigraphic measures of sleep quality between active treatment and placebo groups of poor sleepers. There also were no significant differences between self-reported sleep quality on the PSQI between treatment groups.

In an attempt to limit selection bias and confounding, subjects with conditions or disorders that are known to negatively effect sleep (e.g., sleep disordered breathing, cognitive impairment) were excluded. Other eligibility criteria were clearly specified in the article and treatment groups were similar at baseline. Randomization and blinding were reported and appeared adequate. Of the 20 subjects randomized to receive placebo or melatonin, only 15 completed the trial. Sample size calculation were based on an earlier pilot study, and included: 1) 15-minute change in sleep latency, 2) six percent change in sleep efficiency and 3) a 0.6 decrease in the number of awakenings. This estimate required 12 participants in each group (α=0.05, β=80%). Since no intent-to-treat analysis was reported regarding the five subjects who withdrew after randomization but before

the treatment period, the possibility of attrition bias must be considered. Due to small sample sizes and skewed data, the median of the continuous outcome measures, standard deviations and 95 percent confidence intervals were reported. The continuous variables of actigraphic outcome measures were analyzed using two-tailed t-tests, reporting standard deviations and significance levels of <0.05.

Discussion

In this systematic review of the effectiveness of melatonin use in patients over 65 years of age, only 74 total subjects were studied. In three of four randomized, placebo-controlled trials, sleep efficiency was significantly improved compared to placebo, while sleep latency was significantly improved in two, with a trend toward significance in a third (Garfinkel et al., 1995). In two others (Garfinkel et al., 1995+1997), total sleep time improved significantly. Further, in all but one of the included studies, melatonin significantly improved at least one actigraphic measure of sleep quality.

Limitations

Since only English-language articles were included in this review there may have been a publication bias. Another limiting factor of the included studies was the small sample sizes. Even though all of the

included studies were of a crossover design, the generalizability of the results may be lessened.

In terms of subject variability among studies, a potential limitation of both studies by Garfinkel, et al., 1995 & 1997, may be the fact that subjects were to taper their dose of benzodiazepines during the study. Thus, the positive effects of melatonin may have been confounded by ongoing or previous hypnotic therapy.

Two proposed mechanisms of potentiation were suggested in this study.[67] Melatonin has been shown to increase benzodiazepine receptor binding in animal models and benzodiazepines themselves may decrease endogenous melatonin secretion. However, since insomnia patients often are prescribed these agents, their use in experimental subjects may be more representative of this population. Interestingly, in a later article by Garfinkel, et al., 1999, controlled-released melatonin appeared to facilitate benzodiazepine discontinuation without worsening any sleep quality indicator.[71]

Selection bias may complicate the internal validity, especially the studies by Garfinkel, et al., 1995 & 1997. In both studies, subjects were recruited from a senior center after a lecture on sleep disorders and may represent a highly motivated population. Other sources of selection bias may be found in Haimov, et al., 1995. In this trial, not only did the authors fail to document recruitment procedures, they also included insomnia participants who were both community-dwelling and residents of nursing

homes. Due to comorbidities, decreased activity levels and medication usage, these two groups may be too dissimilar to group together.

Baskett, et al., 2003, on the other hand, may have been too restrictive in subject inclusion. Their exclusion criteria may have self-selected an unrepresentative healthy population that does not accurately represent the vast majority of elderly persons.

Other potential threats to internal validity and clinical usefulness of these studies may include the lack of reported outcome measures of sleep quality. Even though all studies reported using a subjective sleep quality instrument in their enrollment, only Baskett, et al., 2003, reported results after treatment (which was not significantly different between groups). Since a daytime dysfunction is considered part of the diagnostic criteria for insomnia, this omission may be problematic.

Are the results of this review consistent with prior studies?

In a previous review by Rikkert and Rigaud (2001), six randomized, placebo-controlled trials were included. Three of the studies in that review were excluded in this present review since subjects in those studies included some less than age 65 years and one also had subjects with mild cognitive impairment or dementia. Results from this systematic review found that sleep latency decreased in four of the six included studies, and that other indicators of sleep quality (sleep efficiency, total sleep time, and wake time after sleep onset) improved in three. The authors' conclusions did, however, support the use of melatonin for elderly patients suffering

from insomnia, especially if they had lower than normal nighttime melatonin levels and/or were taking benzodiazepines.[72]

A few studies of middle-aged and older insomniacs not meeting this review's inclusion criteria suggest evening melatonin may be effective in improving sleep quality and duration. [73, 74, 75] In a study of the effects of a single evening dose of melatonin (0.3 mg and 1.0 mg orally) on polysomnographic measured sleep in 15 healthy middle-aged volunteers using a placebo-controlled, double-blind, crossover design, 1.0 mg dose of melatonin significantly increased actual sleep time, sleep efficiency, non-REM sleep and REM sleep latency.[61] A significant increase in the subjective assessment of total sleep time and daytime alertness was demonstrated with melatonin but not with placebo.[73] In an open pilot study on the efficacy of melatonin in the treatment of sleep disorders, patients with sleep disturbances alone, patients with sleep disturbances and signs of depression, and patients with sleep disorders and dementia received 3 mg melatonin p.o. for 21 days, at bedtime. After two to three days of treatment, melatonin significantly augmented sleep quality and decreased the number of awakening episodes in patients with sleep disturbances, whether those episodes were associated with depression or not. Estimates of next-day alertness improved significantly only in patients with primary insomnia.[76]

There appears to be more evidence supporting the use of melatonin as an agent decreasing sleep latency. The effects of immediate-release melatonin on circadian rest-activity profiles, cognition and mood were

investigated in 10 elderly individuals with self-reported sleep-wake disturbances. Melatonin (6 mg) administered two hours before habitual bedtime enhanced the rest-activity rhythm and improved sleep quality as observed in a reduction in sleep onset latency and in the number of transitions from sleep to wakefulness. However, total sleep time was not significantly increased nor was wake within sleep significantly reduced. The ability to remember previously learned items improved along with a significant reduction in depressed moods. No side effects or contraindications were reported by any of the participants during the 10-day trials. These results suggest that melatonin can safely improve some aspects of sleep, memory and mood in the elderly in short-term use.[77]

In another study, the effects of 5mg melatonin administration on sleep latency among elderly patients (older than 55 years of age) were compared with a placebo group. Exogenous melatonin resulted in statistically significant reduction in sleep latency between good and poor sleepers.[78]

Other studies are more consistent with results from Baskett, et al., 2003. In a recent study, Almeida, et al., reported no significant improvement in any sleep indicator of 10 primary insomnia patients, ranging in age from 30-72 years, who took melatonin (0.3mg and 1.0mg) or placebo.[79] The limited or lack of improvement in sleep after evening melatonin dosing has been reproduced in other trials as well.[80, 81, 82] The hypnotic effects of transbuccal melatonin in 12 elderly patients with sleep maintenance insomnia failed to show any polysomnographic evidence for

improved sleep.[83] A study to evaluate melatonin treatment effects in normal sleepers and insomnia patients (age 50 years and older) revealed that significant improvements in sleep efficiency were noted at all dosage ranges of melatonin among subjects with insomnia but not among normal sleepers.[84] In another study of three different regimens of melatonin supplementation, only sleep latency was improved in those with age-related sleep-maintenance insomnia. There were no significant differences in total sleep time, sleep efficiency, nighttime awakenings or daytime alertness compared to placebo. These results were noted even in low melatonin producers.[85] In a study using a self-report questionnaire comparing melatonin treatment to placebo, no significant difference in sleep measurements was noted.[81]

Implications for Medical Practice

Melatonin, for reasons discussed above, is an attractive alternative for elders suffering from insomnia. Benzodiazepines, which often are prescribed in this population, are associated with significant side effects, such as hospital admission and falls.[85] Although many questions remain regarding the use of melatonin for insomnia, namely who will likely benefit the most and at what dosage, melatonin's limited side effect profile and low cost should make it a reasonable option for a therapeutic trial, especially for those older patients on benzodiazepines.

Implications for Research

Several areas of research need to be addressed. First, establishing an appropriate age cut-off for age-related insomnia and second, the development of a precise definition of age-related insomnia. Other authors have included patients as young as 50 years of age in their investigation of the effects of melatonin on insomnia in older adults.[85] Further research to determine the differences in etiology between age groups would be helpful in designing additional studies.

Standardization of sleep assessment measures also would be helpful in future studies, as well as determining which of these correlates most consistently with subjective symptoms. Dosage standardization of melatonin is another area of concern. Many studies use varying amounts of melatonin and differing routes of administration, limiting generalizing results.[87] Additionally, any possible effects of melatonin on orthostasis should be further studied, especially among the elderly who may be more sensitive to orthostasis.

Many studies have tried to use rigid exclusion criteria for enrollment. This methodology is problematic due to the significant amount of comorbidities and medications used in this population, some of which effect sleep quality (e.g., nocturia associated with benign prostatic hypertrophy, pain associated with osteoarthritis). For instance, in regards to concurrent medication usage, atenolol is a commonly prescribed antihypertensive in older adults and has been associated with attenuating melatonin secretion in human studies. Studies that are less restrictive

toward medication used and comorbidities may vastly increase sample sizes and also increase generalizability.

Finally, outcome measurement of daytime dysfunction should be included in all studies. Poor objective sleep parameters should be correlated with factors such as daytime sleepiness and cognitive impairment, since much of the morbidity of insomnia is associated with these subjective measures.

Conclusions

A variety of different soporific agents are available to older persons suffering from insomnia. Although melatonin may be a safe alternative to standard hypnotic therapy, its use will be limited until more information is available regarding appropriate patient selection and dosing, especially when effective therapies exist (e.g., cognitive behavioral, standard hypnotics). This information will need to be obtained from much larger, well-designed, randomized controlled trials.

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Table 1. Summary of results from 4 randomized controlled trials of melatonin in elderly insomniacs

Author	Year	Number of Treatment Subjects	Age Range (yrs)	Melatonin Dosage	Duration	Time (before bed)	Outcome Measures	Adverse Events	Quality Rating and Comments
Haimov, et al.	1995	26	69-90	2mg fast-release 2mg slow-release 1mg slow-release	1 week 1 week 2 months	2h 2h 2h	Actigraphy	None Reported‡	*Fair* Incomplete exclusion criteria reported. Subjects less similar at baseline.
Garfinkel, et al.	1995	12	68-93	2mg slow-release	3 weeks	2h	Actigraphy	One case of pruritis in melatonin and placebo groups.	*Good* Subjects were using benzodiazepines.
Garfinkel, et al.	1997	21	68-93	2mg slow-release	3 weeks	2h	Actigraphy	None Reported‡	*Good* Subjects were using benzodiazepines
Baskett, et al.	2003	20	65-84	5mg immediate release	4 weeks	30min*	Actigraphy Sleep Diary Questionnaire	Drowsiness†	*Good*

*not specifically noted, "on retiring to bed"
†no significant difference compared to placebo
‡no mention of, or monitoring for, adverse events were reported in text

Table 2. Summary of Results

Author	Sleep Efficiency			Sleep Latency			Total Sleep Time			Awake after Sleep Onset		
	Placebo	Melatonin	P	Placebo	Melatonin	P	Placebo	Melatonin	P	Placebo	Melatonin	P
Haimov et al. 1995	77.4 (1.9)	78.8 (1.7)* 80.4 (1.8)* 84.3 (2.3)*	<0.001	54(13)	32(7) 37(11) 14(5)	0.05	Not reported			26.9	25.8 (3.8) 23.0 (2.5) 18.6 (2.5)	<0.001
Garfinkel, et al. 1995	75 (3; 53-89)	83 (4; 56-96)	<0.001	33 (7; 10-102)	19 (5; 3-49)	<0.088	365 (20; 249-535)	360 (21; 212-508)	<0.49	73 (13; 10-179)	49 (14; 6-194)	0.001
Garfinkel et al. 1997	75.23 (2.2)	85.44 (2.4)	0.001	29.24 (6.24)	11.75 (2.0)	0.007	351.02(14.9)	384.06 (14.6)	0.027	76.80 (12.5)	39.58 (7.6)	0.001
Baskett et al. 2003	86.2 (84.9, 87.1)	84.1 (83.8, 86.3)	NS	1.4 (0.4, 2.0)	1.6 (0.6, 2.8)	NS	7.4 (7.0, 7.8)	7.3 (7.2, 7.6)	NS	40.2 (34.6, 43.6)	41.2 (36.0, 45.2)	NS

*Haimov et al., melatonin 2mg fast-release for 1 week; 2mg sustained-release for 1 week; 1mg sustained-release for 2 months.