Management of Late-Life Insomnia

Chien-Ming Yang¹, Hsin-Chien Lee²–⁴ and Zai-Ting Yeh⁵

¹Department of Psychology/The Research Center for Mind, Brain, and Learning, National Cheng-Chi University, Taipei, Taiwan. ²Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. ³Department of Psychiatry, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan. ⁴Sleep Center, Taipei Medical University Hospital, Taipei, Taiwan. ⁵Catholic Fu-Jen University, New Taipei City, Taiwan.

Corresponding author email: dryangcm@gmail.com

Abstract: Insomnia is a common complaint that can have significant daytime consequences. The prevalence of chronic insomnia may increase with age. The management of late-life insomnia can be complicated because aging is associated with normal changes in sleep structure, continuity, and timing, as well as a higher rate of medical and psychiatric disorders. A thorough evaluation and conceptualization of patients' problems should be conducted for effective treatment planning. Both non-pharmacological and pharmacological strategies have been proven effective in treating insomnia in elderly populations. Behavioral intervention and cognitive behavioral therapy for insomnia are recommended as first considerations. Light therapy may be administered for misalignment of the circadian phase. When necessary, hypnotic medications may be added with adequate safety precautions and consideration of comorbid conditions.

Keywords: insomnia, elderly, pharmacological treatment, cognitive behavioral therapy
Introduction

Insomnia, defined as subjective complaints of difficulty initiating or maintaining sleep or non-restorative sleep, is one of the most common health-related problems that can affect several aspects of life quality. An estimated one third of adults in the general population display insomnia symptoms, 9%–15% report sleep difficulties with daytime consequences, and about 6% show diagnosable insomnia. The prevalence could be even higher in elderly populations. Because elderly individuals have been found to have a progressive decrease in total sleep time (TST), sleep efficiency (SE), percentage of slow wave sleep, and percentage of rapid-eye-movement sleep, as well as increased sleep fragmentation and awakening after sleep onset, they may be particularly vulnerable to sleep disruptions. In addition, the increased rate of psychiatric and medical comorbidities may make them susceptible to sleep disruptions.

The prevalence of insomnia in elderly populations has been reported to range from 20% to more than 50%. A study with in-person interviews of more than 9000 participants aged 65 years and older recruited from three communities in the United States found that 23%–34% of participants had symptoms of insomnia, and 7%–15% rarely or never felt rested after waking up in the morning. Another study of more than 6000 elderly participants reported more than 50% with at least one sleep complaint and 35%–40% with sleep disturbances on a chronic basis. A more recent community-based longitudinal study in Korea found that 27% of participants older than 65 years reported difficulty initiating or maintaining sleep at least 3 nights per week. At a follow-up 2 years later, 40% of those individuals reported continued sleep difficulty. Of those without insomnia at baseline, 23% reported insomnia at follow-up. The association between aging and insomnia may not be as large when insomnia is defined more strictly, however. It has been suggested that insomnia symptoms may have an increased rate in elderly populations, but insomnia with sleep dissatisfaction or an insomnia diagnosis may not be age dependant. One study of more than 13,500 participants aged 47 to 69 years reported that increasing age was significantly associated with difficulty staying asleep only, not with difficulty initiating sleep or non-restorative sleep.

In addition to concerns stemming from its high prevalence, late-life insomnia should not be ignored by clinicians because of its consequences. Insomnia has been shown to affect several aspects of quality of life in the general population. Older individuals may be even more vulnerable both psychologically and physically to the impacts of sleep disturbance. Poor sleep quality and insomnia symptoms in older individuals have been associated with decreased physical strength, risk of fall, poor cognitive performance, and emotional disturbance. Insomnia also increases the risk of mortality in older adults; a study of sleep evaluation with a follow-up after 4 to 19 years showed that those with sleep latencies longer than 30 minutes or SE less than 80% initially had about twice the risk for mortality. Therefore, late-life insomnia should be well managed by medical professions caring for geriatric patients.

Some recent review articles have nicely addressed sleep characteristics and etiology of late-life insomnia, and/or specific treatment modalities for insomnia in elderly population. Due to the multifacetal nature of insomnia in elderly, a clear conceptualization of the problem is important for a good treatment planning. We therefore focus our article not only on reviewing the research evidences for the effectiveness of different treatment approaches, but also to provide an etiological framework for the understanding and evaluation of insomnia, as well as some basic practical principles for conducting the different strategies for the management of late-life insomnia.

Evaluation and Conceptualization of Insomnia in Elderly Patients

The management of late-life insomnia can be complicated by its high rate of comorbidity with other psychiatric disorders, medical conditions, and sleep disorders. Psychiatric conditions such as depression and anxiety disorders and physical problems such as heart disease, respiratory disturbances, bodily pain, and memory problems have been reported to be risk factors for late-life insomnia in previous studies. For example, in a longitudinal study of more than 6000 elderly participants with a 3-year follow-up, the incidence rates of insomnia were highest in those with chronic medical conditions, such as heart disease, stroke, and diabetes. Remission rates were also found to be associated with improvements in
perceived health. Another study following more than 1000 older adults for 2 years found that baseline depression level and number of physical disorders were significantly associated with prevalence and incidence of insomnia. Furthermore, some studies reported very low prevalence of insomnia in an elderly population when participants with comorbid conditions were carefully excluded. It has therefore been suggested that the increased rate of insomnia symptoms in elderly patients may not be the result of aging but rather a reflection of the increase in medical and psychiatric disorders in this population. Therefore, the management of insomnia in this population should take into consideration comorbid conditions. Although comorbid conditions may play an important role in the initiation and maintenance of insomnia, however, sleep-specific factors may develop along the course of chronic insomnia. The common assumption that sleep disturbance is secondary to comorbid medical, psychiatric, or sleep disorders has often lead to the undertreatment of insomnia, as highlighted by a consensus statement by the US National Institutes of Health. The use of the term “comorbid insomnia” is recommended to highlight the coexistence of the pathology of the primary condition and sleep-specific pathology.

Among the etiological factors specific to sleep are many psychological and behavioral factors. These factors can interfere with the neurophysiological mechanisms that normally regulate sleep and wake and lead to insomnia. These factors include dysfunctional beliefs and attitudes about sleep, maladaptive sleep hygiene, and emotional or cognitive arousal. For example, heightened concerns about the consequences of sleeplessness may increase arousal before bedtime and lead to difficulty initiating sleep. Such beliefs may lead patients to go to bed earlier and to stay in bed longer, in turn leading to insufficient homeostatic sleep drive at bedtime. Given the complexity of the contributing factors in insomnia, the 3-P model proposed by Spielman, which refers to the categories of predisposing, precipitating, and perpetuating factors, can be a useful framework for conceptualizing the development of insomnia in an elderly individual. Anxiety-prone personality traits, tendency toward stress reactivity, circadian typology and flexibility, and aging-related deterioration of sleep mechanisms, for example, can be predisposing factors that make an individual more vulnerable to sleep disruption. Daily life stressors, medical and psychiatric conditions, and age-related psychosocial factors can be precipitating factors that trigger insomnia. Psychological and behavioral factors, such as hyperarousal, dysfunctional sleep beliefs, and maladaptive sleep hygiene can then be the perpetuating factors that maintain the sleep problem long term. Treatment strategies, whether targeting comorbid conditions or sleep mechanisms, therefore, can be derived from the conceptualization of a patient’s problem.

To obtain a good conceptualization of the sleep problem in an individual, it is essential to conduct a comprehensive evaluation to identify possible contributing factors to insomnia. The evaluation should include a thorough sleep history of the symptoms and course of insomnia, nocturnal sleep schedule and daytime naps, daily routine, daytime consequences of insomnia, medication used, and assessment of possible comorbid conditions such as emotional disturbances, medical conditions, and other sleep disorders. A 1- to 2- week sleep log is usually recommended to get an overview of patient sleep patterns. Some self-rating scales can be administered to evaluate the severity of sleep disturbances and to monitor the patients’ progress in treatment. The Insomnia Severity Index and the Pittsburgh Sleep Quality Index are among the scales commonly used for these purposes in both clinical practice and research. Other scales can also be used to assess emotions, attitudes and beliefs about sleep, and sleep hygiene. Because the prevalence of many physiological sleep disorders is higher in the elderly population, polysomnography is recommended when other sleep disorders are suspected.

**Management of Insomnia**

Both non-pharmacological and pharmacological treatments have demonstrated efficacy in the management of late-life insomnia. We review the rationale, procedures, safety considerations, and research evaluations of these treatments below.

**Non-pharmacological treatments**

Given the high prevalence and adverse consequences associated with late-life insomnia, clinicians must address this problem proactively in the
elderly population. The goal of insomnia management is not only to alleviate nighttime sleep symptoms but also to decrease daytime impairments. In elderly insomnia patients without severe medical conditions, non-pharmacologic interventions should be considered first because elderly individuals may be more prone to the adverse side effects of pharmacotherapy owing to the impact of poly-pharmacy, drug-drug interactions, and diminished metabolism. The clinical guidelines for the management of chronic insomnia proposed by the American Academy of Sleep Medicine recommend that clinicians initially conduct behavioral and psychological therapies with or without pharmacotherapy when possible. Even with comorbid conditions, behavioral and psychological therapy is recommended after optimizing treatment for underlying comorbid conditions, followed by pharmacological treatment. In geriatric patients with more severe comorbidities, pharmacological treatment however might be the primary treatment modality since their sleep disturbances may demand too much support by the caregivers.

Sleep hygiene education
To manage insomnia in elderly populations, clinicians may start with a sleep consultation that provides sleep hygiene education and recommendations for good sleep hygiene. Sleep hygiene refers to the practices of everyday living and sleep-related activities that promote high-quality sleep. The objectives of sleep hygiene education are to improve basic knowledge about sleep and modify counterproductive sleep practices. The clinician reviews daily life practices and sleep-wake habits with the patient and identifies a set of practices that are inconsistent with good sleep hygiene. The patient is asked to refrain from maladaptive activities and, in some cases, engage in sleep-promoting behaviors. Among elderly insomnia patients, sleep hygiene education may cover additional areas such as the distinction between sleep disorders and normal sleep change related to aging, and the association of medical conditions or medication with sleep.

Sleep restriction therapy
The basic idea of sleep restriction therapy (SRT) is to restrict patients’ allowed time in bed (TIB), in order to induce partial sleep deprivation initially to increase the homeostatic sleep drive and facilitate rapid sleep onset and well-consolidated nights of quality sleep. Patients are asked to maintain a sleep log, and the therapist may choose a beginning bedtime and wake-up time to with sufficient sleep consultation and sleep hygiene modifications, some behavioral and psychological treatment strategies can then be applied.

Behavioral and psychological management of insomnia
Many behavioral and psychological interventions have been shown effective in the treatment of chronic insomnia. Several meta-analyses and reviews have demonstrated that psychological treatments for insomnia could benefit approximately 70%–80% of patients with the condition. The 2005 State-of-the-Science Conference of the National Institutes of Health has also recognized the effectiveness of psychological and behavioral therapies to treat chronic insomnia in adults. These treatment techniques are usually combined into cognitive behavioral therapy for insomnia (CBTI).

CBTI is a multicomponent intervention that is usually conducted in groups with a structured program or administered individually with selected techniques tailored to the individual. The course of treatment usually consist of 4 to 8 weekly or biweekly treatment sessions with the maintenance of a sleep log between sessions, although 2-session CBTI was also reported effective in primary care settings in one study. CBTI consists of educational, cognitive and behavioral components. The educational component aims to enhance understanding of the basic mechanisms of sleep regulation, etiological factors of insomnia, and good sleep hygiene. The behavioral component includes relaxation techniques that can reduce tension and anxiety and other techniques that enhance sleep quality by adjusting the sleep schedule. Finally, the cognitive component aims to correct dysfunctional beliefs and attitudes about sleep that may provoke anxiety about sleep or lead to maladaptive sleep practices. In the following section, we describe the rationale and procedures of the main techniques.

Sleep restriction therapy
The basic idea of sleep restriction therapy (SRT) is to restrict patients’ allowed time in bed (TIB), in order to induce partial sleep deprivation initially to increase the homeostatic sleep drive and facilitate rapid sleep onset and well-consolidated nights of quality sleep. Patients are asked to maintain a sleep log, and the therapist may choose a beginning bedtime and wake-up time to
set the lowest TIB that corresponds to their TST. The shortest TIB should not less than 4.5 hours. The TIB is adjusted every 5–7 days according to self-reported SE: lengthened by 15 minutes when the average SE is over 85% or shortened 15 minutes when the average SE is lower than 80%.

One potential problem of SRT is that many patients may resist cutting down their allowed TIB very radically. A modified form of SRT called sleep compression has been designed to avoid this resistance and has been shown to generate successful outcomes in late-life insomnia. Although SRT and sleep compression share the assumption that individuals with insomnia benefit from a reduction of TIB, sleep compression starts with a TIB reduction that is modest as compared to that in SRT. During the first session, patients are advised to reduce TIB by half the difference between baseline TIB and baseline TST. During sessions two and three, TIB was further reduced by one-fourth the difference between baseline TIB and baseline TST. The final goal of both strategies is make the participants’ TIB equal to their TST. Alternatively, the initial TIB can be set by negotiating with patients to minimize their resistance during SRT.

Stimulus control instruction
The underlying rationale of stimulus control is to break the associations between the sleep environment and wakefulness by directing patients to get out of bed if unable to fall asleep and to rebuild associations between the bedroom and sleep by having them return to bed only when feeling ready to sleep. The following are specific instructions for patients to follow in stimulus control therapy: (1) go to sleep only when feeling sleepy; (2) do not use the bed or bedroom for activities other than sleep or sexual activity; (3) if you do not fall asleep within approximately 20 minutes, go into another room and do something relaxing; (4) go back to bed only when feeling sleepy again; (5) repeat the procedure of getting out of bed if you still cannot fall asleep rapidly; (6) get up at the same time each morning regardless of how much you have slept; and (7) avoid napping during the daytime. Over time, the repeated association of bedroom cues with rapid sleep onset brings sleep under the stimulus control of the bedroom environment. Since some geriatric patients may be lonely and tend to sleep with their TV or radio on, it is important to address their loneliness while emphasize the importance of taking the TV/radio out of their bedroom.

Relaxation training
Cognitive and physiological hyperarousal has been recognized as a major etiological factor in insomnia. Thus, various relaxation techniques developed to reduce tension and arousal have been applied to facilitate sleep onset and improve sleep continuation. Positive results have been reported for a variety of techniques for facilitating sleep—for example, progressive muscle relaxation that reduces muscle tension by sequential tensing and relaxing of the main muscle groups, autogenic training that produces somatic relaxation by inducing sensations of warmth and heaviness in the body, guided imagery that aims to channel mental processes into a vivid story line, and biofeedback that assists the mastering of relaxation through the recording and feedback of physiological activities. Relaxation training usually proceeds with a demonstration of the procedure during the session followed by between-session practice of the techniques once or twice each day at home. Some individuals may require weeks to master the techniques. Motivating patients to continue practicing these techniques and helping them deal with obstacles they encounter is crucial.

Cognitive restructuring
As described above, dysfunctional beliefs and attitudes about sleep may lead to increased arousal or sleep-disruptive behavioral practices. Changing these thoughts may reduce anxiety and maladaptive sleep practices, thereby improving sleep. The procedure consists of three steps. The first step is to identify the dysfunctional sleep cognition of the patient. This step can be completed by discussing with patients their worries about sleep or by using self-report questionnaires. The common dysfunctional beliefs in insomnia patients can be categorized into (1) perceived consequences of insomnia (e.g., “My insomnia symptoms may impair my immune system.”), (2) unrealistic expectations about sleep requirements (e.g., “I must sleep 8 hours a day.”), and (3) erroneous beliefs about strategies to promote sleep (e.g., “Excessive TIB increases the chances of falling asleep,” or “A nightcap to facilitate sleep onset is
better than taking hypnotics.”). Once dysfunctional beliefs have been identified, their validity can be challenged with scientific evidence as well as by monitoring the patient’s experiences. For example, if a patient believes that he will perform poorly in his job if he gets inadequate sleep, the clinician may inform the patient about the scientific facts showing that the effect of a few nights of poor sleep on performance is minimal. The clinician might also ask patients to rate their level of job performance while maintaining a sleep log to show that the association between job performance and sleep quality may not be as consistent as the patient expects. After the patient accepts that the thought may be invalid part of the time, the third step is to replace it with more adaptive beliefs, such as “Although sleeplessness may impair daytime performance, the effect is tolerable; excessive worry is more harmful than a few nights of poor sleep.”

CBTI has accumulated sufficient research evidence to support its effects in the treatment of primary as well as comorbid insomnia. The 2008 AASM clinical guidelines for the evaluation and management of chronic insomnia recommend stimulus control, relaxation training, and CBTI as the initial treatments with the highest level of evidence from clinical trials. Multicomponent therapy without cognitive therapy, SRT, paradoxical intention, and biofeedback are considered to reach moderate levels of evidence for efficacy. Sleep hygiene education, although lacking sufficient evidence to indicate treatment effectiveness when provided alone, is recommended in combination with other therapies.

A recent meta-analysis further supports that CBTI and behavioral interventions are effective for insomnia in elderly adults (older than 55 years). Behavioral interventions alone and CBTI generate similar effects and have shown moderate to large effects in the reduction of sleep onset latency (SOL) and wake after sleep onset (WASO) and the improvement of SE. Here we review several studies to illustrate the effectiveness of CBTI and behavioral techniques in treating late-life insomnia. In one early study, 7 elderly patients with sleep maintenance difficulty received relaxation training followed by CBTI (including sleep hygiene, stimulus control, and TIB prescriptions similar to those in SRT). The patients showed significant improvements in both subjective and objective measures of WASO and SE and significant reductions in objective SOL, TST, and SE but no improvement after relaxation training alone. Moreover, the improvements in WASO and SE were maintained through the follow-up period. Another study randomly assigned 24 elderly insomnia patients into a CBTI group and a waiting-list group. Patients in CBTI group improved significantly in subjective measures of WASO, TWT, and SE compared to those in the waiting-list group. Polysomnography revealed that CBTI patients showed significant improvement in WASO, total wake time, and SE as well as an increase in rapid-eye-movement sleep percentage. The patients in the CBTI group also felt less distress and more satisfaction with their sleep patterns than did those in the waiting-list group. The improvements remained at a 3-month follow-up.

CBTI was also compared to pharmacological therapy in elderly patients with sleep maintenance insomnia in a randomized controlled trial. Seventy-two participants were randomly assigned to a CBTI group, a pharmacotherapy (temazepam, 7.5–30 mg) group, a combined group receiving both CBTI and pharmacotherapy, and a placebo group. The results showed that the 3 active treatments were effective in improving sleep continuity compared to placebo, with a slightly increased benefit for the combined treatment. At a 2-year follow-up, however, the effects were sustained only in the CBTI and combined groups, especially in the CBTI-only group. A more recent study compared the efficacy of CBTI with pharmacotherapy for the treatment of chronic primary insomnia in older adults. Forty-eight patients were randomly assigned into 3 groups: a CBTI group, a hypnotic group (treated with zopiclone), and a placebo group. For the CBTI group, wake time was significantly reduced, and SE and slow-wave sleep were significantly increased at both 6-week and 6-month follow-ups compared to those in the zopiclone and placebo groups. Therefore, CBTI provides a promising option for treating insomnia in elderly individuals.

The efficacy of CBTI in older adults with comorbid insomnia has also been examined. Ninety-two participants older than 55 years with insomnia comorbid with coronary artery disease, osteoarthritis, or chronic obstructive pulmonary disease participated in the study. They were randomly assigned to either a CBTI group or a control group that received a...
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stress management and wellness program. The results showed that compared with patients in the control group, those in the CBTI group improved significantly more in SE, SOL, WASO, and global measures of sleep.

At the 2005 NIH State-of-the-Science Conference on Insomnia, it was therefore concluded that CBTI was at least as effective as hypnotic medications for the brief treatment of chronic insomnia, with indications that the beneficial effects of CBTI, in contrast to those produced by medications, may last well beyond the termination of treatment.38

In general, CBTI and behavioral treatment for insomnia are very safe. As stated in the NIH consensus, no evidence thus far indicates that CBTI produces significant adverse effects. The consensus also points out, however, that little, if any, study of the possibility of adverse effects has taken place.38 Theoretically, the restricted TIB in SRT may enhance daytime sleepiness at the beginning of treatment. While under treatment with SRT, elderly patients should exercise caution to avoid activities that require a higher level of vigilance.

Light therapy
In addition to changes in sleep structure, susceptibility to misalignment of endogenous circadian rhythms with environmental time also occurs with aging.4,5 Because light is the most potent environmental cue that can shift circadian phase, light therapy is a common treatment for sleep problems associated with circadian phase misalignment. Exposure to bright light has been shown to shift the phase of circadian rhythms. The magnitude and direction of the phase shift depend on the intensity and timing of light exposure.72,73 As a general rule, exposure to bright light right after body temperature minimum (early morning) results in circadian system phase delay, whereas exposure before body temperature minimum (in the late evening) results in circadian system phase advance.

Circadian phase misalignment can result in the complaint of insomnia. Advanced circadian phase, a condition more commonly seen in the elderly population, is characterized by an advancement of the timing of sleep. Patients may complain of difficulty staying awake in the evening and early morning awakenings. Because circadian rhythm advancement may be a normal change associated with aging, it may require no treatment if the timing of sleep is not interfering with social or occupational commitments. Evening light exposure is indicated when light therapy is applied. The use of blue-blocking sunglasses in the morning hours may also be helpful to avoid the phase advance effect of morning light exposure. In contrast, delayed circadian phase may lead to sleep onset problems and difficulty waking up in the morning. Morning light exposure is recommended to treat this condition.74–76

In conducting light therapy, patients initially keep their typical bedtimes. As treatment proceeds, bedtimes and rising times are progressively shifted toward the target schedule for about an hour each week, with light exposure also shifting to an earlier or later time. Bright light therapy can be administered with artificial light boxes or natural sunlight when plausible. Traditional commercial devices use low ultraviolet fluorescent bulbs and special reflectors to provide illuminances of 2,500–10,000 lux at the eye when placed 1.5–3 feet away. Exposure times are typically 30 minutes to 1 hour. The higher the light intensity and the longer the exposure, the greater the extent the circadian phase may be shifted. Patients can engage in their daily life activities, such as watching television, reading, or having meals, while conducting the light exposure as long as the light can reach their eyes.

Evening bright light exposure has been examined for the treatment of advanced sleep schedule in elderly patients with mixed results. One early study reported the effectiveness of evening light exposure for sleep maintenance insomnia in patients older than 60 years. Daily exposure to 2 hours of 4000-lux light administered between 20:00 and 23:00 for 12 consecutive days was found to delay core body temperature rhythm for more than 2 hours, as well as induce an average delay in bedtime of 29 minutes, an approximately 13% increase in SE, and a decrease in WASO.74 A more recent study by the same group that implemented an essentially identical protocol failed to replicate most of the findings, however.77 Although light exposure resulted in significant delays in core body temperature minimum (94 minutes) and sleep onset time (44 minutes), no improvements in sleep quality indices were obtained.78 Subsequently, patients received light therapy twice weekly for a 3-month
period of treatment maintenance and demonstrated a gradual reversion of core body temperature minimum toward pretreatment levels.

Similar results were reported in another study that examined the effects of bright evening light exposure in 31 patients older than 55 years with complaints of early morning awakening. Subjects were exposed to a 10,000-lux light for 30 minutes beginning approximately 1 hour before their habitual bedtimes for a duration of 3 weeks. Only subjective improvement in early morning awakening, as manifested by an approximately 20-minute decrease of TIB before final morning arising, was reported. No differences were observed in other subjective and objective measures examined with actigraphy.

Bright light exposure was also tested in elderly patients with psycho physiological insomnia in a recent study. Subjects were assigned to an evening bright light condition (4,000 lux 1 hour before bedtime), a morning bright light condition (4,000 lux light 15 minutes after waking up), and a dim light condition. Sleep hygiene education was also administrated in combination with the light exposure. Although some of the sleep measures did improve at the end of a 12-week treatment program compared with baseline values, only TST in the evening bright light condition was different from that in the dim-light control condition.

Recently, a study with more careful selection of subjects generated better results. The researchers specifically selected individuals with problems of early morning awakening but no difficulties in sleep initiation or sleep maintainence. These patients were found to have an earlier circadian phase at baseline. Two consecutive nights of light exposure (2500 lux, administered for 4 hours from 20:00 to 01:00) were shown to delay circadian phase for more than 2 hours. Significant improvements in WASO as measured by actigraphy and TST in sleep logs were reported.

Another recent study tested the effects of “enhanced evening light” (an average 265 lux administered for 2–3 hours between 15:00 and 17:00) in 47 older adults with self-reported symptoms of advanced sleep phase. Evening light enhancement was not found to be more effective than placebo in delaying the advanced sleep phase as measured by actigraphy and urinary 6-sulphatoxymelatonin excretion. Patients in the treatment group reported subjective benefits and a significant delay in sleep onset compared with those in the placebo group, however.

The above review demonstrates the consistent effects of evening bright light exposure on subjective measures of sleep in late-life insomnia patients characterized by early morning awakening. Objective results are conflicting, however. The inconsistent results are probably partially related to the heterogeneous nature of the patient population or poor treatment adherence. In clinical practice, light exposure may be combined with other CBTI techniques if factors other than misalignment of circadian phase are present.

Because light exposure may produce adverse effects to the eyes in vulnerable individuals—a common occurrence in elderly populations—an ophthalmic consultation may be appropriate before patients begin bright light treatment.

**Pharmacological Treatment**

As mentioned above, elderly individuals may be more susceptible to the adverse effects of medication due to diminished metabolism, high comorbidity rate, and the interactions among different medications. We therefore review the rationale, procedures, safety considerations, and research evaluations of the newer medication that has a better safety profile. We also review the treatment efficacy of a natural hormone-melatonin since it has been raised by some researchers that there may be a melatonin deficiency in some of the elderly patients with insomnia.

**Melatonin**

Alternative and complementary therapies are popular and frequently used by patients with insomnia. Based on the 2002 US National Health Interview Survey, the most commonly mentioned herbal products and nutritional supplements associated with insomnia treatment were echinacea, ginseng, valerian, ginkgo biloba and melatonin. Some of their uses may confer stimulant effects. Among those products, melatonin has been extensively discussed for insomnia treatment in the literature.

**Mechanism of action, metabolism and pharmacokinetic profile**

Endogenous melatonin, mainly synthesized in the pineal gland, is a reliable marker for the circadian
change in human. Binding to melatonin $MT_1$ and $MT_2$ receptors abundant in the important circadian pacemaker, the suprachiasmatic nucleus of the hypothalamus, melatonin could regulate sleep by phase shifting human’s circadian system. Therefore, evening melatonin administration could advance the phase of the circadian rhythms and re-set the time of sleep onset. Exogenous melatonin is rapidly absorbed and has approximately one-hour elimination half-life. To mimic the physiologically nocturnal secretion, extended release preparations of melatonin are available in the market mainly for the management of insomnia. Melatonin is metabolized by CYP1A2 and CYP2C19 in the liver and excreted via renal after glucuronate and sulfate conjugation. Melatonin can be secreted in breast milk.

Clinical studies and efficacy
Although earlier studies supported the efficacy of melatonin treatment for insomnia patients, their sample sizes tended to be relatively small. A study consisting of 14 insomnia patients aged between 55 and 80 years found administration of melatonin could shorten sleep latency but was not effective in sleep maintenance. Besides, subjective sleep quality did not improve under melatonin treatment. Consecutive studies yield controversial results. Therefore, in the 2005 NIH consensus statement concluded that little evidence existed for efficacy of melatonin in the treatment of insomnia.

The results of a randomized placebo-controlled study regarding the efficacy and safety of the prolonged release melatonin preparation came out in 2007. Among 334 insomnia patients aged between 55 and 80 years, prolonged release melatonin resulted in significant improvements in sleep quality during the 3-week treatment period. Recent reports proved a sustained efficacy over a 6-month period of melatonin treatment without signs of tolerance. Based on those findings, prolonged release melatonin has been recommended as first-line treatment for late-life insomnia.

Safety
As an endogenously synthesized hormone, melatonin is considered to be non-addicting and safe. Although no prominent health threats have been reported under widespread consumption of exogenous melatonin, the actual risks of long-term use remain uncertain. As regards to prolonged release melatonin, there were no differences in adverse effects reported between treatment and placebo groups during 6-month treatment period in the larger sample study mentioned above. There were also no withdrawal effects after discontinuing treatment with prolonged release melatonin.

Hypnotics: benzodiazepine-receptor agonists
Benzodiazepine-receptor agonists have been widely used for insomnia after the barbiturate era. A substantial body of evidence has supported the efficacy of benzodiazepine-receptor agonists in the short-term management of insomnia.

Mechanism of action, metabolism and pharmacokinetic profile
Benzodiazepine-receptor agonists are able to facilitate the inhibitory activity of gamma-aminobutyric acid (GABA), a key neurotransmitter regulating the sleep/wake switch. The agents, as positive allosteric modulators, may bind to inotropic benzodiazepine receptors at the GABA$_A$ receptor complex. The combination of GABA with benzodiazepine-receptor agonists can increase the frequency of opening of inhibitory chloride channels, and thus may promote sleep due to the end result of more inhibition.

There are two groups of benzodiazepine-receptor agents: traditional benzodiazepines (eg, lorazepam, diazepam, estazolam, and triazolam) and the later introduced agents that still act as benzodiazepine receptors but have a non-benzodiazepine structure (eg, zaleplon, zolpidem, zopiclone and eszopiclone, sometimes also called “Z”-drugs). Some Z-drugs were developed with selectivity for the alpha 1 subtype of GABA$_A$ receptor, which is considered to link to sedation. The function of selectivity was suggested to contribute to a lower risk of tolerance and dependence.

The metabolism and pharmacokinetic profiles of benzodiazepine-receptor agents contribute to their clinical differences, particularly duration of action. Elimination half-life, together with distribution and absorption, are strongly associated with duration of drug action. Short-intermediate acting benzodiazepine-receptor agonists have been recommended to
be the first-line pharmacological treatment for patients with primary insomnia because of less residual daytime symptoms. However, significant population differences exist in the duration of action of benzodiazepine-receptor agonists. Among older people, the duration of action may be lengthened and can result in increased risks of daytime sleepiness and falls.

Clinical studies and efficacy

Insomnia clinical trials with benzodiazepine-receptor agonists have demonstrated reliable improvement in various sleep variables including sleep latency, number of awakenings, wake after sleep onset, and sleep efficiency among patients with primary insomnia. However, most clinical trials contain few older patients. An earlier study comparing of triazolam, flurazepam, and placebo for insomnia treatment concluded both agents superior than placebo in onset of sleep and quality of sleep during a four-week study period. The sample size was small with only 41 geriatric patients recruited, however.

The meta-analysis by Glass and colleagues identified 24 randomized controlled trials of insomnia treatment among patients aged 60 or over. The results indicate that improvements in sleep with the use of benzodiazepine-receptor agonist, although statistically significant, are relatively small with effect size estimated at 0.14. Therefore, authors suggest that the benefits associated with sedative use are marginal and are outweighed by the risks in the treatment of late-life insomnia. Some might argue that all benzodiazepine-receptor agents, no matter benzodiazepines or Z-drugs, were grouped together for analyses in such a meta-analysis. However, there are still insufficient evidence to support the use of individual Z-drugs including eszopiclone for insomnia treatment among older patients. Studies on newly developing benzodiazepine-receptor drugs have yielded more positive results. These results may pave the way to develop ideal hypnotics for older patients with insomnia in the near future.

Another issue regarding efficacy is the length of treatment. Almost all previous clinical trials with benzodiazepine-receptor agonist were designed for the short-term management of chronic insomnia. Only 2 out of 24 clinical trials included in the meta-analysis by Glass et al had study duration more than one month. Recent studies support sustained efficacy of the use of some Z-drugs including eszopiclone and the extended-release formulation of zolpidem for more than 6 months, even up to 12 months. Nevertheless, insufficient evidence warrant extended use of those drugs for the treatment of late-life insomnia because of few older patients recruited in the above studies.

Safety

Safety is a major concern about the use of hypnotics among older patients, given the age-related changes in pharmacodynamics, pharmacokinetics, and drug-drug interactions. For these kinetic changes, a lower dose is recommended for most benzodiazepine-receptor agonist while applied to older patients.

A prospective study found that benzodiazepines or neuroleptics being involved in the majority of falls precipitated by drugs among older people living in residential care facilities. Based on Taiwan’s national insurance claims data, Chang and colleague pointed out that benzodiazepine exposure in people aged 65 and over might increase the risk of hip fractures. Although inconclusive for risks for falls of Z-drugs, close monitoring of the elderly beginning drug treatment for insomnia is a necessary rule of thumb.

Cognitive impairment is another safety concern about long-term use of hypnotics. Adverse cognitive events were found to be close to five times more common with hypnotics than with placebo in the meta-analysis mentioned above. Z-drugs have been considered to produce fewer and less severe adverse effects including cognitive impairment. However, a recent large-scale study found the long-term use of zolpidem and zopiclone might potentially contribute to an increased risk of dementia.

The use of hypnotics, Z-drugs in particular, might induce complex sleep-related behaviors including sleepwalking and sleep-related eating behaviors. The FDA has requested manufacturers of hypnotics to highlight these potential dangerous behaviors in product labeling in 2007. In a retrospective survey, Hwang and colleague found higher doses of hypnotics and bad sleep practices would be associated with complex sleep-related behaviors induced by hypnotics.

Thus, for above safety concerns, the use of benzodiazepine-receptor agonists for late-life insomnia
is strictly restricted to a short period of time and a lower dose.

Hypnotics: other than benzodiazepine-receptor agonists
Several sedating medications including antihistamine (eg, diphenhydramine), antidepressants (eg, trazodone, doxepine, mirtazapine), and antipsychotics (eg, quetiapine and olanzepine) have been utilized for insomnia treatment among older patients. However, the majority of these agents are not indicated or approved by the Food and Drug Administration for this condition. Furthermore, there is scant information regarding their applications for older patients with insomnia. Even for the most commonly prescribed sedating antidepressant trazodone, a comprehensive review has concluded that evidence for its efficacy in treating insomnia is very limited.108 Mirtazapine, a potent antagonist at the postsynaptic 5-HT₄ and 5-HT₃ serotonin receptor, has been shown to have significant improvement in sleep quality among depressive patients compared to fluoxetine.109 However, there is no direct evidence supporting its application for the treatment of late-life insomnia. For elderly, these sedating medications may carry serious safety concerns including cognitive impairment and falls and thus, are not optimal alternatives to benzodiazepine-receptor agonists.

A recent study supports the efficacy of doxepin, a traditional antidepressant, for the treatment of late-life insomnia while delivered at low doses (1 mg and 3 mg).110 To act as a selective histamine H₁-receptor antagonist at low doses, doxepin showed a significant improvement in sleep quality and was well tolerated in insomniac patients aged 65 and older in this 12-week placebo-control trial. In 2010, doxepin has been approved by the FDA for the treatment of adults with transient or chronic insomnia, characterized by difficulty with sleep maintenance in particular.

Ramelteon, a highly selective melatonin MT₁ and MT₂-receptor agonist, has also been approved by the FDA for insomnia treatment and is recommended for elderly patients for its relative safety and no abuse liability.111 A one-year, open-label study recruited 248 patients aged 65 and older and found a sustained therapeutic effects with a low incidence of adverse events under ramelteon 8 mg.112 This agent might not impair balance and mobility in the middle of the night and could expectedly reduce the risk of falls among older patients during insomnia treatment.113

Conclusion
Symptoms of insomnia are highly prevalent in the elderly population. These symptoms are often neglected because they may be attributed to comorbid medical or psychiatric conditions. Accumulated evidence of the significant consequences of insomnia warrants careful evaluation and appropriate management of the condition in this population. Insomnia in the elderly population may be complicated by normal age-related sleep changes as well as the higher prevalence of comorbid conditions. These factors should be considered in the evaluation and treatment of late-life insomnia. Both non-pharmacological and pharmacological treatments have been demonstrated to result in effective treatment outcomes. Proper treatment of insomnia in this age group is effective and can improve the overall quality of life of the patients. Educational programs directed at physicians, psychologists, other geriatric care providers, and the general public are needed to acknowledge insomnia and its treatment options in the elderly population.

Disclosures
Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References
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