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REVIEW ARTICLE

Insomnia in Elderly Patients: Recommendations for Pharmacological Management

Vivien C. Abad[1] · **Christian Guilleminault**[1]

Abstract

Chronic insomnia affects 57% of the elderly in the United States, with impairment of quality of life, function, and health. Chronic insomnia burdens society with billions of dollars in direct and indirect costs of care. The main modalities in the treatment of insomnia in the elderly are psychological/behavioral therapies, pharmacological treatment, or a combination of both. Various specialty societies view psychological/behavioral therapies as the initial treatment intervention. Pharmacotherapy plays an adjunctive role when insomnia symptoms persist or when patients are unable to pursue cognitive behavioral therapies. Current drugs for insomnia fall into different classes: orexin agonists, histamine receptor antagonists, non-benzodiazepine gamma aminobutyric acid receptor agonists, and benzodiazepines. This review focuses on Food and Drug Administration (FDA)-approved drugs for insomnia, including suvorexant, low-dose doxepin, Z-drugs (eszopiclone, zolpidem, zaleplon), benzodiazepines (triazolam, temazepam), and ramelteon. We review the indications, dosing, efficacy, benefits, and harms of these drugs in the elderly, and discuss data on drugs that are commonly used off-label to treat insomnia, and those that are in clinical development. The choice of a hypnotic agent in the elderly is symptom-based. Ramelteon or short-acting Z-drugs can treat sleep-onset insomnia. Suvorexant or low-dose doxepin can improve sleep maintenance. Eszopiclone or zolpidem extended release can be utilized for both sleep onset and sleep maintenance. Low-dose zolpidem sublingual tablets or zaleplon can alleviate middle-of-the-night awakenings. Benzodiazepines should not be used routinely. Trazodone, a commonly used off-label drug for insomnia, improves sleep quality and sleep continuity but carries significant risks. Tiagabine, sometimes used off-label for insomnia, is not effective and should not be utilized. Non-FDA-approved hypnotic agents that are commonly used include melatonin, diphenhydramine, tryptophan, and valerian, despite limited data on benefits and harms. Melatonin slightly improves sleep onset and sleep duration, but product quality and efficacy may vary. Tryptophan decreases sleep onset in adults, but data in the elderly are not available. Valerian is relatively safe but has equivocal benefits on sleep quality. Phase II studies of dual orexin receptor antagonists (almorexant, lemborexant, and filorexant) have shown some improvement in sleep maintenance and sleep continuity. Piromelatine may improve sleep maintenance. Histamine receptor inverse agonists (APD-125, eplivanserin, and LY2624803) improve slow-wave sleep but, for various reasons, the drug companies withdrew their products.

✉ Christian Guilleminault
cguil@stanford.edu

Vivien C. Abad
vivien.abad@stanford.edu

[1] Division of Sleep Medicine, Department of Psychiatry and Behavioral Sciences, Stanford Outpatient Medical Center, Stanford University, 450 Broadway St. Pavilion C 2nd Floor MC 5704, Redwood City, CA, 94063, USA

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Key Points

Insomnia in the elderly has severe individual and societal consequences and should be treated primarily with cognitive behavioral therapy for insomnia, but pharmacological treatment and combination therapies are adjunctive.

Pharmacologic treatment of insomnia in the elderly requires joint decision-making between the healthcare provider and patient, balancing benefits versus risks, optimizing dosing and scheduling of drugs, and monitoring for efficacy and side effects. Timing of insomnia symptoms (sleep onset, sleep maintenance, and middle of the night awakenings) can help guide the initial choice of drug.

Current available hypnotic drugs (Z-drugs, benzodiazepines, low-dose doxepin, and suvorexant) all have significant risks in the elderly, and short-term or intermittent use should be considered when prescribing these drugs. Ramelteon appears to be a slightly safer alternative that may slightly improve sleep-onset difficulties, but has no significant effect on sleep maintenance problems.

1 Introduction

F. Scott Fitzgerald declared that "the worst thing in the world is to try to sleep and not to" [1]. Insomnia is a significant public health problem that remains under-recognized, underdiagnosed, and under-treated [2, 3].

Though present in 33–50% of the United States (US) general adult population, insomnia is particularly prevalent among the elderly, usually defined as individuals aged 65 years and older [4]. A study of three cohorts in the US with more than 9000 participants aged 65 years and older reported a 57% prevalence of chronic sleep difficulties occurring most of the time, with 25% of the elderly napping during the day [5]. Forty-eight percent of 'older adults' ($n = 1506$, aged 55–84 years) in the 2003 Sleep in America Poll reported insomnia symptoms and daytime dysfunction [6]. The incidence of insomnia in the elderly in the US has been reported to be about 5% per year [7]. Epidemiologic studies of insomnia in the elderly in other countries (France, Australia, United Kingdom, Italy, Hong Kong, Thailand, and Sweden) reported an 11–46% prevalence [8–14]. Elderly women are 50% more likely to report insomnia symptoms compared with men [15].

Psychological and behavioral therapies, particularly Cognitive Behavioral Therapy for Insomnia (CBT-I), are the major treatments for insomnia. Because not all patients will improve with only CBT-I, pharmacotherapy—alone or with CBT-I—is commonly utilized to treat disordered sleep, including in the elderly. Thirty-one percent of all over-the-counter (OTC) and prescription drugs used to treat insomnia are consumed by patients aged 65–79 years [16]. Patients aged 65 years and older have an almost five times increased odds ratio (OR) of being prescribed a medication for sleep difficulty or insomnia during office visits compared with those aged 18–35 years [17], and 18% of older Americans have received prescriptions for sleep problems [6]. Despite the common prescription of medications to treat insomnia, significant knowledge deficiencies and anxieties exist among prescribers regarding the appropriate use of such medications [18].

This paper discusses the treatment of insomnia in the elderly, with special attention to (1) the efficacy of prescription and non-prescription medications in the elderly, (2) the potential for adverse effects from these medications in the elderly, (3) specific concerns regarding drugs and dietary supplements used to treat insomnia in the elderly, (4) basic pharmacology of these medications, and (5) recommendations for approaching insomnia in the elderly that can be utilized in clinical practice.

1.1 Sleep in the Elderly

Sleep patterns change with age. The elderly experience advanced sleep timing (earlier bedtimes and rise times), difficulty falling asleep, and increased sleep onset latency (SOL). The duration of light sleep (Stages I and II non-rapid eye movement [NREM] sleep) increases, slow wave sleep (SWS = Stage III NREM) decreases, rapid eye movement (REM) sleep decreases (usually around age 80 years), and NREM/REM sleep cycles are fewer and shorter. Sleep is more vulnerable with easy arousability to external stimuli and more interrupted with increased arousals, brief awakenings, and sleep stage transitions to lighter sleep. Wake after sleep onset (WASO) increases with more time spent awake, sleep efficiency (SE, the percentage of time asleep/time in bed [TIB]) decreases, and total sleep time (TST) decreases [19, 20].

1.2 Co-Morbidities and Consequences of Insomnia in the Elderly

Insomnia exacts a heavy toll. Quality of life (QOL), daytime function, and mental, physical, and emotional health deteriorate [4, 21–32]. Untreated insomnia and hypnotic-treated insomnia are risk factors for falls in the elderly [21–23]. Depression, anxiety disorders, and alcohol and drug abuse/dependence are increased, while immune function seems decreased and cognitive function declines [24, 32].

Cognitive impairment can impact daily activities. In the elderly, daytime cognitive and attentional impairments

associated with insomnia may be misconstrued as symptoms of early dementia or mild cognitive impairment [24]. Mean memory span, integration of visual and semantic dimensions, and executive function are significantly worse in elderly insomniacs [25]. Longitudinal studies conducted over 3 and 3.4 years in the US [26] and in Germany [27] reported cognitive decline in elderly insomnia patients who exhibited longer sleep duration [27], depression [26], sleep continuity [27], or sleep maintenance difficulties [28, 29]. A meta-analysis of studies in adults > 60 years showed that insomnia is associated with a significant risk of all-cause dementia [30].

Elderly Americans with poor sleep have almost twice the mortality rates from stroke, cancer, heart disease, and suicide compared with good sleepers [24]. Ten to twelve percent of elderly Americans sleep < 6 h per night, while 8–9% sleep > 9 h per night [6]. Short sleep duration with insomnia poses increased risks for cardio-metabolic disease, minimal cognitive impairment, stroke, chronic pain, depression, and anxiety [31–33]. A study of mortality rates showed that Americans who slept ≤ 6 h or ≥ 9 h/night had increased risk of dying over a 9-year follow-up period [33].

Difficulty initiating and maintaining sleep was associated with moderate increase in acute myocardial infarction risk in a mixed (non-elderly/elderly) group of Norwegians followed over 11.4 years [34]. In elderly Japanese, carotid intima media thickness, a marker of carotid vascular disease, was found to be significantly greater in the insomnia group and in subjects who slept ≤ 5 h [35].

Insomnia creates a heavy burden for both the affected individual and society [36–41]. Society incurs direct and indirect costs from insomnia, but the latter are more difficult to estimate. Direct costs of insomnia care for all age groups vary. In the US, estimates range from US$1.8–15.4 billion annually (1994 USD) to US$13.9 billion (1995 USD) [36–38]; Ozminkowski et al. reported that untreated chronic insomnia in the US increased direct costs in the elderly by US$1143 (2003 USD) over 6 months when compared with controls without insomnia [41]. It is imperative that insomnia be addressed effectively.

1.3 Treatment of Insomnia in the Elderly

Treatment of adult patients, including the elderly, whose insomnia is burdensome may include (1) psychological therapies, (2) pharmacotherapy, or (3) a combination of psychological and pharmacological treatment [4, 18, 24, 42–53]. Professional society guidelines are helpful in directing therapy, but individual factors to consider include severity and impact of insomnia, urgency for symptom relief, patient preference, effectiveness of interventions, availability and ease of access to advanced behavioral therapies, potential for harm, and the cost of therapy, including insurance coverage and/or reimbursement. Rapidity of symptom relief varies: hypnotic agents can work immediately, while psychological therapy results are delayed over several weeks. The patient's perceptions towards treatment should be assessed prior to, during, and after treatment [54]. Two validated measures that can be used to evaluate the patient's preference for either psychological or pharmacological therapy are the Insomnia Treatment Acceptability Scale [55] and the Treatment Acceptability Preferences measure [56].

2 Psychological Treatment for Insomnia

A National Institutes of Health consensus conference in 2005 found moderate- to high-grade evidence supporting the efficacy of cognitive behavioral therapy (CBT) in the short-term management of chronic insomnia in adults, but noted paucity of data for long-term use [57]. Psychological therapies for insomnia in all adults include CBT-I, brief behavioral therapy for insomnia (BBT-I), cognitive restructuring, multicomponent behavioral therapy, sleep restriction therapy, stimulus control, relaxation therapy, and mindfulness-based interventions [4, 18, 42, 44–46, 58].

Various psychological/behavioral therapies have been used successfully to treat older adults/elderly with insomnia [45, 58–73]. Randomized control studies in the elderly using polysomnographic parameters have demonstrated that CBT-I surpasses drugs in efficacy and duration of therapeutic effects, both subjectively and objectively [59–61]. For older adults, CBT-I improved the Insomnia Severity Index (ISI) by 3.6 points and the Pittsburgh Sleep Quality Index (PSQI) by 3 points. CBT-I improved SOL by 8.2 min, reduced WASO by 37.6 min, and improved SE and sleep quality (QUAL) [18, 45, 59, 60, 62–67]. Stimulus control improved TST in older adults by 40.4 min [45, 68]. Multicomponent behavioral therapy or BBT-I improved SOL, WASO, SE, and QUAL in the elderly [4, 45, 69–71].

BBT-I effectively reduced sleep variability (assessed via sleep diary and actigraphy) in older adults with chronic insomnia by increasing consistency in bedtime and wake time and by decreasing TIB. Sleep variability at baseline may serve as an indicator for high responsiveness to BBT-I [73].

The American Academy of Sleep Medicine (AASM), American College of Physicians (ACP), and the British Association of Psychopharmacology (BAP) have conducted reviews of psychological and behavioral treatments for chronic insomnia in adults (including the elderly) and endorsed the significantly favorable benefit to risk ratio for behavioral therapies. Position papers and guidelines from these organizations recommend CBT-I as initial treatment for adults with chronic insomnia [4, 18, 44–46]. However, access issues to psychological/behavioral therapy remain.

The absence of trained specialists in many parts of the world has led to the development of CBT-I through telemedicine, website CBT-I, and do-it-yourself books and mobile device applications [74–77]. Currently, several research projects, such as those at the University of Colorado and Stanford University, are evaluating the success rates of smart phone or computerized approaches without the intervention of CBT-I specialists.

3 Pharmacologic Therapy of Insomnia

3.1 Considerations in Drug Prescribing for Older/Elderly Patients

Polypharmacy is common in the elderly. More than 20% of elderly Americans have five or more chronic conditions, and 50% receive five or more medications [78]. Insomnia can be a side effect of existing medications, and adding a hypnotic can add to the 'prescribing cascade' unless changes are made to the causative drug. Adverse drug effects (ADE) can occur with the emergence of geriatric syndromes [78].

Aging alters pharmacokinetics and pharmacodynamics. A proportional increase in body fat relative to skeletal muscle in older adults may increase the volume of distribution. Reduced renal function due to age, even without renal disease, may prolong drug half-life ($t_{½}$) [78]. Drugs that bypass phase I oxidation and are metabolized only by phase II conjugation (which does not decline with age) are less likely to accumulate toxic levels and may be safer in the elderly [79]. Drug dosing in general should start at the lowest available dose and should be utilized for short-term relief while adding psychological/behavioral therapy measures for long-term relief. All Food and Drug Administration (FDA)-approved drugs for insomnia can be associated with clinically significant ADE [49]. Antihistamines, antidepressants, and anticonvulsants are sometimes prescribed off-label for insomnia but may be associated with more risks than benefits when treating older persons [49]. The choice of a pharmacologic agent involves considering the symptom pattern [sleep onset, sleep maintenance, both sleep onset and sleep maintenance, middle of the night (MOTN) awakenings], treatment goals, patient preference, past treatment responses, co-morbid conditions, contraindications, concurrent medication interactions, side effects, cost, and availability of other treatments [4].

Preservation of cognitive functioning is an important consideration in the elderly. Hypnotic drugs can affect sleep architecture and/or various sleep parameters, and it is important to look at drug effects on sleep continuity, TST, SWS, spindles, and REM sleep. Sleep continuity has more benefits with respect to controlled and executive abilities compared with other cognitive domains, such as processing speed, simple response time, or motor aspects of cognition [80]. Longer TST is associated with poor performance in older adults on the modified mini-mental state test (3 M) [80–82]. SWS activity reflects neural synchrony within the prefrontal cortex, which may enhance cortical connections. SWS has been associated with executive function and declarative memory consolidation [80]. Sleep spindles in the sigma frequency (12–16 Hz) are thought to promote synaptic plasticity, thereby benefiting intellectual abilities and memory consolidation [80, 83]. REM sleep is associated with memory consolidation, procedural memory, and emotional memory [84].

A word of caution about hypnotic therapy and sleep disordered breathing (SDB) in the elderly: in clinical practice, many elderly patients present with disturbed sleep that is primarily due to unrecognized and untreated SDB [85–87]. The Medicare guidelines in the US mandate usage of oxygen saturation (SpO_2) as the number-one index determining the presence of abnormal breathing during sleep, and 'home studies' monitoring sleep and breathing usually do not include electroencephalography [88–90]. These tests are useless in recognizing SDB that leads to arousals and awakening and complaints of insomnia. Oxygen tension is not the same as oxygen saturation, and circulating CO_2 or bicarbonates are better indicators of abnormal breathing events, but end-tidal CO_2 is never monitored in home studies and rarely in many laboratory-based sleep studies. Randomized studies of nasal continuous positive airway pressure (CPAP) compared with treatment of insomnia have been performed in middle-aged adults but not in the elderly [87]. The presence of associated SDB behind the complaint of insomnia in the elderly is commonly ignored. Improvements in nasal CPAP equipment and interfaces in the last year have been associated with better compliance with prescription of this newest equipment. However, many elderly patients with unrecognized SDB will be prescribed hypnotic medications, increasing the risk of confusional arousals [85–87, 91]. Also, hypnotic medications have been prescribed at the onset of positive airway pressure treatment in the elderly without systematic follow-up and hypnotic dose reduction once the patient has reached good habituation to the equipment [87]. No systematic long-term trials involving the elderly, hypnotics, and the above issues with a large number of subjects exist to date.

With the above considerations and caveats, we review the various options for pharmacotherapy in the next section. With this section, please also refer to Tables 1 and 2. Table 1 describes FDA-approved drugs for insomnia, their mechanisms of action, the various formulations, dosing in the elderly, basic pharmacology, and our comments. Table 2 describes hypnotic drugs that are commonly used off-label to treat insomnia (trazodone and tiagabine) and sleep-aid supplements (melatonin, tryptophan, and valerian).

Table 1 FDA-approved hypnotic drugs for insomnia [4, 43–45, 93, 94, 104, 105, 107, 108, 114, 143, 145, 156, 166, 170, 175, 229, 231–242]

Class and mechanism of action	Drug (generic)	Trade name	Dose in elderly (mg)	T_{max} (h)	$t_{½}$	Metabolism	Indication by type of symptoms	Comments in elderly
Dual orexin receptor antagonist inhibits binding of orexin A and B to receptors OX1R and OX2R	Suvorexant	Belsomra®	Usual starting dose is 10 mg. Use lowest effective dose; available as 5–20 mg	2	12	CYP 3A4 and CYP2C19	SMI mainly and less effect on SO	Take 30 min before bedtime. Starting dose 10 mg in elderly and maximum is 20 mg. Start with 5 mg (max 10 mg) for elderly on moderate CYP3A inhibitors. It should not be used with strong CYP3A4 inhibitors. It is contraindicated in narcolepsy patients. Concentration levels in elderly are higher by 15% compared with non-elderly
Histamine receptor 1 antagonist has antagonistic effects at α adrenergic, muscarinic, cholinergic receptors	Doxepin	Silenor®	3 mg; maximum is 6 mg	2–8	20	CYP2D6, CYP2C19	SMI	Take 30 min before bedtime. Do not take within 3 h of a meal; it is contraindicated in untreated narrow-angle glaucoma, severe urinary retention; do not co-administer with monoamine oxidase inhibitors
Cyclopyrrolone benzodiazepine receptor agonist at $GABA_A$ receptor α1, 2, 3, 5 subunits	Eszopiclone	Lunesta®	1 mg; maximum is 2 mg	1	9	CYP3A4 and CYP2E1	SOI, SMI	Take immediately before bedtime. Decrease dose if taking CYP3A4 inhibitors
Imidazopyridine benzodiazepine receptor agonist binds to α1 and α5 subunits of $GABA_A$	Zolpidem IR	Ambien®	5 mg	1.6	2.5	CYP3A4 and CYP2C9	SOI	Take immediately before bedtime. For Ambien, Edluar, or Zolpimist, do not use unless have 7–8 h TIB If using CR, sedative effect may last > 9 h, so postpone activities that require alertness, such as driving, to afternoon Use Intermezzo only if at least 5 h TIB remaining
	Zolpidem SL	Edluar™	5 mg	1.4	2.70		SOI	
	Zolpidem oral spray	Zolpimist®	5 mg = 1 spray	0.9	2.8		SOI	
	Zolpidem ER	Ambien CR®	6.25 mg	1.5	2.8		SMI	
	Zolpidem ZST	Intermezzo®	1.75 mg	0.6	2.5		MOTN	

Table 1 (continued)

Class and mechanism of action	Drug (generic)	Trade name	Dose in elderly (mg)	T_{max} (h)	$t_{½}$	Metabolism	Indication by type of symptoms	Comments in elderly
Pyrazolopyrimidine benzodiazepine receptor agonist binds to $GABA_A$ α1β2γ2 subunits	Zaleplon	Sonata®	5 mg	1	1	CYP3A4	SOI, MOTN	Take immediately before bedtime A high fat/heavy meal can delay absorption
Benzodiazepine binds to $GABA_A$ receptor at junction of α and γ subunits	Triazolam	Halcion®	0.125 mg; maximum is 0.25 mg	1–3	2–5.5	CYP3A4 and glucoronide conjugation	SOI	Potential for respiratory depression with opiates; overdose can occur at 2 mg; avoid prescribing if there is history of drug abuse, as this can be insufflated
Benzodiazepine binds to $GABA_A$ receptor	Temazepam	Restoril®	7.5 mg	1.2–1.6	3.5–18.4	Glucoronide conjugation	SOI, SMI	Take 30 min before bedtime
Indenofuran melatonin receptor agonist; binds to MT_1 and MT_2 receptors	Ramelteon	Rozerem®	8 mg	0.5–1.5	1–2.6	CYP1A2, CYO2C, CYP3A4	SOI	Take within 30 min of bedtime. Do not administer with strong CYP1A2 inhibitor like fluvoxamine

CR controlled release, *CYP* cytochrome P450, *ER* extended release, *FDA* Food and Drug Administration, *GABA* gamma aminobutyric acid, *IR* immediate release, *MOTN* middle of the night, *MT* melatonin, *OX* orexin, *SL* sublingual, *SMI* sleep maintenance insomnia, *SOI* sleep onset insomnia, *TIB* time in bed, T_{max} time to maximum concentration, $t_{½}$ elimination half-life, *ZST* zolpidem sublingual tablet

Table 2 Other hypnotic agents and herbal preparations [166, 167, 175, 176, 181, 189, 190, 228, 240]

Class and mechanism of action	Agent (generic)	Trade name	Dose in elderly (mg)	T_{max} (h)	$t_{½}$	Metabolism	Indication by type of symptoms	Comments in elderly
Hormone acts on MT1 receptors	Melatonin dietary supplement		0.3–0.5 mg	NA	NA	Oxidation, conjugation	SOI	Nervousness, irritability, abnormal dreams, and anxiety are infrequent
	Prolonged-release melatonin	Circadin™	2 mg	3	3.5–4	CYP1A1, CYP1A2, CYP2C19	SOI	
Triazolopyridine inhibits reuptake 5-HT1 and antagonist at 5-HT_{1A}, 5-HT_2, α1 and α2 receptors; low anticholinergic and dopaminergic activity, and moderate antihistamine activity	Trazodone	Desyrel™	25–50 mg	0.5–1.33	5–9	CYP3A4 to active metabolite mCPP	SOI, SMI	Dizziness and orthostatic hypotension, increased risk for falls, psychomotor cognitive dysfunction, memory impairment
Anticonvulsant that inhibits GABA transporter	Tiagabine	Gabitril™	4 mg	0.75	7–9	CYP3A4	SMI	No improvement in sleep quality
Amino acid precursor for 5-HT and melatonin	Tryptophan	L-Trypt	1000 mg	NA	NA	NA	SMI	
Herb with GABA-like effects, serotonin receptor activity, adenosine receptor antagonism	Valerian	Valerian root	225–1215 mg; no standardized dose	NA	NA	NA	SMI	Relatively safe

5-HT 5-hydroxytryptamine, *CYP* cytochrome P450, *GABA* gamma aminobutyric acid, *mCPP* m-chlorophenylpiperazine, *MT* melatonin, *NA* not available, *SMI* sleep maintenance insomnia, *SOI* sleep onset insomnia, T_{max} time to maximum concentration, $t_{½}$ elimination half-life

4 Hypnotic Drugs That Are FDA-Approved for Treating Insomnia

4.1 Orexin Receptor Antagonists

4.1.1 Suvorexant

Suvorexant is the first dual orexin receptor antagonist (DORA) that is FDA-approved in the US at doses of 5–20 mg to treat sleep onset and sleep maintenance insomnia [92, 93]. It inhibits binding of wakefulness-promoting neuropeptides orexin (OX) A and B to receptors OX1R and OX2R [92, 93].

Sleep Architecture In the mixed group of non-elderly and elderly subjects, suvorexant increases the time spent in all sleep stages and, in general, sleep architecture is preserved, except for the first night of use, when it very slightly reduced percent of NREM sleep Stages I, I, III and slightly improved REM sleep by 3.9% [94]. On the first night only, NREM decreased 3–6% in the gamma and beta bands, while delta bands slightly increased by 4–8%, but these were not seen at month 1 and month 3 [94].

Benefits Herring et al. pooled efficacy data in the elderly from two 12-week randomized controlled trials (RCTs; P028 and P029) [95, 96]; elderly patients taking suvorexant 15 mg ($n = 319$) and 30 mg ($n = 202$) were compared with placebo. Subjective (s) and polysomnography (PSG) parameters were utilized. At the 15-mg dose, the following changes in the least squares mean difference (MD) were reported: sTST increased by 15.5 and 18.9 min at months 1 and 3, respectively; sWASO decreased by 10.8 and 10.8 min; PSG WASO decreased by 26.9 and 23.4 min; and sSOL decreased by 3.6 and 6.5 min. The PSG sleep onset parameter, latency to persistent sleep (LPS), decreased by 5 and 6.2 min. Suvorexant 30 mg showed greater efficacy for sleep maintenance and more sustained improvements but is higher than the recommended FDA dose and is not currently available. These changes indicate clinically significant improvement in sleep maintenance measures with statistically small improvement in sleep onset. The ACP's analysis of these RCTs (P028 and P029) reported that in the mixed group (elderly and non-elderly on suvorexant 15 and 20 mg), ISI score improved, with MD − 1.2 [95% confidence interval (CI) − 1.8 to − 0.6] [44, 45].

Harms In the mixed group of non-elderly and elderly subjects, there was low-quality evidence that study withdrawals and withdrawals due to ADE were not significant [45]. At the FDA-approved doses of 15 and 20 mg, no difference was found between treatment and placebo groups in the proportion of ADE > 1.

Two studies addressed harms from suvorexant in the elderly [96, 97]. Driving performance with suvorexant (15, 30 mg) in healthy elderly men and women did not significantly differ from placebo based upon standard deviation of lateral position (SDLP) and variability in speed [97]. However, the percentage of motor vehicle accidents or violations was increased by 2.8% versus 1.0% in placebo at the 15-mg dose [96]. Suvorexant use in the elderly was not associated with any statistically significant impairments in memory, balance, or residual daytime effect [97]. Somnolence occurred in 7% and severe daytime sleepiness in 0.5% at the 15-mg dose [96]. The fall rate at 15 mg was 1.5%. Other side effects included headache, dizziness, and nasopharyngitis [96]. There was one report of sleep paralysis and one of sleep-related hallucination. No adjudicated narcolepsy symptoms were reported. Suicidal ideation was reported in one patient. No rebound insomnia occurred with abrupt termination after 3, 6, or 12 months, and no withdrawal symptoms occurred following abrupt termination of doses in the elderly [96].

Safety of suvorexant has not been established in patients of any age with co-morbid respiratory difficulties [severe sleep apnea or chronic obstructive pulmonary disease [COPD] or obstructive sleep apnea (OSA)-COPD overlap syndrome] [98, 99]. Although no significant change in mean SpO_2 occurred during sleep in 26 patients (mean age 49 years) who took suvorexant 40 mg (which is higher than the maximum approved doses in US and Japan), a small increase in mean apnea–hypopnea index (AHI) has been reported [98, 99].

Comment Suvorexant is more useful for sleep maintenance insomnia and has less effect on sleep-onset difficulties. At Stanford, it has been helpful when used in combination with CBT-I sleep restriction protocol. Although somnolence is dose related, there is variability in individual somnolence response. A few older adults on suvorexant 30 mg had micro-sleep episodes and excessive sleepiness while driving [93]. Therefore, driving precautions should be discussed with patients. Because the effects of suvorexant in patients with sleep apnea are not well studied, as a precaution, patients with sleep apnea on CPAP therapy who are taking suvorexant should monitor their AHI.

4.2 Histamine Receptor Antagonists

4.2.1 Doxepin

Low-dose doxepin is a sedating tricyclic antidepressant that blocks the wake-promoting effects of histamine through selective H1 receptor antagonism [100–104].

Sleep Architecture Low-dose doxepin in the elderly has minimal to no effect on NREM sleep Stage I or Stage III, but it increases Stage II minutes. REM sleep is not suppressed [100].

Benefits Three RCTs in the elderly using doxepin 1, 3, and 6 mg showed efficacy in treating sleep maintenance insomnia with decreased sWASO and PSG WASO and increased PSG SE and duration of sleep (sTST and PSG TST). Doxepin had no effect on LPS [100–102]. Sleep maintenance and duration endpoints persisted into the final hour of the night, which is important since the earlier morning hours are when sleep in the elderly is more disturbed. There were no residual effects. Improvements in subjective sleep parameters were sustained from weeks 2–4 of therapy. Clinical Global Impression (CGI) scale improved during weeks 1 and 2 and ISI improved during weeks 1–4 when compared with placebo [100, 101]. There were no significant next-day residual effects and no impairment in memory at any of the three doses used [100, 101].

Moderate quality evidence showed that doxepin 1, 3, or 6 mg improved TST in older adults, with weighted mean difference (WMD) 23.9 min (CI 12.0 to 35.7) [44, 45], and that ISI mean change improved, with WMD − 1.7 (CI − 2.6 to − 0.9). There is low-quality evidence that WASO improved, with MD − 17.0 (CI − 29.3 to − 4.7), and that SOL improved, with MD − 14.7 min (CI − 24.0 to − 5.4) [44, 45].

Harms In the elderly, side effects were similar to placebo and included nausea (4–5%), somnolence (8–9%), and dizziness (2%) [100, 101]. There were no reports of complex sleep behaviors (CSBs), memory impairment, or cognitive disorders in the doxepin-treated elderly patients [102, 103].

In adults, including the elderly, drug–drug interactions may occur with cytochrome P (CYP) inducers and inhibitors, including OTC medications like cimetidine [104]. Patients with decreased renal function may have delayed clearance of doxepin, leading to sedation. Low-dose doxepin is not recommended for insomnia patients of any age who have severe sleep apnea [104].

Comment Low-dose doxepin improves sleep continuity and sleep duration and appears to be a good alternative for elderly insomniacs with sleep maintenance problems. Because it does not affect SWS or REM sleep, it should have fewer deleterious effects on memory consolidation and executive function.

4.3 Non-Benzodiazepine Gamma Aminobutyric Acid $(GABA)_A$ Receptor Agonists (Z-Drugs)

$GABA_A$ receptors, the main neuroinhibitory transmitter receptors, are composed of pentameric protein subunits, most of which consist of α, β, and γ isoforms [105]. Nonbenzodiazepine receptor agonists typically act on α1, α2, α3, α5, β2, β3, and γ2 subunits. The Z-drugs (eszopiclone, zolpidem, and zaleplon) promote sleep through GABA by binding selectively to $GABA_A$ receptors. Z-drugs in general do not affect SWS or REM sleep and thus should have little effects on memory.

4.3.1 Eszopiclone

Eszopiclone is a cyclopyrrolone nonbenzodiazepine hypnotic that is FDA-approved for sleep-onset and sleep-maintenance insomnia with no short-term usage restriction. It acts through $GABA_A$ receptor sub-types α1, 2, 3 and 5 subunits [106–108]. It is the S-isomer of racemic zopiclone, a hypnotic drug that is approved in Europe, Canada, and Latin America.

Sleep Architecture Eszopiclone in the elderly increases Stage II NREM sleep, but does not affect Stage I or Stage III NREM sleep or REM sleep [107, 109].

Benefits Three RCTs of eszopiclone in the elderly—which included two 2-week trials ($n = 231$, mean age 72.3 years [110], and $n = 264$, mean age 71.5 years) [109] and one 12-week trial ($n = 194$, mean age 71.6 years) [106]—each reported that eszopiclone 2 mg improved both sleep initiation and sleep maintenance subjective and objective parameters and improved daytime function with improved alertness, ability to concentrate, and physical well-being [106, 109, 110]. However, eszopiclone 1 mg improved LPS only on week 1 and had no effect on other parameters [106].

A meta-analysis by the ACP indicated that in older adults, there is low-quality evidence that eszopiclone improves ISI score, with MD − 2.3 (CI − 3.3 to − 1.3); TST improves, with MD 30.0 min (CI 19.7 to 40.3); and WASO improves, with MD − 21.6 min (CI − 29.6 to − 13.6) [44, 45].

Harms: The most common adverse effects in the elderly were headaches (13.9%), unpleasant taste (12.4%), nasopharyngitis (5.7%), and dizziness (4.1%) [106]. Less common adverse effects were anxiety (2.1%), nervousness (1.5%), falls (1.0%), memory disturbance (1.0%), and hallucinations (0.5%) [106]. In a study of elderly patients who were hospitalized for either traumatic brain injury or hip fracture, the use of eszopiclone the month before admission did not increase the risk for either of these events, unlike zolpidem [111].

Comment RCTs in the elderly suggest improvement in sleep onset and sleep maintenance and daytime function with short-term and up to 12 weeks of use. The recommended dose of 1 mg in the elderly may help sleep onset but if sleep

maintenance is a significant problem, consider increasing the dose to 2 mg. Intermittent dosing is preferred, but in the small subgroup of elderly patients who require longer term hypnotic therapy, eszopiclone may be an alternative.

4.3.2 Zolpidem

Zolpidem, an imidazopyridine hypnotic, binds selectively to the α1 and α5 subunits of the $GABA_A$ complex [112].

Sleep Architecture Zolpidem 5 mg in elderly non-insomniacs did not alter sleep architecture, but doses of 10 and 20 mg slightly reduced REM sleep percentage [113].

Benefits A systematic review by Glass et al. included three RCTs comparing zolpidem with placebo but reported that these data in the elderly were insufficient to be included in their meta-analysis of benefits [114]. Another systematic review [115], which included four RCTs in the elderly [116–119], reported that zolpidem may be effective at improving sleep latency, decreasing nocturnal awakenings, and increasing sleep duration and quality compared with placebo, but the authors rated the evidence as low quality [115].

An RCT ($n = 205$, mean age 70.2 years) using zolpidem extended release 6.25 mg nightly for 3 weeks described more significant improvements in PSG measures of sleep continuity (WASO), sleep onset (LPS), and TST on nights 1 and 2 compared with nights 15 and 16. Sleep efficiency also improved on nights 1 and 2, but not on nights 15 and 16. These findings could suggest tolerance with longer use [120]. Patient-reported measures also improved.

A study in 768 elderly French insomniacs utilized a two-phase trial (4 weeks each) of each patient's usual treatment versus 4 weeks of zolpidem 5 or 10 mg. Subjective SOL, average time awake at night, and number of awakenings (NOA) decreased, and TST increased using zolpidem immediate release (IR) at both 5 and 10 mg. [113] Alertness on awakening improved, memory complaints decreased, and napping also decreased with zolpidem use [121]. A systematic review comparing treatment with zolpidem to benzodiazepines in the elderly reported low-quality evidence that zolpidem may not be more effective than benzodiazepines at improving QUAL, TST, SOL, and ease of falling asleep [115]. An ACP meta-analysis concluded there is low-quality evidence in older adults that zolpidem IR improves SOL, with MD − 18.3 min (CI − 31.5 to − 5.4) [45].

Harms In adult patients, including the elderly, side effects of zolpidem include headache, somnolence, dizziness, nausea, diarrhea, myalgia, and CSBs, including sleepwalking, sleep driving, sleep shopping, sleep eating, and sleep sex [112, 122]. Dependency is a risk. In 2011, 3233 emergency room (ER) visits by the elderly in the US (~3% of all ER visits) were related to zolpidem abuse [123]. In Taiwan, zolpidem use in adults (mean age = 50.1 years) increased the hazard risk for developing infections, although the reasons are unclear [124]. High-dose zolpidem use (≥ 300 mg/year) in a mixed-age cohort was linked to 2.38 times site-specific cancer risk (oral, renal, esophageal, breast, liver, lung, and bladder) compared with non-zolpidem users [125]. Elderly subjects taking zolpidem are more likely to fall, with increased risks of traumatic brain injury and hip fracture [111, 126]. In South Korea, zolpidem use significantly increased the risk of fracture (adjusted OR 1.72; CI 1.37–2.16) among the elderly [127].

Next-day residual effects can occur depending on the timing of administration. Zolpidem use is associated with impaired performance by elderly subjects in driving simulation tests as well as actual road tests [128–131]. In contrast, zolpidem sublingual tablet (ZST) 3 mg or zaleplon (10, 20 mg) did not impair driving performance [131]. In Washington State in the US, zolpidem use in adults, including the elderly, was associated with hazard risk (HR) 2.20 (CI 1.64–2.95) of increased motor vehicle crash rate [132]. It is important to stress to all patients that they should allow at least 8.5–9 h after intake of rapidly released medications before driving, as this time period coincides with the lowest serum levels of zolpidem [112, 122, 133]. Adult and elderly women and those taking the extended-release formulations may be more susceptible to next-morning sedation—consider postponing activities requiring alertness to the afternoon [112, 122, 133].

In adults, CSBs—sleepwalking, sleep eating, sleep conversations, sleep driving, sleep sex—have been reported in case studies, but these are rare and are usually seen in patients who took large doses of zolpidem, had underlying psychiatric diseases, had medical diseases, or experienced drug–drug interactions [133, 134]. CSBs do not appear to be a problem in the elderly taking the appropriate doses.

MOTN insomnia is a common problem in the elderly. There are no published reports on ZST trials in the elderly, but when zolpidem IR 10 mg was used for MOTN insomnia in adults, driving performance 4 h after intake was significantly impaired. However, neither MOTN ZST 3.5 mg nor zaleplon 10 mg impaired driving performance in adults if taken more than 4 h before testing [129, 131]. MOTN insomnia improved in adult insomniacs using low-dose ZST (1.75 or 3.75 mg), with improved return to sleep and increased TST.

Comment Zolpidem is effective for sleep initiation, MOTN awakenings, and sleep maintenance problems, depending on the formulation chosen. Zolpidem IR should not be used for MOTN insomnia. Zolpidem should be used with caution in the elderly due to significant harms. Physicians should advise patients to observe the recommended TIB and to

avoid activities requiring vigilance, including driving, unless they feel alert. Intermittent dosing with the IR and ZST formulations has been explored in adult insomniacs. Perlis et al. used four treatment strategies for intermittent dosing. All four were better than placebo in maintaining treatment effect, although intermittent dosing exhibited poorer sleep continuity [135]. Roth et al. reported that ZST intermittent dosing on 62% of the nights during a 4-week study showed significant improvement in decreasing SOL and in improving morning alertness and sleep quality compared with placebo [136]. MOTN and intermittent dosing studies are needed in the elderly.

4.3.3 Zaleplon

Zaleplon is a pyrazolopyrimidine that targets $GABA_A$ receptor α1, β2, γ2, α2, and α3 subunits [137]. It is FDA-approved for short-term use for insomnia. It is used for sleep-onset insomnia or MOTN awakening, provided there are still at least 4 h TIB remaining. The dose in the elderly is 5 mg taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep.

Sleep Architecture Zaleplon had no effect on percentages of NREM sleep (Stages I, II, III) or REM sleep in the elderly at doses of 5 or 10 mg; however, REM latency increased by ~ 8 and ~ 13 min with zaleplon 5 and 10 mg, respectively [138].

Benefits Zaleplon improves sleep onset and may transiently increase sleep duration. Three 2-week RCTs in the elderly demonstrated that the 10-mg dose is more effective in reducing subjective SOL [116, 139] and PSG SOL [139] compared with the 5-mg dose [138–140]. Both doses significantly increased PSG TST, but did not improve quality of sleep [138]. The 10-mg dose reduced NOA and increased TST only during week 1 [139]. There was weak evidence for rebound insomnia on the first night after discontinuing the 10-mg dose.

Ancoli-Israel et al. examined long-term (6–12 months) nightly use of zaleplon 5 and 10 mg by elderly (mean age 73 years) insomniacs in a single-blind extension trial conducted in the US and Europe [140]. Insomnia participants and data suggested statistically significant improvement in LPS (decreased by 35 min compared with baseline, but still > 30 min), NOA (decreased by 0.62), and TST (increased by 56 min) [140]. We found no studies of MOTN dosing with zaleplon in the elderly. In a study of adults (mean age 42 years), zaleplon 10 mg improved SOL after MOTN awakening without residual sedation the next day documented on testing, including with the multiple sleep latency test (MSLT) [141].

Harms In the elderly, the most common side effects from short-term use were headache, pain, and dizziness [139]. Long-term use in the elderly was associated with headache (27%), infection (13%), backache (10%), bronchitis/pharyngitis (11%), rhinitis (9%), and dizziness (7%) [140]. Zaleplon carries a risk of recreational abuse because it can be insufflated and can produce a high. Hallucinations and anterograde amnesia are common consequences of abuse [142]. There are no reliable estimates of the incidence of dependence during treatment at the recommended doses in adults, including the elderly [143]. In adults, including the elderly, memory, psychomotor functions, and learning are not affected at therapeutic doses, and tolerance and rebound are less frequent than with the other Z-drugs [142]. Increased risk of hip fracture has also been associated with zaleplon use in older adults (> 50 years) [144].

Comment Zaleplon produces modest improvements in sleep initiation and sleep quality. These benefits appear to be sustained even with prolonged use. Because of its short half-life, it is not useful for sleep maintenance: however, it is less likely to impair daytime function, cognition, or driving than longer-acting Z-drugs. In the elderly, benefits versus harms should be weighed, and a shared decision approach is recommended. MOTN dosing and intermittent dosing studies in the elderly are needed.

4.4 Benzodiazepine $GABA_A$ Receptor Agonists

4.4.1 Triazolam

Triazolam is a short-acting benzodiazepine that is FDA-approved for short-term insomnia (7–10 days). It binds to the $GABA_A$ receptor complex at the junction of the α and γ subunits [145]. It is helpful for sleep initiation and sleep continuity.

Sleep Architecture Effects of triazolam on sleep architecture in the elderly vary depending on the dose used. At a dose of 0.25 mg taken for 3 nights, Stage II NREM sleep increased by 48 min and Stage III increased by 6 min, while REM sleep minutes did not change [146]. At a dose of 0.125 mg, percentages of NREM (Stage I, Stage II, Stage III) and REM sleep did not differ from placebo [147].

Benefits In two studies in the elderly with small sample sizes ($n = 13$ [146] and $n = 22$ [147]), triazolam significantly improved mean sleep onset and sleep maintenance PSG parameters, with decreased SOL, increased TST, increased SE, reduced NOA, and reduced total wake time in the first three quarters of the night [146, 147]. MSLT results showed increased alertness in both studies [146, 147], with mean MSLT SOL decreasing from 9.7 to 4.4 min [147]. A study

in elderly nursing home residents showed that triazolam 0.25 and 0.5 mg improved sleep, with reduced sSOL and longer sTST, but the NOA decreased only with the 0.5 mg dose [148].

We found no reports regarding MOTN use of triazolam in the elderly. In adults (mean age 41 years), triazolam doses 0.0625, 0.125, and 0.25 mg given after MOTN awakening significantly improved sleep onset and sleep continuity parameters and increased TST [149].

Harms Side effects of triazolam in older adults include drowsiness, headache, dizziness, ataxia, nervousness, nausea, rebound amnesia, anterograde amnesia, psychological dependence, and anxiety [53, 150]. Chronic use of triazolam in elderly Japanese patients significantly increased the risks for pneumonia by 40%, trauma by 30%, and pressure ulcer by almost 30% [151].

Comment Triazolam is effective for both sleep-onset and sleep-maintenance insomnia. Intermittent dosing may be a consideration. However, risks of falls, cognitive decline, and infections should be discussed with the patient. See also Sect. 4.4.3.

4.4.2 Temazepam

Temazepam is a short- to intermediate-acting benzodiazepine that is FDA-approved for short-term insomnia. It promotes sleep by binding to $GABA_A$ receptors [152–156]. Temazepam is used to treat sleep onset and sleep maintenance insomnia.

Sleep Architecture In the elderly, temazepam 7.5 mg for 7 nights reduced SWS duration but did not affect Stages I and II NREM sleep or REM sleep duration. Mean REM latency decreased significantly by ~31 min initially, but with continued use, REM latency did not differ from placebo [152].

Benefits In a small study ($n = 8$) of elderly insomniacs, temazepam 7.5 mg for 7 nights significantly decreased WASO by 35 min. LPS decreased by 10 min (not significant) and TST increased by 9%. Tolerance developed rapidly; changes in SOL, WASO, NOA, and percent of TST at the end of the week were not significant compared with baseline. Subjective estimates of sleep parameters were favorable throughout the entire week of use. No daytime impairments were reported at this dose [152]. An RCT with cross-over design using temazepam 15 mg, diphenhydramine 50 mg, and placebo each for 2 weeks in 20 elderly subjects showed that temazepam significantly improved subjective measures (SOL, sleep quality, and NOA) compared with placebo. Temazepam was also more effective than diphenhydramine in improving sleep onset and sleep quality [153].

Temazepam improved sSOL, reduced NOA, and improved daytime alertness in 75 elderly outpatients on temazepam 30 mg for 4 nights compared with placebo [154]. In a five-arm trial in 45 elderly insomniacs, Nakra et al. compared the effects of temazepam 15 and 30 mg, triazolam 0.125 and 0.25 mg, and placebo on cognitive and psychomotor performance the next day [155]. Performance improvements on verbal associative fluency, immediate auditory recall, and digit symbol subtest were seen with both temazepam 15 mg and triazolam 0.125 mg; there were no deficits seen on learning of 'difficult' word associations, visual motor tasks, or tests of fine motor speed. On temazepam 30 mg or triazolam 0.25 mg, mixed results occurred [155].

Harms Adverse effects of temazepam in adults, including the elderly, are drowsiness (9%), dizziness (5%), lethargy (5%), hangover effect (3%), euphoria, and dementia risk [156]. Rebound insomnia is variable, moderate, and can happen even with intermittent use in adults, including the elderly [157]. Side effects in the elderly include fatigue, dryness of the mouth, clumsiness or loss of balance or difficulty walking, headache, and anxiety [153].

Comment Temazepam 7.5–15 mg may help improve sleep onset and sleep maintenance, but tolerance develops rapidly. A higher dose (30 mg) worsens psychomotor performance. In the elderly, harms appear to outweigh benefits. If used at all, intermittent dosing should be considered, as tolerance rapidly develops. See also Sect. 4.4.3.

4.4.3 Adverse Effects and General Safety Concerns for Benzodiazepine Agents (Triazolam, Temazepam)

The Beers Criteria of the American Geriatric Society in 2015 listed benzodiazepines as 'potentially inappropriate medication' (PIM) "to be avoided in patients 65 years and older (independent of diagnosis or condition) due to increased risk of impaired cognition, delirium, falls, fractures, and motor vehicle accidents with benzodiazepine use" [43, 44, 78]. Nevertheless, benzodiazepines are still widely prescribed and, at times, inappropriately prescribed throughout the world [158–162].

Benzodiazepines are used around three times more frequently in older adults, and nearly a third of the elderly use them on a long-term basis [53]. Prolonged use is associated with ataxia, sedation, greater risk of falls, fractures, cognitive decline, and dependence [53]. Short-term and long-term cognitive dysfunction and association with dementia are reported in elderly benzodiazepine users [163–165]. Barker et al. performed two meta-analyses of 13 studies and reported that chronic benzodiazepine users (1–34 years of use, mean duration 8.9 years) had impaired cognitive function affecting 12 cognitive domains [163]. Testing performed

6 months after drug withdrawal showed poor performance across all cognitive domains except for sensory processing, suggesting either permanent deficits or that recovery may take longer than 6 months [163]. Another meta-analysis showed that risk for dementia was increased in 'ever users,' 'recent users,' and 'past users' [165]. Continued use increased the risk of dementia by 22% for every additional 20 defined daily doses per year [165]. For benzodiazepines, including triazolam and temazepam, there is a black box warning about combining benzodiazepines and opiates, with risk of sedation, respiratory depression, coma, and death.

Comment Benzodiazepines should not be routinely used to treat insomnia in the elderly.

4.5 Melatonin Receptor Agonists

4.5.1 Ramelteon

Ramelteon, an indenofuran derivative, is highly selective for melatonin MT1 and MT2 receptors. It is approved in the US and Japan but not Europe for the treatment of sleep-onset and sleep-maintenance insomnia at a dose of 8 mg taken 30 min before bedtime [166, 167].

Sleep Architecture Ramelteon has minor effects on sleep architecture in the elderly. NREM sleep Stages I, II, and III increased by 1.2, 1.9, and 3.1%, respectively. REM sleep percentage did not significantly change, but REM sleep latency was significantly reduced by 6.2 min [168].

Benefits RCTs in elderly subjects with chronic insomnia have reported mixed results. In one trial ($n = 829$), sSOL significantly decreased by ~ 13 min and sTST significantly increased [169]. Another trial ($n = 100$) showed significant decrease in LPS, but no significant changes occurred in sSOL, sTST, sQUAL, or PSG parameters (TST, SE) [168].

A meta-analysis of pooled data from 13 trials ($n = 5812$) of ramelteon treatment in adults and elderly subjects with insomnia reported that short-term use improved sSOL, sQUAL, LPS, TST, and SE. The improvements in sleep parameters sSOL and sQUAL were statistically significant but were clinically small (sSOL decreased by 4.53 min and sQUAL improved by 0.07). Changes in sTST and changes in PSG were not significant [170]. Low-quality evidence from the ACP meta-analysis showed that in older adults, SOL improved with MD − 10.1 (CI − 15.6 to − 4.6) minutes [44, 45].

For elderly patients with MOTN insomnia, ramelteon 8 mg may be safer than zolpidem 10 mg. Ramelteon users did not differ from placebo users in terms of balance, turning speed, stability, and memory, while performance by zolpidem users was impaired [171]. These differences are important in terms of risks of falls and injuries.

Ramelteon use is safe in adult patients (> 40 years) with mild, moderate, and severe COPD and in mild to moderate OSA patients, but data are lacking in the elderly [172–174].

Harms Side effects of ramelteon in adults including the elderly are somnolence, headache, upper respiratory tract infection, nasopharyngitis, urinary tract infection, dizziness, and nausea [170].

Comment Ramelteon is weakly beneficial for sleep onset difficulties. It may be safe in elderly patients with balance/mobility problems and those with COPD. It does not cause central nervous system depression and has minimal abuse potential and minimal withdrawal effects.

5 Other Commonly Used Hypnotic Agents not FDA-Approved for Insomnia

5.1 Melatonin

Melatonin, a hormone, initiates and maintains sleep via MT1 receptors and regulates circadian rhythm via MT2 receptors. In the US, melatonin is a dietary supplement that is available as 0.5–3 mg IR tablets, controlled release (CR) tablets, sublingual (SL) tablets, and liquid formulations. The European Food Safety Authority (EFSA) evaluated melatonin, reviewed meta-analyses, and concluded that melatonin IR 1 mg taken close to bedtime shortens SOL [175].

Wurtman recommended that, in older adults, physiologic doses of 0.3–0.5 mg of melatonin IR should be used [175]. Prolonged-release melatonin (PRM) (Circadin™, Neurim Pharmaceuticals) 2 mg is approved in Europe for treatment of primary insomnia, but is not FDA-approved. PRM is rapidly absorbed.

Sleep Architecture: Use of PRM 2 mg for 3 weeks did not alter sleep architecture or electroencephalogram (EEG) spectral activity in older adults (> 55 years) [176].

Benefits: Several meta-analyses in combined groups (including the elderly) showed exogenous melatonin slightly reduced SOL, improved SE, and slightly increased TST [177, 178]. In older insomniacs (> 55 years) on PRM 2 mg, PSG mean SOL significantly decreased by 6.9 min compared with placebo, but REM latency, TST, WASO, and NOA did not [176]. Daytime psychomotor performance [168] and morning alertness improved [179]. Wade and Downie reported significant improvement in sSOL at 3 weeks and 6 months in addition to significantly improved sleep quality, daytime functioning, morning alertness, QOL, and clinical

status on CGI of improvement (CGI-I) with PRM 2 mg in older adults (55–60 years) [180].

Harms Infrequent side effects in adults, including the elderly, are irritability, nervousness, restlessness, insomnia, abnormal dreams, and anxiety.

Comment Melatonin appears mildly helpful in sleep initiation in the elderly. The main issues are product quality and efficacy, which may vary depending on the preparation.

5.2 Trazodone

Trazodone, a triazolopyridine derivative, is a weak inhibitor of synaptosomal re-uptake of serotonin and an antagonist at 5-HT1A, 5-HT1C, 5-HT2, α1, and α2 receptors [181–183]. Although earlier studies of insomnia with depression utilized doses > 100 mg, more recent dosing in off-label prescribing in adults with secondary insomnia has varied from 25 to 100 mg [181, 182]. In the elderly, the lowest effective dose should be used.

Sleep Architecture In adults, including the elderly, trazodone increases SWS percentages in most studies but produces little effect or a very small decrease in REM sleep amount [183]; Roth et al. reported it reduced Stage I NREM minutes [184].

Benefits A small RCT in older adults ($n = 9$, aged 50–70 years) with insomnia reported that trazodone 150 mg nightly for 3 weeks significantly improved sleep quality during weeks 1 and 2, but not during week 3, and also improved PSG WASO. PSG SOL and TST did not improve [185]. Another small RCT in elderly Alzheimer patients ($n = 30$) on trazodone 50 mg for 2 weeks reported decreased WASO, reduced NOA, and increased nocturnal TST. However, neither trazodone nor placebo affected cognitive performance [186]. An observational study in 267 patients (mean age 61 years) with advanced cancer and secondary insomnia with or without nightmares reported improvement in sleep and nightmares using trazodone starting at either 12.5 or 25 mg up to 50 mg/night [187]. Another observational study in 549 individuals with depression and secondary insomnia (all age groups) using trazodone CR 50–300 mg for 6 weeks reported insomnia as the most improved symptom [188].

Harms In adults, including the elderly, dizziness and orthostatic hypotension may increase the risk for falls and injuries. Other adverse effects that may worsen QOL and functional ability in the elderly are psychomotor/cognitive dysfunction and memory impairment. Additionally, cardiac arrhythmias or priapism may occur [53, 181–183].

Comment Trazodone produces transient improvement in sleep quality and sleep continuity in insomnia patients, but carries significant risks. Trazodone may be useful in elderly patients with secondary insomnia associated with depression, Alzheimer's disease, or cancer, with or without nightmares.

5.3 Tiagabine

Tiagabine is an anticonvulsant that is used off-label to treat insomnia with sleep continuity problems. It inhibits GABA transporter GAT-1 [189–191].

Sleep Architecture In older adults and the elderly, tiagabine at 4 and 8 mg increases slow-wave sleep but has no effects on Stage I and Stage II NREM sleep. Tiagabine 8 mg slightly reduces REM sleep, but 4 mg has no effect [189, 190].

Benefits Two RCTs studied the dose–response effects of tiagabine 2, 4, and 8 mg on sleep in the elderly [189, 190]. The 2-mg dose results did not differ from placebo. Neither 4 mg nor 8 mg improved sleep quality despite prolongation of SWS. LPS, TST, and SE did not improve. WASO decreased but remained prolonged. Sleep continuity was impaired.

Harms In the elderly, adverse effect profile at doses ≤ 8 mg was similar to placebo [190]. At a dose of 8 mg, side effects in the elderly included dizziness, nausea, dry mouth, oral hypoesthesia, chest discomfort, sluggishness, confusional state, panic attack, oropharyngeal swelling, and hypotension [190].

Comments Tiagabine is not effective therapy for either sleep-onset or sleep-maintenance insomnia and should not be used in the elderly.

5.4 Diphenhydramine

Diphenhydramine is a first generation anti-histamine with weak anticholinergic properties that is marketed OTC as a sleep aid at 25–50 mg doses [191].

Sleep Architecture In adults including the elderly, diphenhydramine does not alter sleep architecture [192].

Benefits Despite the widespread OTC use of diphenhydramine for insomnia, efficacy studies have been lacking and results are mixed [153, 192].

A study in elderly [153] insomnia subjects compared nightly use of diphenhydramine 50 mg for 2 weeks with placebo. Subjective assessments of QUAL, SOL, and TST did

not differ from placebo. Subjective number of awakenings was significantly reduced but by a very small amount (0.3).

Harms Side effects in adults and elderly include fatigue, drowsiness, dry mouth or throat, constipation, clumsiness/loss of balance, memory loss, cognitive dysfunction, urinary tract symptoms, and pain in the muscles or back [48, 153, 193]. The American Geriatric Society's Beers panel strongly recommended avoiding use of diphenhydramine in older adults due to high anticholinergic effects and toxicity [193].

Comments Though diphenhydramine has a modest hypnotic effect in adults [192], data in the elderly are limited and do not support its efficacy for treating insomnia. In addition, significant side effects should preclude its use in the elderly.

5.5 Tryptophan

Tryptophan, an amino acid precursor for serotonin and melatonin, is marketed in the US as a dietary supplement to support mood, relaxation, and restful sleep [194]. L-tryptophan is available as 500- and 1000-mg tablets.

Sleep Architecture: L-tryptophan 3 g did not affect sleep architecture [195, 196]. Doses exceeding 5 g increased SWS and decreased REM sleep [197].

Benefits Almost all studies are in younger adults [195, 198–200]. Less than 1 g yielded either no effect or negative effects on sleep [195, 198, 200]. At higher doses in young adults, tryptophan had a delayed effect in reducing SOL, minimally reduced WASO, and minimally improved sleep quality [200, 201]. These changes were not deemed by AASM's review to be clinically significant [18]. Data are not available for treatment of insomnia in the elderly.

Harms Side effects in adults include drowsiness, nausea, vomiting, fatigue, clumsiness, and mental slowness [202]. In the 1980s, contamination of the dietary supplement L-tryptophan was associated with eosinophilia myalgia syndrome (EMS), and it was temporarily banned. Even post-epidemic, sporadic cases of EMS have occurred [203, 204].

Comments In adults, tryptophan decreased SOL with doses > 1 g, but benefits can be delayed for several days. Data in the elderly are not available.

5.6 Valerian

Valerian, the 11th best-selling herb in the US in 2016 with sales of US$21,642,672 [205], is marketed either as a single herb or in combination with other herbs as treatment for insomnia and anxiety. It modulates $GABA_A$ receptors in animal models. Aqueous or ethanol extracts of *Valeriana officinalis* are used in Western medicinal valerian, and the usual therapeutic dose is 600 mg daily [206]. Valerian must be used for 2–3 weeks before hypnotic effects are seen [206].

Three systematic reviews of trials of valerian in adults, including the elderly, agreed that valerian is a relatively safe herb for insomnia, though conclusions in these reviews differed regarding efficacy [207–209]. A systematic review by Bent et al. of 16 trials of valerian (total $n = 1093$, dose range 225–1215 mg) concluded that valerian had a statistically significant effect of improved sleep quality, with relative risk of 1.8 (CI 1.2–2.9) [207]. However, Taibi et al. systematically reviewed 37 studies of valerian, some including the elderly, and reported that most studies found no significant differences between valerian and placebo and that the evidence did not support its clinical efficacy as a sleep aide [208]. Fernandez-San Martin et al. analyzed 18 RCTs and concluded that even though valerian use is associated with subjective improvement of insomnia, its effectiveness has not been demonstrated by quantitative or objective measurements [209].

Harms Although valerian is a generally safe herb with rare adverse events, the AASM's review [18] noted that there are limited data on harms in adults, including the elderly.

Comments Valerian use in the elderly may result in subjective improvement of sleep quality, but the drug needs a trial of at least 4–6 weeks. Benefits are equivocal, but the drug is relatively safe.

6 New Drugs

Three DORAs have undergone phase II testing. Almorexant (Actelion Pharmaceuticals Ltd, Switzerland) is a selective, competitive DORA. Phase II trials in adults [210] and in the elderly [211] showed almorexant improved sleep maintenance and sleep duration parameters more than sleep onset. In the elderly, oral almorexant showed significant, dose-related improvement in mean WASO by − 46.5, − 31.4, − 19.2, and − 10.4 min for doses 200, 100, 50, and 25 mg, respectively, compared with placebo. Mean TST showed significant increase, which was dose-related (range 55.1–14.3 min). Mean LPS significantly decreased compared with placebo at the 200-mg dose, but the decrease was slight (10.2 min) [211].

Lemborexant (Eisai 2006), another DORA, underwent a double-blind, placebo-controlled (DBPC), Bayesian, adaptive, parallel-group trial in 291 adults and elderly adults (mean age 49 years) who were randomized to lemborexant or placebo for a combined efficacy and safety trial. At doses ≥ 5 mg, SE and LPS as well as sSE and sSOL

significantly improved. WASO (PSG and subjective) improved at doses > 1 mg. Mild to moderate somnolence was dose-related [212]. A phase III placebo-controlled trial (NCT02783729) of lemborexant comparing lemborexant 5 and 10 mg with zolpidem ER 6.25 mg in adults aged > 55 years is ongoing.

Filorexant (Merck & Co, MK6096), a DORA with a short $t_{½}$ of 3–6 h, underwent a phase II DBPC, two 4-week period adaptive crossover PSG study in 324 adults (18–64 years) [NCT01554176] [213]. All filorexant doses (2.5, 5, 10, 20 mg) improved sleep efficiency and reduced WASO on night 1 and at the end of week 4. Doses 10 and 20 mg improved LPS compared with placebo. Somnolence was the most common ADE. Three episodes of sleep-onset paralysis occurred in one patient. There was no evidence of withdrawal effect.

A novel formulation of zaleplon (zaleplon delayed SR SK-1041, Somnus Therapeutics) underwent a phase 2, DBPC, double-dummy, crossover study (NCT00878553) at doses of 10, 15, and 20 mg in adults with primary insomnia (mean age 47.5 years); the trial has completed, but data have not been published. At doses of 10, 15, and 20 mg, mean WASO slightly decreased by 8.6, 9.98, and 9.153 min, respectively [214].

Piromelatine (Neurin Pharmaceuticals, NEU-P11) is a multimodal drug that acts primarily as an agonist of MT1/MT2/MT3 melatonin receptors and serotonin 5-HT1A and 5-HT1D receptors, but is reportedly also a low-affinity antagonist of 5-HT2B, P2X3, and TRPV1 receptors. It underwent a phase II trial in 120 adults 18 years and older (NCT01489969). At doses of 20 and 50 mg for 4 weeks, it significantly improved PSG WASO. At 50 mg, SE, TST, and total time awake improved, together with sQUAL and sTST. Piromelatine enhanced NREM sleep EEG delta power and significantly reduced beta activity, suggesting decreased arousal. These results suggest efficacy in sleep maintenance. The drug is being tested mainly as a treatment of Alzheimer disease [215].

Three companies withdrew their products after phase II testing. Arena Pharmaceutical's APD-125, a selective 5-HT_{2A} receptor inverse agonist, was being tested for sleep maintenance insomnia (NCT00452179) and (NCT00664664) [216]. APD-125 is non-hypnotic and non-sedating so that even at peak drug levels, psychomotor impairment and somnolence do not occur [216]. A phase II RCT in 173 adults showed that APD-125 increased SWS and decreased both WASO and NOA [216]. Phase IIb studies did not meet primary or secondary endpoints and, in 2008, Arena Pharmaceuticals withdrew the drug [217]. Sanofi-Aventis completed phase III trials for its drug, eplivanserin (SR46349), a selective serotonin 5-HT2A receptor agonist that increases SWS and was intended to treat sleep maintenance insomnia [NCT00805350] [218]. The company withdrew its application for FDA approval in 2009 after receiving an FDA letter questioning its benefit/risk ratio [219]. Eli Lilly's LY2624803 is an H1 receptor antagonist that was undergoing phase II trials [NCT00784875] when the company withdrew it in 2011 [220].

7 Combination and Other Therapies

Combination therapy involves using a hypnotic medication (usually for 6–8 weeks) while starting CBT-I, continuing with CBT-I while tapering off the medication, and using medications only as needed. Starting with combined therapy appears more efficacious than starting with medication only, followed by combined therapy, or using behavioral therapy alone [221].

Other insomnia treatments in adults, including the elderly, have utilized off-label use of drugs/supplements such as other antidepressants, antipsychotics, gabapentin, pramipexole [18, 43–45, 53], and tasimelteon [222]. Complementary and alternative approaches are also used to treat chronic insomnia, including acupuncture, meditative movement, exercise training, and herbal medicine (valerian, chamomile, kava, wuling) [223–227].

8 Specialty Society Recommendations for Pharmacologic Treatment of Insomnia in Adults, Including the Elderly

The AASM issued the following recommendations (considered to be 'weak') to clinicians regarding the pharmacologic treatment of insomnia in adults: consider using (1) either suvorexant or doxepin for sleep maintenance insomnia (vs no treatment), (2) eszopiclone, zolpidem ER, or temazepam for sleep onset and sleep maintenance insomnia (vs no treatment), and (3) zaleplon, triazolam, ramelteon, or zolpidem IR for sleep-onset insomnia (vs no treatment). Consider not using trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, valerian for sleep-onset or sleep-maintenance insomnia (vs no treatment) [18].

AASM's review encompassed drugs and other hypnotic agents that are described in Tables 1 and 2 [18, 228–243]. A limitation to AASM's recommendations with regards to the elderly is that many of the studies cited in the AASM meta-analyses [7] were in non-elderly subjects. The ACP guidelines recommended a shared-decision approach by clinicians and patients in discussing benefits, harms, and costs of short-term use of medications to decide on whether pharmacological treatment should be added in adults with chronic insomnia in whom CBT-I alone was unsuccessful [44, 45]. The BAP recommends that when a hypnotic is indicated in adults > 55 years, prolonged release melatonin

should be tried first; if a $GABA_A$ hypnotic is used, then a drug with a shorter half-life should be considered to minimize hangover [46].

9 General Recommendations for Management of Insomnia in the Elderly

Insomnia is a frustrating and health-impairing problem that requires a strong partnership between the provider and the patient. Primary care providers should screen for insomnia. We cannot treat what we do not know. Two screening questions can be asked: (a) Are you satisfied with your sleep timing, ability to fall asleep, ability to stay asleep, the duration and quality of your sleep? (b) Are you satisfied with how your sleep affects your daytime alertness, energy, attention or memory, thinking processes, fatigue, or other bodily functions? If the answer is no to either one, then further exploration is needed.

At the minimum, the patient should complete the following: a general medical/psychiatric questionnaire to identify co-morbid medical and psychiatric disorders; a list of current medications, including OTC preparations; a list of recently discontinued medications; allergies and adverse reactions; and the Epworth Sleepiness Scale to identify sleepy patients. A 2-week sleep diary clarifies the patient's sleep patterns. Our patients complete a sleep medicine questionnaire to identify co-morbid sleep disorders, in addition to an Insomnia Sleep Questionnaire Packet that incorporates the ISI, the Glasgow Content of Thoughts (Glasgow Scale), and the Inventory of Depressive Symptomatology (Self-Report). A Fatigue Scale Score is optional, depending on the presentation.

We review the history with the patient, clarify and discuss the patient's major concerns, and conduct a pertinent physical and mental status examination. Questions we focus on are: What are your most common sleep complaints—problems with timing of sleep (bedtime and wake-up times), difficulty falling asleep, difficulty staying asleep, frequent awakenings at night, prolonged wakefulness after falling asleep, awakening earlier than you want to, quality of your sleep, or lack of refreshment on awakening? Do your symptoms occur more than three times/week and how long have you had them (<3 months for short-term/acute insomnia, ≥ 3 months for chronic insomnia)? If acute insomnia, we try to identify any triggering factors (financial problems, health worries, relationship issues, death of a loved one, situational anxiety, hospitalization, nursing home confinement, prolonged bed rest, non-diuretic nocturia, lack of exercise, environmental noise or light).

We evaluate for co-morbid sleep disorders—any snoring or pauses in breathing, any restless leg symptoms or periodic leg movements of sleep, any abnormal behaviors during sleep, any abnormalities in sleep–wake cycles that could suggest a circadian rhythm disorder. Advanced sleep phase disorder is common in the elderly, and they may complain bitterly about early morning awakening at 3–4 AM with inability to return to sleep, but bedtimes are also early at 8–9 PM. Some elderly adults have delayed sleep phase syndrome with late bedtimes and awakening late in the morning or early afternoon. Other elderly adults have a biphasic sleep pattern with short night sleep and a prolonged nap during the day, while still others have a completely irregular sleep pattern. This is where the sleep diary is very helpful in understanding the patient's sleep patterns.

Co-morbid medical and neurological problems can impact sleep, such as respiratory disease, cardiac disease, pain syndromes, arthritis, gastro-esophageal reflux disease (GERD), prostate disease, endocrine disease, Alzheimer's disease, or delirium. Psychiatric disorders are common and should not be forgotten. We inquire about major depressive disorders, anxiety disorders, or post-traumatic stress disorder (PTSD). Polypharmacy is common in the elderly, and there are many drugs that can contribute to insomnia. It is helpful to review current medications and any recently discontinued medications that may contribute to insomnia. Table 3 lists drugs that can produce insomnia [244, 245]. The possibility of substance abuse and alcoholism should also be explored, as patients may not necessarily list these in their history. Prior treatments for insomnia and perceived results/problems with therapy should also be reviewed with the patient.

Regardless of whether the insomnia is transient/acute or chronic, whether it is primary or secondary, focus on the patient's perspective and inquire about disabling symptoms and effects on daytime function and QOL. Prioritize treatment goals, and formulate and implement strategies that are jointly acceptable to the patient and the provider. The primary goals are usually to improve the quantity and quality of sleep and to improve insomnia-related daytime impairments [8].

Acute insomnia is usually self-limited and improves when the trigger(s) are addressed or resolved. Discussions with the patient are focused on interventions to resolve or mitigate these triggers. We also discuss at least one behavioral intervention—stimulus control therapy, relaxation therapy, sleep restriction, or CBT-I, and we educate the patient on good sleep hygiene measures. If the insomnia symptoms are severe or impactful on daytime functioning, a short course of hypnotic therapy (7–10 days) that targets the predominant insomnia symptom may be warranted. Table 4 is an insomnia handout for the patient.

If the insomnia is chronic and is primary insomnia, we strongly recommend a course of CBT-I, either in a group setting or through individual therapy sessions. If there are access issues to in-person CBT-I, then on-line CBT-I can

Table 3 Insomnia contributing medications and substances [243–245]

Category	Examples
α Blockers	Alfuzosin, doxazosin, prazosin, silodosin, terazosin, tamsulosin
β Blockers	Atenolol, carvedilol, metoprolol, propranolol, sotalol, timolol
Antidepressants	Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram), monoamine oxidase inhibitors (phenelzine, trancylpromine, selegeline), venlafaxine, duloxetine
Cholinesterase inhibitors	Donezepil, galantamine, rivastagmine, tacrine
Corticosteroids	Prednisone, methylprednisolone, triamcinolone
Angiotensin II receptor blockers	Dandesartan, irbesartan, losartan, telmisartan, valsartan
Angiotensin converting enzyme inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Antihistamines, second-generation	Azelastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine
Dietary supplements	Glucosamine/chondroitin
Lipid-lowering agents	Cerivastatin, fluvastatin, lovastatin, simvastatin
Calcium channel blockers	Diltiazem, verapamil, felodipine, nisoldipine
Cardiovascular drugs	Amiodarone, dofetilide, profenone
Decongestants	Pseudoephedrine, phenylephrine, phenylpropanolamine
Narcotic analgesics	Oxycodone, codeine, propoxyphene
Antibiotics	Levofloxacin, ciprofloxacin
Antiviral agents	Abacavir, amantadine, efavirenz
Antifungal agents	Amphotericin B
Anticonvulsants	Ethosuximide, ethotoin, felbamate, lamotrigine, mephobarbital
Dopamine agonist	L-dopa, pergolide
Bronchodilators	Albuterol, ipratropium, metaproterenol, salmeterol, theophylline
Antineoplastics	Flutamide, procarbazine
Stimulants	Caffeine, methylphenidate, amphetamine derivatives, ephedrine, cocaine, armodafinil
Nonsteroidals	Diclofenac, mefenamic acid, nabumetone

be considered. A review of these options from various providers, including costs, is available at http://www.sleepreviewmag.com/2014/12/online-options-insomnia-therapy/. If the chronic insomnia patient has severe symptoms impairing function or QOL, adjunctive short-term hypnotic therapy is added. Based on the timing of the insomnia symptoms (sleep onset, sleep maintenance, combined sleep-onset and sleep maintenance, or MOTN awakening), a hypnotic is chosen (see Table 1).

If sleep onset is problematic, then either ramelteon or a Z-drug, such as zaleplon or zolpidem fast-acting formulations (IR, SL, or spray), is prescribed. If sleep maintenance problems predominate, then either suvorexant or low-dose doxepin can be considered. If both sleep-onset and sleep-maintenance issues are present, consider eszopiclone or zolpidem ER. For MOTN insomnia, consider zaleplon or zolpidem ZST. Use benzodiazepines only as second-line therapy; shorter-acting drugs that target insomnia symptoms are preferred (see Table 1).

Start with a nightly hypnotic for 1 week, then decrease by one dose every week until it is discontinued, but allow intermittent use as needed, while simultaneously pursuing CBT-I. If the patient has secondary insomnia, in addition to treating insomnia, it is important to effectively address the underlying sleep, medical, or psychiatric disorder(s) in collaboration with the other providers who are managing these issues. Patients with co-morbid COPD and insomnia may benefit from use of Z-drugs (eszopiclone, zolpidem, and zaleplon) or ramelteon. Polysomnography may be a consideration in these patients to identify any co-morbid sleep disorders.

The patient is instructed to contact us if there is no improvement after 7–10 days of therapy, and the patient is reassessed. If there is improvement, then a routine follow-up visit is scheduled after 3–4 weeks of starting hypnotic drugs. If this is not feasible due to patient or scheduling constraints, the patient is instructed to contact us either electronically or by phone to provide an interim report and to schedule a face-to-face visit. Dose adjustments may be considered depending on response to therapy. At the follow-up visit, if the patient is doing well, then dose tapering may be considered with instructions for intermittent use and to continue with behavioral therapy.

Table 4 CBT-I and sleep hygiene handout for patients

The goal in cognitive behavioral therapy for insomnia (CBT-I) is to reduce anxiety and build up your sleep drive. Many insomniacs tend to have a higher level of alertness (some call it hyper-arousal) than non-insomniacs, who don't have to worry about falling asleep, awakening during the night and not being able to return to sleep, or if they should take a sleeping pill. CBT-I involves cognitive therapy to correct faulty beliefs, thoughts, and associations that perpetuate insomnia, plus behavioral treatments (stimulus control, sleep restriction therapy) with or without relaxation therapy. CBT-I takes time to have its desired effect of helping you sleep solidly through the night. Be patient with CBT-I—it can really help. Studies have shown that up to 90% of people who use CBT-I are successful in achieving the kind of sleep they desire

General Pointers:

1. Caffeine has a half-life of 8 h. Try to limit your caffeine intake and discontinue use after noon
2. Exercise daily early in the day and avoid strenuous exercise within 3 h of bedtime as it can delay sleep onset
3. Nicotine (cigarettes or patches) is a stimulant and may make insomnia worse. Discontinue use 4–6 h before bedtime
4. Avoid moderate to heavy use of alcohol in the late evening as it tends to fragment sleep and you may have multiple awakenings at night
5. Create a stress list and allow 'worry time'—to reduce thought racing that can occur at night, allow 10-30 min per day to reflect. Do this earlier in the evening, not close to bedtime. This is your time to focus on any stressors in your life (past, present, future), any chores, or any topic at all. Write it down and then tear up your list
6. Engage in a buffer zone. This is a transition period between your daytime activities and your bedtime. Ease into a state of mind that allows you to get ready for sleep. Allow 60 min for this relaxation phase. Do three different activities that you enjoy such as reading, listening to music etc. that do not involve your eyes being exposed to light. Do not pay bills, cook, clean, work on alerting projects, or engage in arguments at this time. Keep the lights relatively dim
7. Avoid bright light exposure at night within an hour of bedtime as it can delay your sleep. Adjust your devices (cell phone, laptop, iPad, iPod) to night shift to dim the screen

Specific instructions for CBT-I:

1. Stimulus control
   A. Go to bed only when sleepy. Maintain a regular sleep–wake schedule. Avoid regular naps. If you are fatigued, you can nap in the early afternoon, but limit it to 30 min
   B. Use the bed only for sleep and sex. If you cannot fall asleep in what feels like 20 min (your estimate—do not look at a clock) get out of bed and engage in a relaxing activity that does not involve light stimuli to your eyes then return to bed—repeat this if necessary
2. Sleep restriction (only if specifically instructed by your sleep doctor)
   A. Maintain a nightly sleep log for 2 weeks and calculate your total sleep time each night. Determine the average total sleep time for this baseline 2-week period (i.e., add your daily total sleep time [TST] over 14 days/14 = average TST)
   B. Set your desired wake-up time and bedtime to approximate your mean TST and maintain this schedule for a week including on weekend nights. If you are not sleepy at your appointed bedtime, engage in relaxing activities and go to bed when you are sleepy, but keep your appointed wake-up time. You must be upright, vertical, and out of bed at your wake time. Your goal is to achieve sleep efficiency (SE) of 85–89% while matching time in bed (TIB) (not < 5 h) to your TST
   C. Continue your weekly log. Make weekly adjustments of your bedtime (keep the wake-up time constant) depending on your SE the week before. TIB can be increased by 15–20 min if SE is ≥ 90%; reduce TIB by 15–20 min if SE is < 85%. Maintain the schedule if SE is 85–89%
   D. Repeat TIB adjustments every 7 days
   E. Do not engage in hazardous activities, such as driving, if you are sleepy
3. Relaxation training (optional)
   A. Progressive muscle relaxation is based on sequential tensing and relaxing of a group of muscles until the entire body is relaxed. The sequence is to breathe, hold your breath, and tense a group of muscles for 4–10 s, then exhale, and quickly relax the group of muscles. Relax for 10–20 s before moving on to the next muscle group. Clench both fists, tighten biceps and forearms. Relax. Roll your head around your neck clockwise in a circle and then reverse direction. Relax. Wrinkle your forehead, squint your eyes, open your mouth, hunch your shoulders. Relax. Arch your shoulders backwards, take a deep breath, and hold. Relax. Take a deep breath and exhale and press out the stomach. Relax. Straighten your legs, point your toes towards your face, and tighten the shins. Relax. Straighten your legs, point your toes downward and tighten your calves, and buttocks. Relax. You can repeat this sequence for up to 45 min. Follow these instructions and give yourself 1–2 weeks to master the technique, using two 15-min practice sessions/day. Once mastered, you can go to one 15-min session daily
   B. Breathing exercises: Sitting upright with your eyes closed, forearms resting on your thigh, palms up, rest the tip of your tongue on the roof of your mouth right behind your front teeth. Maintain that position, close your mouth, and inhale through your nose for four counts, hold that breath for seven counts, and then exhale through your mouth around your tongue for eight counts. Repeat this pattern to complete four full breaths

At Stanford, as is common in other tertiary care centers, we see patients who have been on chronic daily hypnotic therapy with benzodiazepines or Z-drugs as their sole treatment, then present to us because of relapse in symptoms. Tolerance to the drug, lifestyle changes, illnesses, new co-morbidities, or drug–drug interactions may precipitate relapse. Dose escalation or switching to a different category of drug has usually already been tried by the primary providers with little improvement, but maladaptive behaviors and faulty cognitions may not have been addressed. Drug tapering and a drug holiday may be considered in addition to instituting or reinforcing CBT-I.

Patients seem more amenable to a slow taper, and we suggest withdrawing by one hypnotic dose each week until they are off medications. Patients who are on chronic benzodiazepine therapy during the day and at night may have an anxiety disorder that should be addressed. Different tapering schedules for benzodiazepines have been used—25%

decrease in initial dose each week until the lowest dose is reached or decrease in total dose by 25% on week 1, then 25% decrease on week 2, then 10% reduction each week until discontinuation. Even when patients assure us they are following CBT principles and good sleep hygiene practices they have learned in the past, detailed questioning often reveals lapses in compliance, and additional sessions of CBT-I may be needed for reinforcement. The key is to problem solve high-risk situations with the patient, immediately address signs/symptoms, educate the patient regarding faulty cognitions and expectations about sleep and treatment of insomnia, persuade the patient to engage in behavioral measures, and develop strategies for preventing relapse.

10 Conclusions

Treating insomnia in the elderly requires multi-pronged approaches. Behavioral/psychological therapies remain primary therapies. Current research is devoted primarily to solving access issues through innovative channels of distribution (web-based, telephone, self-help). Short-term efficacy has been shown, but we still need studies to demonstrate long-term adherence to CBT-I. Longitudinal studies can also look at barriers to adherence. Long-term efficacy outcomes, including effects on cognitive function, mood, myocardial infarction rates, vascular events, and mortality risks, would be helpful as well. Research is also needed to compare the long-term effects of CBT-I with optimized long-term hypnotic therapy (intermittent). For insomnia with co-morbid disorders in the elderly, comparative efficacy trials of drugs in patients with heart disease, depression, or arthritis are needed with sleep outcome parameters. Does improvement in sleep parameters affect disease outcomes in depression (including suicide risk), coronary artery disease, or arthritis? Fatigue is a common daytime impairment in the elderly with chronic insomnia as well as a common symptom in patients with medical co-morbidities. What sleep parameters best correlate with fatigue symptoms and which types of hypnotic agents improve fatigue better in these patients? Cognitive outcomes are of great importance to the elderly. It has been suggested that insomnia patients have more subtle cognitive deficits that may be sufficiently compensated for with increased cognitive effort, which may then lead to increased fatigue and self-perception of poor performance [246]. Many of the studies of efficacy of hypnotic drugs use standardized tests that are not designed to detect subtle neuropsychological deficits. Future studies in the elderly should consider incorporating neurocognitive tests that evaluate the deficits seen with insomnia patients. It would also be interesting to see longitudinal studies comparing effects of CBT-I versus chronic intermittent hypnotic therapy on brain neuroplasticity as documented by functional magnetic resonance imaging and neuropsychological testing.

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