Insomnia treatment for the medically ill hospitalized patient

Jennifer Kelly, Pharm.D., M.SPharm., M.B.A., BCPS[1]

[1]Clinical Pharmacy Specialist, Residential Rehabilitation Treatment Programs (RRTPs), (A-PRRTP, CWT/TR, DRRTP, G-PRRTP, STARR Programs), Albuquerque, NM

ABSTRACT

Insomnia is a common sleep disorder which has been shown to adversely affect outcomes in hospitalized patients. This article reviews the available classes of medications that may be considered in the treatment of insomnia in the hospital setting.

KEYWORDS

insomnia, pharmacologic treatment, $GABA_A$ receptor agonist, melatonin agonist, hospitalized patient

BACKGROUND/INTRODUCTION

Insomnia is a medical disorder which can be described by an individual as difficulty falling or staying asleep, early morning awakenings, and/or having non-restorative sleep, which interferes with daytime activities.[1-4] Insomnia affects an estimated 10 to 20 percent of the population; of these individuals, approximately 50 percent will develop a chronic insomnia disorder.[2] The incidence of chronic insomnia among individuals varies greatly from the general population to patients seen in primary care outpatient settings. Estimates range from approximately 5 to 30 percent up to greater than 50 percent of patients, with more women being affected by the disorder when compared to men.[5-7] Also affecting older individuals, "chronic insomnia has been shown to independently increase the risk of cognitive decline in adults."[8]

Not surprisingly, insomnia contributes to increases in health care utilization, health care costs, is associated with losses in productivity, and negatively affects work performance.[4-6,8-10] Impairing daytime function, it may be in part attributable to falls, motor vehicle accidents, and an individual's perception of reduced quality of life.[6-9,11,12] Insomnia can affect social and family relationships, and may closely be tied to psychiatric disorders, including depression.[5,6,8,9]

The sequelae of untreated insomnia may negatively impact patient outcomes and ultimately impede a speedy recovery and positive outcome for the patient – in both the outpatient setting and especially during an inpatient hospitalization.[1,5,6,8,9,11,13] Insomnia, whether acute or chronic, can be both upsetting to patients and challenging for clinicians to adequately treat in the medically ill patient.[1,5,13,14] In the acute hospital setting, insomnia has been shown to adversely affect the individual's health, increase morbidity and mortality, and contribute to psychiatric and/or cardiovascular health outcomes.[1,5,11,13-15] Unfortunately, this disorder may be due to or a result from many factors: a symptom of a patient's acute condition, a chronic disorder, medications, or due to the inherent nature of the hospital environment.[1,5,13]

The hospital setting itself is not an environment which is conducive for sleep. Numerous barriers exist and may impede one's ability to get a restful night's sleep while being cared for in a hospital or medical intensive care unit. In particular, noise levels and lighting are a concern in the inpatient setting. Equipment and monitors designed to assess patients' clinical status may make it difficult to fall asleep with their beeping noises and alerts. Lighting in the inpatient area or lights from the medical equipment may prove to be a challenge and interfere with the body's natural ability to sleep well.[13,16] The temperature of the room may be too hot or too cold for the patient to get comfortable.[13,16] In addition to these factors, other patients, hospital staff and visitors may contribute to the noise level.[13] Trammer and colleagues found that, overall, surgical and intensive-care unit patients tend to receive more procedures and/or nursing care during the night. In addition, the use of sedative hypnotics in medical patients at night increased relative to surgical patients. Post-operatively, however, this higher level of care was shown to decrease as the length of stay increased. Compared to surgical patients, medical patients typically receive less procedural care during the night such as venipuncture, vital sign monitoring, or dressing changes.[17]

In consideration of possible causes of and potential treatments for insomnia in acutely ill patients, there are many factors to consider when choosing pharmacologic therapies. In selecting a particular agent, the clinician should inquire of the individual's past medical history, social habits, diet, and medications as these may prove

helpful in determining which treatments may be most beneficial for the patient or may be contributing to an insomnia disorder.[1,6]

Upon admission to the hospital, the patient and/or caregiver should be asked about medication and supplement use at home. Many common herbal supplements that may be associated with difficulty sleeping are ephedra, ginseng, and St. John's wort.[1] Medications to treat a chronic or acute illness can cause insomnia, or if discontinued abruptly, can contribute to insomnia.[1] Select agents that may contribute to or worsen insomnia are listed in Figure 1.[1,18,19] The use of herbal supplements to promote sleep is generally restricted in the hospital setting, and is not FDA-approved due to safety and potential adverse reactions or drug-interactions associated with these agents.[1]

In the hospital setting, given numerous factors which may be linked to insomnia, a multifactorial approach to treatment should be recommended. A clinician should consider the patient's acute and chronic condition(s), environment of care, and potential adjustments that can be made to the environment – in addition to medications – to assist with successful treatment.[6,13]

Figure 1. Select agents that may contribute to insomnia[1,18,19]

Alcohol	Monoamine oxidase inhibitors (MAOIs)
α_2 agonists	Phenelzine
Clonidine	Tranylcypromine
Methyldopa	Nicotine
Anticholinergics	Quinidine
Antiparkinsonian agents	SSRIs
β-adrenergic agonists	Citalopram
β-adrenergic antagonists	Fluoxetine
Propranolol	Fluvoxamine
Timolol	Paroxetine
Contraceptives (oral)	Sertraline
Corticosteroids	SNRIs
Decongestants	Buproprion
Daunorubicin	Venlafaxine
Ephedra	Stimulants
Ginseng	Caffeine
Interferon-α	Cocaine
Leuprolide	Methylphenidate
Medroxyprogesterone	Theophylline
	St. John's wort

NON-PHARMACOLOGIC OPTIONS

In addition to medications, modifications of the hospital setting environment should be made to help make certain that the surroundings are conducive for sleep. Simple adjustments and interventions by the staff made at night to the environment may show benefit and promote sleep hygiene.[13,16] Although many treatments targeted to treat insomnia exist such as cognitive-behavioral therapy, progressive relaxation, sleep restriction, sleep hygiene, paradoxical intention, and complementary and alternative medicine strategies may be available to individuals in an outpatient setting, these will not be discussed in detail in this article.[6] It is notable, though, that non-pharmacologic therapies including relaxation or behavioral therapy have been found effective for inpatients during hospitalization and could be considered for individuals diagnosed with chronic insomnia upon discharge.[1]

Prior to consideration of pharmacologic treatments for treating short-term insomnia in the hospital inpatient setting, it is prudent for the clinician to also consider non-pharmacologic and sleep hygiene measures for adequate sleep (see Figure 2). Particularly in the hospital, modifications to the environment must be considered to see if these interventions can improve the patient's quality of sleep throughout the duration of stay in the inpatient setting.[1,5,13]

Figure 2: Non-pharmacologic interventions to assist with sleep[1,13]

- Closing doors leading into patient rooms if able
- Adherence to policy for visiting hours
- Modify appropriate machine alerts to vibrate at night
- Modify phone ringers in patients' rooms to "off" setting at night
- Dim inpatient room lights
- Offer patients use of an eye mask or ear plugs if available
- Encourage healthy sleep hygiene and daytime activity if possible
- Use of CPAP machine from home, if obstructive sleep apnea

PHARMACOLOGIC OPTIONS

In choosing a particular pharmacologic agent for short term treatment of insomnia, as always, patient-specific characteristics and safety should prompt the clinician if the benefit(s) of using a pharmacologic agent outweigh the potential risk(s). When choosing among pharmacologic agents, the pharmacokinetic/pharmacodynamic properties of a particular class and/or agent(s) should be considered: mechanism of action, duration, half-life, adverse effect profile, potential drug interactions, concomitant therapy, and the patient's clinical picture, past medical history and social habits.

When considering FDA-approved medications for the treatment of insomnia, the available classes of medications include: benzodiazepine gamma-amino butyric acid $(GABA)_A$ receptor agonists (BzRAs), non-benzodiazepine $GABA_A$ receptor agonists (non-BzRAs), melatonin (MT)-receptor agonists, and a tricyclic antidepressant. Despite these FDA-approved treatments available, many clinicians may also prescribe medications for insomnia which do not have an indication. To note, older agents such as the barbiturates and others including chloral hydrate and similar drugs (i.e., ethchlorvynol) should not be recommended due to the toxicity associated with their use.[1,5,13] Although many agents or classes such as the antipsychotics, antiepileptic or antidepressants may be used for "off-label" or unapproved uses for insomnia for special populations, this type of use will not be discussed in detail.[20,21]

In the hospitalized inpatient, the risk for potential adverse drug reactions of medications, including the BzRAs, may be increased due to factors such as acute illness, older age, polypharmacy, and drug-drug interactions.[13] An ideal agent would be one that could decrease the amount of time for an individual to fall asleep and increase the total time spent asleep, but at the same time be free of residual "hangover" side effects or sedation the following day. The agent should be effective and reduce the potential for tolerance, while at the same time improve the individual's functioning during daytime hours.

BZRAS

The BzRAs exert their effects by binding to the $GABA_A$ receptors in the central nervous system, thereby inhibiting excitation of neurons which leads to their desired effect on an individual's sleep.[13] These agents (Table 1), reduce sleep latency and increase the total amount of time spent asleep, but decrease deep, restorative sleep.[22-29] Unfortunately, this class of agents has the potential to cause day-time sedation, impair cognition, cause anterograde amnesia, dependence, motor incoordination, tolerance, and re-bound insomnia. Thus, in general, these agents are reserved for otherwise healthy, younger individuals whose anticipated length of stay will be short.[13]

BzRAs with a short-acting half-life are preferable to long-acting agents due to adverse reactions; however, a BzRA with a short duration may not adequately address insomnia symptoms.[13] Especially in the medically ill patient, long-acting BzRAs should not be used for insomnia due to potential for adverse effects such as delirium, decrease in cognition, and respiratory depression. In addition, their long half-lives (i.e., flurazepam and quazepam) can potentially increase the risk for drug-drug interactions.[1,13] Although, it should be noted that this class of hypnotic drugs are most commonly prescribed for sleep among hospitalized patients.[1,13,29]

BzRAs approved for the treatment of insomnia include estazolam (ProSom®), flurazepam (Dalmane®), quazepam (Doral®), temazepam (Restoril®), and triazolam (Halcion®). Other short-acting BzRAs , such as lorazepam (Ativan®) although not FDA-indicated, are commonly used because of their short half-life, rapid absorption, and anxiolytic properties, which may be helpful in patients who also present with anxiety.[5,13] If use of this agent is considered, a lower one-time dose such as 0.25 or 0.5 mg may be considered as appropriate.[13] BzRAs which are more slowly absorbed by the body and take longer to take effect are generally not used due to lack of efficacy in treating insomnia.[5] Alprazolam (Xanax®), another agent in the class is rapidly absorbed, thus fast-acting, but has a short half-life. This agent should not be used due to its addictive potential, withdrawal effects, and potential for rebound insomnia once discontinued.[13]

A clinician should consider limiting prescribing to one particular agent to cover a particular disorder due to the similar pharmacodynamic profiles of the BzRAs and additive effects. For example, choosing one agent vs. two may be more appropriate than treating a patient with temazepam for insomnia and lorazepam for anxiety.[13] In this case, the more appropriate agent between the two would be lorazepam. Temazepam should not be considered, as this would be inappropriate to treat anxiety throughout the daytime for the patient. Both patients and nursing staff should be educated regarding the proper use of these agents. The orders should include stop dates and indicate whether the medication should be used 'as needed' or as a 'one-time' medication dose.[1,13]

Limitations and adverse effects of the BzRAs may include sedation, next-day sedation, anterograde amnesia, impaired coordination, sleep walking and/or driving, or other behaviors while sleeping.[5] Troublesome effects following discontinuation of BzRAs include rebound insomnia, dependence potential and withdrawal, especially upon abrupt discontinuation.[5] Strategies to mitigate potential for adverse reactions upon discontinuation of the agent can be achieved by slow tapering of the medication dosage over a period of days to weeks.[5]

Although effective, the long-term use of BzRAs should be minimized, if possible, due to risks associated with this

Table 1. Benzodiazepines commonly used to treat insomnia[1,5,9,13,22-29]

BzRA	Usual Dose (mg)	Half-life (hr)	Duration Onset (hr)	Comment(s) FDA and Non-FDA Indication(s)
*Alprazolam (Xanax®)	Avoid use as sedative hypnotic	6 to 20	Short 0.6 to 1.4	Avoid abrupt discontinuation; consider lower doses in debilitated and geriatric patients Contraindications: acute narrow angle glaucoma, concurrent use with ketoconazole or itraconazole Approved for: anxiety, panic disorder with or without agoraphobia Off-label use: depression, EtOH withdrawal
*Clonazepam (Klonopin®)	0.5 to 3	20 to 40	Short 1 to 2.5	Contraindications: acute narrow angle glaucoma, liver disease (significant) Approved for: panic disorder, seizures Off-label use: insomnia, restless legs syndrome, social phobia
Estazolam (ProSom®)	1 to 2	10 to 24 (mean)	Intermediate 1.5 to 2	Decrease dose in debilitated patients Contraindications: pregnancy Brand-name product discontinued; available as generic product
Flurazepam (Dalmane®)	15 to 30	47 to 100	Long 1.5 to 4.5	Initial dose 15 mg in debilitated, liver disease, and geriatric patients Avoid in acutely ill due to long-half life, potential for drug-drug interactions, and adverse drug reactions Contraindications: pregnancy
Lorazepam (Ativan®)	1 to 4	10 to 20	Short 0.7 to 1	Lack of CYP drug-drug interactions: undergoes metabolism via conjugation Females also prescribed contraceptives may require an increased dose No dose adjustment in mild to moderate renal or liver dysfunction Contraindications: acute narrow angle glaucoma, intraarterial administration (inj), severe respiratory insufficiency if facility is without resuscitative equipment (inj), sleep apnea syndrome (inj); hypersensitivity to polyethylene glycol, propylene glycol or benzyl alcohol (inj) Approved for: anxiety, insomnia, status epilepticus Off-label use: chemo-induced n/v prophylaxis, EtOH withdrawal, insomnia, sedation, seizure
Quazepam (Doral®)	7.5 to 15	39	Long 2 to 3	Use caution with concomitant CNS depressant drugs Avoid in acutely ill due to long-half life, potential for drug-drug interactions, and adverse drug reactions Contraindications: pulmonary insufficiency, sleep apnea (suspected or established)
Temazepam (Restoril®)	7.5 to 30	3.5 to 18.4	Intermediate 1 to 2	Avoid abrupt discontinuation Consider lower doses in debilitated and geriatric patients Contraindications: pregnancy Off-label use: anxiety
Triazolam (Halcion®)	0.125 to 0.5	1.5 to 5.5	Short 1 to 2	Avoid abrupt discontinuation; consider lower doses in debilitated and geriatric patients Contraindications: concurrent use with HIV protease inhibitors, efavirenz, or elvitegravir/cobicistat; itraconazole, ketoconazole, or nefazodone; pregnancy

*Non-FDA approved indication for insomnia; CNS: central nervous system; EtOH: alcohol; Inj: injection formulation; N/V: nausea/vomiting

type of use in the elderly or patients considered high risk for delirium. Patients at higher risk for delirium include patients being treated for stroke, traumatic brain injury, or those with multiple new medications.[13] It has been shown that longer-acting agents are associated (in a dose-dependent fashion) with an increase in the risk of falls, hip fractures, motor vehicle accidents, and daytime sedation in this population – and should be avoided.[5,13] To note, the use of BzRAs in individuals who have a history of alcohol dependence, sedative-hypnotic abuse, obstructive or untreated sleep apnea, pulmonary or hepatic failure, or in pregnant females should be avoided.[5,9,13] When appropriate, a short- or intermediate-acting BzRA at the lowest effective dose with (no active metabolites) should be considered for as short a duration as possible.[1,7,21] Depending upon the individual's age and

medical/social history, lower doses should be recommended in those older than 65 years of age if an agent from this class is chosen in this population.[1]

NON-BZRAS

This class of agents (Table 2) tend to have an improved adverse reaction profile in comparison to the BzRAs; however, these should also be used with caution in treating insomnia among elderly patients.[13,31-37] The mechanism of action of the non-BzRAs is similar to the BzRAs through the potentiation of $GABA_A$. However, they have more selectivity for the $alpha_1$ subunit of the GABA receptor, which is thought to be more selective for sedation. It is this selectivity which is also thought to lead to fewer adverse reactions.

Table 2. Non-benzodiazepines commonly used to treat insomnia[1,5,9,13,30-37]

Non-BzRAs	Usual Dose (mg)	Half-life (hr)	Onset (hr)	Comment(s) FDA and Non-FDA Indications(s)
Eszopiclone (Lunesta®)	1 to 3	6 (5 to 8)	1.5 (0.5 to 2)	Take immediately prior to bedtime Do not administer with high-fat meal No dose adjustment in renal impairment Lower dose in severe liver dysfunction Use with caution with CNS-depressant drugs or in patients with compromised lung function CYP3A4 inhibitors: lower initial and max dose Off-label use: breathing-related sleep disorder, insomnia (due to generalized anxiety disorder, major depressive disorder, or menopause)
Zaleplon (Sonata®)	5 to 20	1	1 (0.5 to 2)	Debilitated, geriatric, and mild to moderate liver dysfunction patients may require lower dose Avoid in severe liver dysfunction Use with caution in patients with COPD and OSA
Zolpidem IR (Ambien®)	5 to 10	2.5 (1.4 to 4.5)	1.6 (0.5 to 1.4)	ALL zolpidem formulations: Avoid use of other concomitant sedative hypnotics No dose adjustment in renal dysfunction Lower doses recommended in debilitated, geriatric, and hepatic dysfunction patients Lower dosing (5 mg) for women Use with caution in patients with severe COPD and OSA Approved for: Insomnia (short term) Off-label use: insomnia (long-term and SSRI ADR)
Zolpidem ER (Ambien® CR)	6.25 to12.5	2.8 (1.6 to 4.5)	1.5 (1.5 to 2.0)	Do not crush or chew tablet Lower dosing (6.25 mg) for women Off label use: Insomnia (long-term), Insomnia (SSRI ADR)
Zolpidem SL (Intermezzo®)	1.75 to 3.5	2.5 (1.4 to 3.6)	0.6 (0.6 to 1.3)	For faster onset avoid administering following or with a meal Do not swallow or take with water Approved for: insomnia (difficulty returning to sleep following middle of night awakening) Off-label use: insomnia (SSRI ADR)
Zolpidem SL (Edluar®)	10	2.7 (1.5 to 6.7)	1.4 (0.5 to 3.0)	For faster onset avoid administering following or with a meal Do not swallow or take with water Lower dosing (5 mg) for women Approved for: insomnia (short term) Off-label use: Insomnia (long-term), Insomnia (SSRI ADR)
Zolpidem Oral Spray (Zolpimist®)	10	2.8 (1.7 to 8.4)	0.9	For faster onset avoid administering following or with a meal Lower dosing (5 mg) for women Approved for: insomnia (short term) Off-label use: Insomnia (long-term), Insomnia (SSRI ADR)

ADR: adverse drug reaction; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; SSRI: selective-serotonin reuptake inhibitor

Medications in this class include eszopiclone (Lunesta®), zaleplon (Sonata®), zolpidem immediate release (Ambien®), and zolpidem extended release (multiple formulations), and zopiclone (Imovane®).[11,13] These newer agents are associated with lower incidence of next-day sedation as well as psycho-motor dysfunction, development of tolerance, lower abuse potential and also fewer withdrawal side effects.[13] In addition to considering patient-specific factors when choosing a particular agent in this class vs. the BzRAs, the non-BzRAs vary in their effects on sleep latency, quality of sleep, and side effects.[13] It should be noted that these agents are similar in efficacy (vs. the BzRAs) and for patients with a substance abuse history these would be preferred, having a lower abuse potential.[9]

When comparing these agents, zolpidem tends to be associated with headache, fatigue, dizziness, and parasomnias including sleep-related eating disorders and somnambulism.[9] Zolpidem may have a profile more favorable for improving sleep latency and increasing quality of sleep vs. temazepam.[13] Zaleplon may be a desirable agent to choose due to its rapid onset with lack of adverse or residual side effects of sedation the following day or rebound insomnia upon discontinuation due to its short half-life. It may be a better option for patients having difficulty with sleep onset when compared to the BzRAs and zolpidem.[1] However, it is most effective if taken on an empty stomach. Of commonly reported adverse reactions, use of this agent is most closely associated with headache (vs. other agents in this class), which appears to be dose-dependent; however, there may be a small proportion of patients who may report side effects such as ataxia, dizziness, or hallucinations.[9] Eszopiclone, like zaleplon, also has a quick onset of action and may be an alternate option in patients who also have difficulty falling asleep. Another benefit to eszopiclone, however, is that it may be more beneficial in instances whereby the individually is having both difficulty falling asleep as well as maintaining sleep due to its fast onset and intermediate length of action, respectively.[1,9] Similar to zolpidem, the absorption both eszopiclone and zaleplon will be delayed if taken with food or a heavy meal.[30-37]

Although there are no direct comparisons made between this class of agents vs. the BzRAs, these are considered a reasonable alternative, have similar efficacy and a more favorable adverse effect profile. It should be noted that due to their lower potential for abuse, non-BzRAs should be considered in patients with a history of substance abuse.[10,13] Analogous to the BzRAs, however, these agents should be used with caution in the elderly population.[13]

MELATONIN-RECEPTOR AGONISTS

Melatonin (MT) receptor agonists (Table 3) act by binding to MT receptors, thereby regulating the sleep-wake cycle.[9,13,38-44] Ramelteon (Rozerem®), a MT receptor agonist, is another agent to consider in patients who may be having difficulty falling asleep. It has higher affinity for the MT_1 and MT_2 sites vs. MT_3 receptor sites. MT receptor agonists bind to sites that endogenous melatonin binds, promoting sleep and maintenance of the body's circadian rhythm.[38] Melatonin, produced by the pineal gland, is a neurohormone which is available in over-the-counter formulations as a dietary supplement.[39,40] However, these two agents may not be as effective in maintaining sleep latency (vs. BzRAs and non-BzRAs).[41,42]

Since these drugs do not bind to $GABA_A$, the benefit to this class of agents is the lack of adverse drug reactions the following day. Unlike commonly seen adverse effects of the BzRAs and non-BzRAs, this class lacks effects such as daytime sedation or in-coordination of movements or unwanted effects on memory.[9,13] The most common

Table 3. Melatonin receptor agonists commonly used to treat insomnia[9,13,38-44]

Melatonin receptor agonists	Usual Dose (mg)	Half-life (hr)	Onset (hr)	Comment(s) FDA and Non-FDA Indication(s)
Ramelteon (Rozerem®)	8	1 to 2.6	0.75 (0.5 to 1.5)	Do not administer with or immediately after a high-fat meal May be considered in patients with substance use disorder Avoid in severe liver dysfunction or sleep apnea Approved for: insomnia Contraindications: angioedema with prior exposure or concurrent use of fluvoxamine
Melatonin	1.5 to 3	0.5 to 1	0.3 to 1	Administer within 30 minutes of bedtime No FDA approved indication Considered a dietary supplement May be considered for circadian rhythm disorders or jet lag

adverse reactions reported from these agents are dizziness, headache, somnolence, and fatigue.[13,38,39] It should be noted, though, that in the literature there has been a reported recent case of ramelteon-induced autoimmune hepatitis shortly following the administration of ramelteon.[43]

With both agents, there is potential for drug-drug interactions with other medications also metabolized by CYP1A2, although the use of the MT receptor agonists is not associated with rebound insomnia or "hangover" effect the following day. Use of these agents should, however, be avoided in individuals with severe liver disease or sleep apnea.[13] Ramelteon may be a preferred alternative in patients who have a history of or substance use disorder.[9]

OTHER MEDICATIONS FOR INSOMNIA

In some instances, use of medications as "off-label" for insomnia may be done during an individual's course of stay in the hospital (Table 4).[11,13,20,21,45-49] Medications which are sometimes considered, despite sparse efficacy data are: antidepressants, atypical antipsychotics, antihistamines, older barbiturate medications, and herbal supplements.[13,20,42] However, these drugs too, are not without adverse drug reactions or risks, such as anticholinergic and gastrointestinal adverse effects specifically with the older antidepressants such as doxepin and trazodone, respectively.[13,18,21,41,42]

Low-dose doxepin (Silenor®) is approved for insomnia at doses of 3 to 6 mg. At this dosage, doxepin exerts its effects on H_1 receptors, which makes it beneficial for sedation without unwanted anti-cholinergic effects which are seen at higher antidepressant doses.[5,13,20,21,41,42,45] The benefit of this agent over the BzRAs in particular, is that it affects quality of sleep and reduces wakefulness after sleep onset. By comparison, the efficacy of the short-acting BzRAs diminishes over the course of the night, notably in the final third of the night.[5]

Trazodone, an antidepressant in the triazolopyridine class is used for the treatment for insomnia and may reduce sleep latency; however, these effects may wane after continued use (vs. zolpidem) but also put the individual at risk for adverse effects such as orthostatic hypotension, dizziness, headache and somnolence.[41,48] In addition, the use of trazodone (as well as tricyclic antidepressants) has been found to contribute to arrhythmias in patients with cardiac disease and use should be avoided in this patient population.[13,41] Unfortunately, there is little safety and efficacy data on the use of this agent in the treatment of

Table 4. Miscellaneous medications for insomnia[1,13,20,21,45-49]

Medication	Usual Dose (mg)	Half-life (hr)	Onset (hr)	Comment(s) FDA and Non-FDA Indication(s)
Doxepin (Silenor®)	3 to 6	15 (10 to 30)	3.5 (1.5 to 4)	Do not administer within 3 hours of meal Initial low dose in geriatric and liver dysfunction and patients with urinary retention Contraindications: with concurrent use or use within 2 weeks of an MAOI; in untreated narrow angle glaucoma or severe urinary retention Approved for: insomnia Off-label use: urticaria
Diphenhyramine (Benadryl®)	25 to 50	4 to 8	1 to 4	Lower doses in geriatric and renal dysfunction Avoid in prolonged QTc syndrome Contraindications: newborn or premature infants; nursing mothers Approved for: allergic reactions, common cold, insomnia, motion sickness, puritis, rhinitis, Parkinsonism
Doxylamine	25 to 50	10	2 to 3	Administer 30 min prior to bedtime
Trazodone IR (Desyrel®)	50 to 100	9 (7 to 15)	1 to 2	Administer with food Caution in CV disease Use with caution and monitor in patients with irregular heart rate or at risk/risk factors for QTc prolongation May consider in patients with COPD or lung diseases Possible ADR: priapism Contraindications: with concurrent use or use within 2 weeks of an MAOI; with linezolid or IV methylene blue; concurrent use with saquinavir/ritonavir Off-label use: insomnia

*ADR: adverse drug reaction; COPD: chronic obstructive pulmonary disorder; CV: cardiovascular; MAOI: mono-amine oxidase inhibitor

insomnia, although it may be an alternative agent in individuals with chronic obstructive pulmonary or lung diseseases.[13,20]

Many over-the-counter products which contain diphenhydramine or doxylamine are limited due to the potential for anticholinergic adverse reactions such as urinary retention or impaired cognition, and tend to be not as effective relative to other agents such as the BzRAs and non-BzRAs reviewed.[5,41] Although antidepressants such as trazodone may be shown to be beneficial in improving nighttime awakenings; this is not without risk due to adverse reactions, including potential impairment in cognition and motor impairment, in addition to adverse effects mentioned above.[5,9,20,21] Due to adverse effect profiles of the antihistamines diphenhydramine and doxylamine, as well as the development of tolerance to these agents, their use is not recommended.[13,19]

Despite current available treatments, there is still a need for both safe and effective pharmacologic options to choose from, depending upon needs that best suit the patient in the inpatient hospital setting. Upcoming agents in the pipeline for the treatment of insomnia include other melatonin receptor agonists, serotonin 5-HT_2 receptor modulators, H_1 antagonists, dual-acting orexin antagonists, and tachykinin inhibitors.[11,13,21,42]

CONCLUSIONS

It is important to note that although insomnia is a chronic condition, there are many factors responsible for acute insomnia in the hospital setting. In treating insomnia in the hospitalized inpatient population, identification of underlying etiology should be investigated and treated prior to initiation of medication therapy and modifications to the hospital environment should be made whenever feasible.[1,9,13,19] Numerous pharmacologic options are currently available for the treatment of insomnia. These, along with non-pharmacologic strategies may help optimize or improve a hospitalized inpatient's quality of sleep and promote daytime functioning.

Of the many medications available, intermediate-acting BzRAs that do not have active metabolites (i.e., lorazepam or temazepam) and the non-BzRAs are commonly prescribed, reasonable sedative hypnotic agents to consider when treating insomnia.[1,9] The use of the non-BzRAs may also be considered for use and have similar efficacy and in some cases a more favorable adverse effect profile when compared to the BzRAs.[9,13] Individuals with a history of substance abuse and/or alcohol dependence may favor the choice of a non-BzRA agent or the use of ramelteon in these individuals (vs. the BzRAs).[9,13] Often, a patient's home or chronic insomnia medication may be continued upon admission to the hospital.[9] However, many patients treated in the inpatient setting for acute insomnia generally do not require medications following discharge.[1] To note, the use of medications "off-label" is not without the potential for risks or adverse drug reactions in the hospitalized patient.[13] Thus, unapproved medication uses are generally not recommended. When appropriate, a medication (in addition to non-pharmacologic options) in the inpatient setting should be prescribed which best suits patient-specific factors while addressing the individual's needs for sleep during his or her course of stay and discontinuation should be assessed periodically per the patient's clinical status and upon discharge.

REFERENCES

1. Lenhart SE, Buysse DJ. Treatment of insomnia in hospitalized patients. Ann Pharmacother. 2001;35(11):1449-57. PubMed PMID: 11724098.
2. Reynolds CF, Redline S, DSM-V Sleep-Wake Disorders Workgroup and Advisors. The DSM-V sleep-wake disorders nosology: an update and an invitation to the sleep community. Sleep. 2010;33(1):10-1. PubMed PMID: 20120613.
3. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text revision; DSM-IV-TR. American Psychiatric Association 2000.
4. Rosekind MR, Gregory KB, Mallis MM, Brandt SL, Seal B, Lerner D. The cost of poor sleep: workplace productivity loss and associated costs. J Occup Environ Med. 2010;52(1):91-8. DOI: 10.1097/JOM.0b013e3181c78c30. PubMed PMID: 20042880.
5. Buysse DJ. Insomnia. JAMA. 2013;309(7):706-16. DOI: 10.1001/jama.2013.193. PubMed PMID: 23423416.
6. Kierlin L. Sleeping without a pill: nonpharmacologic treatments for insomnia. J Psychiatr Pract. 2008;14(6):403-7. DOI: 10.1097/01.pra.0000341896.73926.6c. PubMed PMID: 19057243.
7. Morin CM, Benca R. Chronic insomnia. Lancet. 2012;379(9821):1129- 41. DOI: 10.1016/S0140-6736(11)60750-2.
8. Isaia G, Corsinovi L, Bo M, Santos-Pereira P, Michelis G, Aimonino N, et al. Insomnia among hospitalized elderly patients: prevalence, clinical characteristics and risk factors. Arch Gerontol Geriatr. 2011;52(2):133-7. DOI: 10.1016/j.archger.2010.03.001. PubMed PMID: 20338647.
9. Howell HR, McQueeney M, Bostwick JR. Prescription sleep aids for the treatment of insomnia. US Pharm. 2011;36(1):62-6.
10. Hayward R, Jordan KP, Croft P. Healthcare use in adults with insomnia: a longitudinal study. br j gen pract. 2010;60(574):334-40. DOI: 10.3399/bjgp10X501822. PubMed PMID: 20423585; PubMed Central PMCID: PMC2858531.
11. Sullivan S. Update on emerging drugs for insomnia. Expert Opin Emerg Drugs. 2012;17(3):295-8. DOI: 10.1517/14728214.2012.693158. PubMed PMID: 22920041.
12. Sasai T, Inoue Y, Komada Y, Nomura T, Matsuura M, Matsushima E. Effects of insomnia and sleep medication on health-related quality of life. Sleep Med. 2010;11(5):452-7. DOI: 10.1016/j.sleep.2009.09.011. PubMed PMID: 20381419.
13. Young JS, Bourgeois JA, Hilty DM, Hardin KA. Sleep in hospitalized medical patients, part 2: behavioral and pharmacological management of sleep disturbances. J Hosp Med. 2009;4(1):50-9. DOI: 10.1002/jhm.397. PubMed PMID: 19140196.
14. Young JS, Bourgeois JA, Hilty DM, Hardin KA. Sleep in hospitalized medical patients, part 1: factors affecting sleep. J Hosp Med. 2008;3(6):473-82. DOI: 10.1002/jhm.372. PubMed PMID: 19084897.
15. Jaussent I, Empana JP, Ancelin ML, Besset A, Helmer C, Tzourio C, et al. Insomnia, daytime sleepiness and cardio-cerebrovascular diseases in the elderly: a 6-year prospective study. PLoS One. 2013;8(2):e56048. DOI:

10.1371/journal.pone.0056048. PubMed PMID: 23457496; PubMed Central PMCID: PMC3573087.
16. de Niet G, Tiemens B, Hutschemaekers G. Nursing care for sleep problems in psychiatry: is there a problem? Br J Nurs. 2009;18(7):429-33. PubMed PMID: 19373188.
17. Tranmer JE, Minard J, Fox LA, Rebelo L. The sleep experience of medical and surgical patients. Clin Nurs Res. 2003;12(2):159-73. DOI: 10.1177/1054773803012002004.
18. Larive LL. Sleep Disorders. In: Tisdale JE, Miller DA, ed. Drug-Induced Diseases: Prevention, Detection, and Management. Bethesda, MD; ASHP;2005:185-91.
19. Berlin RM. Management of insomnia in hospitalized patients. Ann Intern Med. 1984;100(3):398-404. PubMed PMID: 6141753.
20. McCall C, McCall WV. What is the role of sedating antidepressants, antipsychotics, and anticonvulsants in the management of insomnia? Curr Psychiatry Rep. 2012;14(5):494-502. DOI: 10.1007/s11920-012-0302-y. PubMed PMID: 22923053.
21. Ioachimescu OC, El-Solh AA. Pharmacotherapy of insomnia. Expert Opin Pharmacother. 2012;13(9):1243-60. DOI: 10.1517/14656566.2012.683860. PubMed PMID: 22578014.
22. Xanax® [package insert]. New York, New York. Pfizer; 2011.
23. Klonopin® [package insert]. San Francisco.Genentech; 2013.
24. Estazolam [package insert]. Miami, Florida. Ivax Pharmaceuticals, Inc.; 2002.
25. Dalmane® [package insert]. Aliso Viejo, California. Valeant Pharmaceuticals North America; 2007.
26. Ativan® [package insert]. Philadelphia, Pensylvania. Wyeth Pharmaceuticals Inc.; 2007.
27. Doral® [package insert]. Hayward, California. Questcor Pharmaceuticals, Inc.; 2013.
28. Restoril® [package insert]. Hazelwood, Missouri. Mallinckrodt; 2010.
29. Halcion® [package insert]. New York, New York. Pfizer; 2008.
30. Frighetto L, Marra C, Bandali S, Wilbur K, Naumann T, Jewesson P. An assessment of quality of sleep and the use of drugs with sedating properties in hospitalized adult inpatients. Health Qual Life Outcomes. 2004;2:17-27.
31. Sonata® [package insert]. Bristol, Tennessee. King Pharmaceuticals, Inc.; 2011.
32. Lunesta® [package insert]. Marlborough, Massachusetts. Sunovion Pharmaceuticals, Inc.; 2012.
33. Ambien® [package insert]. Bridgewater, New Jersey. Sanofi-Aventis US LLC.; 2013.
34. Ambien® CR [package insert]. Bridgewater, New Jersey. Sanofi-Aventis US LLC; 2013.
35. Intermezzo® [package insert]. Stamford, Conneticuit. Purdue Pharma LP; 2013.
36. Elduar® [package insert]. Somerset, New Jersey. Meda Pharmaceuticals, Inc.; 2013.
37. Zolpimist® [package insert]. Flemming, New Jersey. NovaDel Pharma, Inc.; 2008.
38. Rozerem® [package insert]. Deerfield, Illinois. Takeda Pharmaceuticals America, Inc.; 2010.
39. Melatonin. [product Information: Melatonin oral capsules, tablets, melatonin oral capsules, tablets]. Las Vegas, Nevada. Longevity Health Group, Inc.; 2011.
40. Lane EA, Moss HB. Pharmacokinetics of melatonin in man: first pass hepatic metabolism. J Clin Endocrinol Metab. 1985;61(6):1214-6. DOI: 10.1210/jcem-61-6-1214. PubMed PMID: 4055987.
41. Zisapel N. Drugs for insomnia. Expert Opin Emerg Drugs. 2012;17(3):299-317. DOI: 10.1517/14728214.2012.690735. PubMed PMID: 22681198.
42. Richey SM, Krystal AD. Pharmacological advances in the treatment of insomnia. Curr Pharm Des. 2011;17(15):1471-5. PubMed PMID: 21476952.
43. Fourman LT, Robert Meyer B. Autoimmune hepatitis in association with ramelteon. J Clin Gastroenterol. 2013;47(7):651-4. DOI: 10.1097/MCG.0b013e31829174f0. PubMed PMID: 23632362.
44. Ardent, J. Melatonin: characteristics, concerns, and prospects. J Biol Rhythms. 2005;20(4):291-303.
45. Silenor® [package insert]. San Diego, California. Somaxon Pharmaceuticals, Inc.; 2010.
46. Benadryl® Allergy oral capsules, diphenhydramine HCl oral capsules [product information]. New York, New York. Pfizer Consumer Healthcare; 2006.
47. Unisom® SleepTabs® doxylamine succinate [product information]. New York, New York. Pfizer; 2002.
48. Kaynak H, Kaynak D, Gözükirmizi E, Guilleminault C. The effects of trazodone on sleep in patients treated with stimulant antidepressants. Sleep Med. 2004;5(1):15-20. PubMed PMID: 14725822.
49. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Some Thyrotropic Agents. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Doxylamine succinate. WHO. 2001;79:145-59.

How to cite this editor-reviewed article
Kelly J. Insomnia treatment for the medically ill hospitalized patient. Ment Health Clin [Internet]. 2014;4(2):82-90. Available from: http://dx.doi.org/10.9740/mhc.n190102