Treatment of Insomnia in Hospitalized Patients

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OBJECTIVE: To provide recommendations for the short-term management of insomnia in hospitalized patients and review patient assessment, nonpharmacologic treatment modalities, and selection of hypnotic medications.

DATA SOURCES: Review articles and primary literature representative of current knowledge regarding the treatment of insomnia were identified by MEDLINE search (1966–January 2001). Search terms included insomnia (sleep initiation and maintenance disorders), benzodiazepines, zaleplon, zolpidem, and trazodone.

DATA SYNTHESIS: Literature regarding the management of insomnia in hospitalized patients is limited; therefore, data pertinent to the treatment of ambulatory patients must be extrapolated to the inpatient setting. When evaluating insomnia in hospitalized patients, it seems reasonable to obtain a thorough history and physical examination to identify potential underlying etiologies. Treatment of these underlying etiologies should be considered. When the use of a sedative–hypnotic agent is necessary, medication and dose selection should be based on the pharmacokinetic and adverse effect profiles of each agent. Patient-specific characteristics should also be considered to provide effective treatment while minimizing adverse effects.

CONCLUSIONS: Nonpharmacologic approaches to the treatment of insomnia should be considered for hospitalized patients. When sedative–hypnotic medications must be administered, the pharmacokinetic profile of intermediate-acting benzodiazepines (e.g., lorazepam, temazepam) makes them good first-line agents. Zaleplon and zolpidem are also attractive hypnotic agents; however, they are typically reserved for second-line therapy due to cost. Trazodone may be an alternative for patients unable to take benzodiazepines.

KEY WORDS: benzodiazepines, insomnia, trazodone, zaleplon, zolpidem.

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Insomnia, defined as the perception of inadequate or nonrestorative sleep often related to difficulty initiating sleep, difficulty maintaining sleep, or frequent awakenings,[1,2] appears to be a common condition among hospitalized patients. Insomnia is often frustrating for the patient, but unfortunately most healthcare professionals view these instances of insomnia as a nuisance. They either disregard the problem or prescribe medications to alleviate the insomnia without investigating the underlying cause of this sleep disorder. Although a generalized approach to the management of insomnia has been addressed at length,[3-7] very little literature focuses specifically on the management of insomnia in hospitalized patients. This article, therefore, focuses on a comprehensive approach to the short-term management of insomnia in these patients. The goal of this approach is to facilitate the assessment and treatment of insomnia while minimizing adverse drug events. This is accomplished by focusing on the key components of patient assessment, selection of nonpharmacologic treatment modalities whenever possible, and assessment of criteria important to the selection and dosing of hypnotic agents.

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Etiology and Assessment

Insomnia in hospitalized patients is likely multifactorial in nature. Anxiety related to the current illness, anticipated procedures, inability to address outstanding personal matters, and unfamiliarity with their surroundings is common among hospitalized patients. Symptoms related to the cur-

rent illness such as cough, pruritus, pain, shortness of breath, and frequent urination may interfere with sleep. Patients who were using illicit drugs or alcohol at home may suffer through withdrawal once admitted to the hospital. Many commonly prescribed medications can interfere with sleep as well (Table 1).[3,5,6,8] Patients with chronic illnesses often experience comorbid depression; this disorder is often associated with sleep disturbances. Advancing age is further associated with changes in sleep patterns; it is not uncommon for geriatric patients to experience nighttime awakenings, resulting in fragmentation of sleep and early-morning awakenings accompanied by an inability to fall back to sleep. Since the total amount of sleep needed to restore daytime functioning does not change, daytime napping or early bedtime may be necessary to achieve an adequate amount of restorative sleep.[1,9] A final consideration is that the hospital environment itself is not conducive to sleep. Hospital wards and intensive care units are often noisy, and patients are frequently awakened for middle-of-the-night assessments and laboratory tests. Constant lighting may also disorient the patient's sense of day versus night.[8]

When a hospitalized patient reports insomnia, a healthcare professional possessing the ability to integrate and process all pertinent information should perform a sleep history and physical examination. The sleep history can be obtained within a few minutes by asking the patient questions focused on defining the nature of the insomnia, which may be difficulty initiating sleep, difficulty maintaining sleep, or a feeling of being unrested despite an adequate amount of sleep. The patient should also be questioned about factors interfering with sleep and those promoting sleep. Additionally, the sleep patterns experienced by the patient prior to admission should be elicited. Other data that should be obtained are a medication history (including caffeine, alcohol, tobacco, and illicit drug use) and a psychiatric history.

All of this information is necessary to determine whether the patient has an underlying disease process, such as depression or psychosis, and would benefit from disease-specific treatment. This information should also help to determine whether the insomnia is related to the patient's current medication therapy. The physical examination may be useful in identifying medical conditions and associated symptoms interfering with sleep.[8] Table 2 summarizes the differential diagnosis of insomnia in hospitalized patients.

Table 1. Medications Associated with Insomnia[3,5,6,8]

Anticholinergic agents	Medroxyprogesterone
β-Adrenergic agonists	Methyldopa
β-Adrenergic antagonists	Methylphenidate
Caffeine	Monoamine oxidase inhibitors
Clonidine	Nicotine
Contraceptives (oral)	Phenylephrine
Corticosteroids	Phenytoin
Daunorubicin	Pseudoephedrine
Dextroamphetamine	Quinidine
Ephedra (ma huang)	Selective serotonin-reuptake inhibitors
Ginseng	St. John's wort
Interferon-α	Theophylline
Levodopa	Thyroid preparations
Leuprolide	

Nonpharmacologic Approaches to Insomnia Management

Little information is available regarding nonpharmacologic approaches to managing insomnia in hospitalized patients. As a primary principle of this approach, it seems logical to treat the underlying factor(s) contributing to the disorder. These underlying factors may be related to psychological disorders, disease symptoms, medications, or environmental issues. Some underlying factors such as depression or psychosis will not respond quickly to therapy and, in these instances, hypnotic medications may be required during the initial treatment phase. Other etiologies of insomnia may be easily resolved using the following strategies, thus negating the need for sleep-enhancing medication.

Patients with anxiety may benefit from open communication with their healthcare providers about their medical condition(s). It may also be helpful to have a family member or social worker speak with the patient and assist with the resolution of any outstanding personal matters, and family members should be encouraged to avoid upsetting the patient. Placing familiar items such as pictures and pil-

Table 2. Differential Diagnosis of Insomnia in Hospitalized Patients

- Acute insomnia
  - psychological factors
    - anxiety
    - grief
  - physical factors
    - pain
    - limited mobility
    - respiratory difficulty
  - miscellaneous
    - delirium
    - infection
    - metabolic disorders
    - polyuria
    - urinary incontinence
- Chronic insomnia
  - secondary to other conditions
    - psychiatric disorders
    - medical/neurologic disorders
    - medication/illicit substance use or discontinuation
  - associated with other sleep disorders
    - sleep apnea
    - restless leg syndrome
    - periodic limb movement disorder
    - circadian rhythm disorders
  - primary insomnia

lows in the hospital room may help the patient feel more comfortable with the surroundings.

When symptoms such as cough, pain, or frequent urination interfere with sleep, attempts should be made to alleviate these symptoms. Often a cough suppressant or analgesic will be all that is needed to help the patient sleep. Limiting fluid intake during the evening hours and administering diuretics prior to 1700 will often prevent awakenings due to the need to void.

For the patient undergoing alcohol, tobacco, or illicit drug withdrawal, recognition and management of the withdrawal may help alleviate insomnia. The inadvertent discontinuation of chronic medications on admission may lead to sleep disturbances. In this case, simply reinitiating the medication may be helpful. Medications known to be associated with insomnia (including caffeine) should be discontinued or administered as early in the day as is medically possible, and scheduled middle-of-the-night administration of any medication should be avoided.

Attempts should be made to increase daytime patient activity while limiting daytime sleep, to decrease late evening stimulation, to decrease nighttime noise levels, and to maintain normal light–dark cycles in patient care areas. Nighttime nursing and medical assessments and procedures should be kept to a minimum as well.

A pilot study[10] performed in patients aged ≥70 years admitted to a general medicine ward showed success with nonpharmacologic therapies. The use of techniques such as ingestion of a warm beverage just prior to bedtime, receiving a back massage, or listening to relaxation tapes led to an absolute reduction of 23% in the number of patients receiving at least one dose of a sedative medication during the hospitalization. These techniques also led to improved patient perceptions of sleep quality.

Pharmacologic Approaches to Insomnia Management

The short-term use of hypnotic medications may be necessary to supplement nonpharmacologic approaches to the treatment of insomnia. An ideal hypnotic medication would have a rapid onset of action, a six- to eight-hour duration of action, and lack residual sedative effects and adverse effects. Such a medication does not exist. In an effort to ensure efficacy while minimizing the risk of adverse events, the choice of hypnotic and dose should be based on the pharmacokinetic and pharmacodynamic properties and adverse effect profile of each agent.[11,12] Patient characteristics including age, concomitant medications, and concomitant disease states should be considered as well.

The normal sleep cycle consists of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep can be further categorized into four stages, with the depth of sleep increasing from stage 1 through stage 4 sleep. Stage 1 sleep lasts for a very brief period of time, while stage 2 sleep accounts for approximately 50% of sleep time. Stage 3 and 4 sleep are collectively referred to as deep sleep or delta sleep. Delta sleep seems to be associated with the patient's perception of sleep quality. REM sleep is associated with high levels of neuronal activity and dreaming. Sleep is initiated through NREM sleep and is followed by REM sleep. Cycling between NREM and REM sleep occurs throughout the night, and each sleep cycle averages 90–100 minutes. NREM sleep accounts for approximately 75–80% of total sleep time. REM sleep accounts for the remaining 20–25%, but while the majority of NREM sleep occurs early in the night, the duration and intensity of REM sleep increase as the night progresses.[1,13] The effects of hypnotic agents on sleep architecture are often touted as an important property of the medication; however, the true importance of maintaining normal sleep architecture has not been defined. Ideally, hypnotic medications would increase total sleep time without altering the natural sleep cycle, but if alterations were to occur, delta sleep prolongation would intuitively be desirable. Avoidance of REM suppression might seem desirable as well, since it has been suggested REM rebound occurring after the discontinuation of medications suppressing REM sleep may lead to vivid dreams or nightmares.[14] This association, however, has not been proven.

The ensuing discussion focuses on the characteristics of the benzodiazepines, benzodiazepine ω-1 receptor agonists, and trazodone. These characteristics are the basis for the development of rational recommendations for the pharmacologic treatment of insomnia in hospitalized patients. Antihistamines and tricyclic antidepressants will not be discussed, because the benefits of these medications rarely outweigh the risks associated with their use, particularly in elderly patients likely to experience orthostatic hypotension, confusion, urinary retention, worsening of glaucoma, and other anticholinergic effects.[3,5,6,11,15] Barbiturates have also fallen into disuse due to their narrow therapeutic index and abuse potential.[5,15,16] Chloral hydrate has been associated with severe withdrawal syndromes and should be avoided in patients with hepatic and/or renal dysfunction,[15] thus limiting its usefulness for many hospitalized patients. L-tryptophan has been associated with eosinophilia–myalgia syndrome, and data regarding its efficacy are inconsistent. Other nontraditional medications such as melatonin and valerian are not discussed here, as many hospitals have implemented policies discouraging the use of alternative medications among inpatients.

BENZODIAZEPINES

The benzodiazepine agents are the most studied hypnotic medications. They have many effects on the central nervous system, including anticonvulsant, myorelaxant, amnestic, and sedative/hypnotic actions. They produce these effects by potentiating the activity of the inhibitory neuro- transmitter γ-aminobutyric acid. All benzodiazepines have similar effects on sleep architecture. A decrease in sleep latency, increase in stage 2 sleep, and a small decrease in delta and REM sleep occur with the use of these agents. Despite the decreased amount of time spent in delta and REM sleep, total sleep time is usually increased.[15,17] Because all

benzodiazepines have somewhat similar effects on the sleep cycle, the differences in their pharmacokinetic properties make certain benzodiazepines more desirable for use as hypnotic agents than others.

Benzodiazepines are often classified as short-, intermediate-, and long-acting, based on the half-life of each agent. Long-acting benzodiazepines are more likely to cause residual daytime effects, while short-acting benzodiazepines are more likely to cause rebound insomnia on discontinuation. The onset and duration of action of benzodiazepines are dependent on their rate of absorption and lipophilicity, which determine tissue distribution. All of these agents generally work well as hypnotics due to their relatively rapid rate of absorption and onset of action, although differences among the benzodiazepines do exist. To date, five benzodiazepines (triazolam, temazepam, estazolam, quazepam, flurazepam) have received approval from the Food and Drug Administration (FDA) for the treatment of insomnia.

Triazolam, with a half-life of two to four hours, is considered a short-acting benzodiazepine and would appear to be a good medication for the treatment of insomnia. The use of triazolam has been associated with rebound insomnia in some studies. The likelihood of rebound insomnia occurring is low with the anticipated short duration of use in hospitalized patients, but is a potential adverse effect that should not be overlooked. High doses of triazolam have been associated with confusion and bizarre behavior; however, an Institute of Medicine review[18] found triazolam to be safe when used at the recommended doses for a period of time not exceeding 10 days.

Estazolam and temazepam are both considered intermediate-acting benzodiazepines with half-lives of approximately eight to 20 hours. Metabolically, temazepam undergoes hepatic conjugation while estazolam undergoes oxidative metabolism.[19] Neither agent is converted to metabolites possessing significant activity. The advantage of temazepam over estazolam is its route of metabolism, because agents undergoing primarily conjugative metabolism are less susceptible to drug interactions than are those undergoing oxidative metabolism. Additionally, the clearance of medications undergoing oxidative metabolism may be decreased and the half-life prolonged in elderly patients and patients with hepatic dysfunction, making them less desirable for use in these patient populations. Thus, temazepam may be safer than estazolam for elderly patients and patients with liver disease.[15,19]

Flurazepam and quazepam are long-acting agents with half-lives typically exceeding 24 hours. Due to their long half-lives and their conversion to active metabolites, flurazepam and quazepam are likely to accumulate and produce daytime sedation. These agents are not ideal for hospitalized patients.

Lorazepam is a benzodiazepine not approved by the FDA for use as a hypnotic agent; however, its pharmacokinetic properties are similar to those of temazepam. The half-life of lorazepam is 10–20 hours, and it undergoes conjugative metabolism to inactive metabolites. It has the added benefits of having a slightly faster onset of action than temazepam (30–60 vs. 45–60 minutes),[6,20] and it is available in an intravenous formulation.

Other benzodiazepines often used to promote sleep include diazepam, clonazepam, alprazolam, and oxazepam. Diazepam and clonazepam both have long half-lives; alprazolam is often abused, and withdrawal syndromes may be especially severe with this agent.[15] All three agents are metabolized via oxidation, which makes them more likely to be involved in drug interactions than are lorazepam or temazepam. Oxazepam is metabolized via conjugation, but its slow onset and variable half-life tend to make it a less desirable hypnotic agent. Table 3 summarizes the pharmacokinetic properties of the benzodiazepines and other commonly used sedative–hypnotic agents.

The efficacy of benzodiazepines over a median duration of therapy of seven to 7.5 days has been shown in two meta-analyses.[21,22] Nowell et al.[21] showed that benzodiazepines (and zolpidem) improve sleep latency, prolong total sleep time, decrease the number of nighttime awakenings, and improve sleep quality. Holbrook et al.[22] showed that benzodiazepines prolong sleep duration. Extrapolation of these results to hospitalized patients should be done with caution, considering both studies focused on patients with primary insomnia and the results were based on combined analysis of all benzodiazepines with no stratification based on half-life. Additionally, Holbrook et al.[22] showed that benzodiazepines are associated with a number of adverse effects, although the relationship of the effects to the dosage used was not explored.

In addition to residual daytime impairment of cognitive and motor functions, the major adverse effects of benzodiazepines are anterograde amnesia and potential compromise of respiratory function. Anterograde amnesia has been reported more frequently with triazolam than with other hypnotic benzodiazepines; as this adverse effect appears to be dose related, use of the lowest effective dose will minimize its occurrence.[5,11,15] Potential compromise of respiratory function may be a risk for patients with severe chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA).[23] Paradoxical effects such as nightmares, hallucinations, bizarre behavior, and hostility and rage, collectively referred to as "disinhibition," have been reported. Benzodiazepines may be abused, and long-term use can lead to dependence. The risk of abuse and dependence is especially severe for patients who have a history of abusing other substances.[15] Agents suppressing the cytochrome P450 enzyme system, particularly CYP3A4, may lead to increased adverse effects of benzodiazepines undergoing oxidative metabolism, while benzodiazepines undergoing conjugative metabolism are unlikely to be affected. Caution should be used with concomitant administration of benzodiazepines and other medications possessing sedative properties.

BENZODIAZEPINE ω-1 RECEPTOR AGONISTS

Zolpidem and zaleplon are nonbenzodiazepine hypnotic agents having relative specificity for the ω-1 benzodi-

azepine receptor. Because they act at the ω-1 subtype receptor, the muscle relaxant, amnestic, and anticonvulsant properties of the medications are less likely to be elicited at doses typically used to promote sleep. Neither agent appears to significantly alter normal sleep architecture.

Zolpidem has an onset of action of 30 minutes and a half-life of approximately 2.5 hours. It is metabolized via oxidation primarily through the CYP3A4 enzyme system to inactive metabolites.[24] Although it was originally thought that zolpidem lacked abuse potential, studies and case reports suggest the drug may be abused.[25-28] The most common adverse effects associated with the short-term (≤10 d) use of zolpidem include drowsiness, dizziness, and diarrhea.[29] Several case reports[30-39] have also associated zolpidem with bizarre adverse central nervous system events including sensory disturbances, sleep walking, psychosis, hallucinations, agitation, and amnesia. Caution should be taken when using this agent in patients with severe COPD or OSA,[23] although one study[40] suggests it is safe for patients with mild to moderate COPD. Because zolpidem is metabolized via the CYP3A4 enzyme system, caution should be used when zolpidem is administered concomitantly with inhibitors of this enzyme system.[41] The effectiveness of zolpidem may be diminished by agents inducing CYP3A4.[42] Coadministration with other central nervous system depressants may potentiate the effects of both agents.

Zaleplon has an onset of action of 15–30 minutes and a half-life of approximately one hour. It is primarily metabolized by aldehyde oxidase to form the inactive metabolite 5-oxo-zaleplon. It is also metabolized to a lesser extent by CYP3A4.[43,44] A study[45] performed in 14 patients with a history of drug abuse suggests that high doses of zaleplon have an abuse potential similar to high doses of triazolam, while a second study[46] performed in 35 patients with no history of substance abuse showed zaleplon to be free of abuse potential. The most common adverse effects associated with zaleplon are headache and dizziness.[43] Caution should be used when administering this agent to patients with COPD and OSA[23]; however, preliminary data[47] show the agent is likely safe in patients with mild to moderate COPD. Thus far, only one case report[48] of zaleplon-induced perceptual disturbances has been published; as it is a relatively new medication, more reports may surface as more experience with the drug is gained. Agents suppressing the activity of CYP3A4 are reportedly unlikely to significantly affect the metabolism of zaleplon. However, the coadministration of zaleplon and rifampin, a potent inducer of CYP3A4, led to a decreased zaleplon mean maximum concentration and AUC, making it seem possible that inhibitors of this enzyme system could potentiate the effects of zaleplon. Concomitant use of cimetidine, an inhibitor of both CYP3A4 and aldehyde oxidase, with zaleplon led to an increase in the mean maximum concentration and AUC of zaleplon; concomitant use of diphenhydramine, an inhibitor of aldehyde oxidase alone, did not have a significant effect on zaleplon pharmacokinetics. Caution is warranted when zaleplon is coadministered with other agents depressing the central nervous system.[43]

Due to zaleplon's short half-life, it appears to lack residual daytime effects on memory and performance.[49-52] This feature allows zaleplon to be administered when only four to five hours of time for sleep remain,[43] although data[49] show it may be administered as early as two hours prior to awakening without significant residual effect. This is a factor distinguishing zaleplon from benzodiazepines[50,51,53] and zolpidem[48,49] and making zaleplon a good medication to have in the armamentarium of hypnotic agents. It is particularly useful for patients who have difficulty only with initiating sleep. Patients who have difficulty maintaining sleep but who prefer an agent that may be taken during the night should they awaken versus a longer-acting agent, which

Table 3. Pharmacokinetic Comparison of Medications Used as Sedative–Hypnotics

Medication	Half-Life (h)	Onset (min)	Route of Metabolism	Active Metabolites
Short-acting benzodiazepines				
triazolam	2–4	15–30	oxidation	no
Intermediate-acting benzodiazepines				
alprazolam	12–15	NA	oxidation	no
estazolam	10–24	15–60	oxidation	no
lorazepam	10–20	30–60	conjugation	no
oxazepam	3–20	45–60	conjugation	no
temazepam	8–20	45–60	conjugation	no
Long-acting benzodiazepines				
clonazepam	18–80	30–60	oxidation/nitroreduction	no
diazepam	20–80	15–30	oxidation	yes
flurazepam	24–100	30–60	oxidation	yes
quazepam	25–41	20–45	oxidation	yes
Benzodiazepine ω-1 receptor agonists				
zaleplon	1	15–30	aldehyde oxidase/oxidation	no
zolpidem	2.5	30	oxidation	no
Antidepressants				
trazodone	5–9	30–60	oxidation	no

NA = not available.

must be taken at bedtime, may also be good candidates to receive zaleplon. It should be noted, however, when zaleplon is administered at bedtime, its duration of action may not be sufficient to ensure a full night of sleep for patients who suffer from difficulty maintaining sleep.

TRAZODONE

In the past, tricyclic antidepressants were often used to treat insomnia, but the anticholinergic and adverse cardiovascular effects of these agents likely outweigh their benefit, particularly in elderly patients.[3,5,6,11,15] Trazodone, a triazolopyridine derivative unrelated to the tricyclic antidepressants, has associated hypnotic effects but appears to have less anticholinergic and cardiovascular effects than do the tricyclic antidepressants, although it does possess α-1 antagonist and antihistaminic properties. According to information obtained from the National Disease and Therapeutic Index, a database of information submitted by office-based physicians in 24 practice specialties, the use of trazodone for the treatment of insomnia increased dramatically between 1987 and 1996. It was, in fact, the most widely prescribed medication for the treatment of insomnia in the US in 1996.[54]

Trazodone has an onset of effect of 30–60 minutes and a half-life of five to nine hours.[6] It is metabolized via hepatic oxidation. Doses ranging from 50 to 600 mg/d have been shown to have beneficial effects on insomnia in a small number of depressed[55-57] as well as nondepressed individuals.[58,59] However, one study[60] involving eight depressed patients failed to show an improvement in subjective sleep quality or objective sleep parameters with the administration of trazodone. Only one study[58] has compared the effects of trazodone to another hypnotic agent. The effects of trazodone 50 mg and zolpidem 10 mg were compared with placebo in 278 nondepressed volunteers. Zolpidem led to shorter sleep latency and had more persistent effects over a two-week period than did trazodone. When compared with placebo, trazodone significantly improved sleep latency ($p < 0.01$) and sleep time ($p < 0.008$) during week 1 and led to improved subjective sleep quality ($p < 0.004$).

The adverse effects most commonly associated with trazodone include gastrointestinal disturbances. Although cardiovascular effects occur less frequently with trazodone than with tricyclic agents, patients should be counseled about the possibility of orthostatic hypotension and dizziness. Atrial and ventricular arrhythmias have occurred in a small number of patients receiving trazodone; thus, it might be wise to avoid use of this agent in patients predisposed to arrhythmias. Anticholinergic effects are experienced by some patients, but at the recommended doses are seldom severe enough to require discontinuation of the medication. The incidence of priapism associated with the use of trazodone is estimated to be between 1 in 1000 and 1 in 10 000 patients. It is considered to be a urologic emergency and must be treated promptly should it occur. Caution should be used when administering trazodone concomitantly with other medications known to cause drowsiness or hypotension. Trazodone has the potential to alter phenytoin and digoxin serum concentrations, and patients receiving these medications concomitantly with trazodone should be carefully monitored.[61] Trazodone has been shown[25] to have a low abuse potential compared with other hypnotic agents. This property, along with its lack of effects on respiratory drive, makes trazodone a good agent to have available for the treatment of patients with a history of previous drug abuse or severe COPD or OSA in whom benzodiazepines and possibly the ω-1 receptor agonists should be avoided.

Recommendations

The use of nonpharmacologic and general medical approaches to the management of insomnia in hospitalized patients is strongly encouraged when feasible, recognizing that some factors are more amenable to change than others. For instance, it may not be feasible to alter hospital routines to eliminate all light and noise at night, but it may well be feasible to treat contributing medical factors. Hypnotic therapy may be necessary when nonpharmacologic or general medical measures fail to produce patient satisfaction with sleep. When hypnotic therapy is necessary, intermediate-acting benzodiazepines undergoing conjugative metabolism (e.g., temazepam, lorazepam) are recommended first-line agents and are particularly useful for patients who experience continued anxiety. The cost of zaleplon and zolpidem is 2.5–8.5 times the cost of benzodiazepines, depending on the brand and dosage used as a comparison, and they should be reserved as second-line agents for patients who experience prolonged sedation with the preferred benzodiazepines. Use of zaleplon as a first-line agent may be warranted for patients who require middle-of-the-night dosing.

Patients with COPD and OSA and patients with a history of substance abuse present a special challenge. Sleep disturbances are often related to the pathophysiologic changes occurring in association with COPD and OSA, and benzodiazepines and benzodiazepine-like medications may worsen these diseases by decreasing respiratory drive. While the use of benzodiazepines and similar agents has traditionally been discouraged, short-acting agents may be safe for patients with mild to moderate COPD, defined as patients who do not have daytime hypercapnea or severe resting hypoxemia.[23,40,47] If it is determined that benzodiazepines and benzodiazepine ω-1 receptor agonists should be avoided in a particular patient, trazodone may be considered. Trazodone may also be a useful alternative for patients with a history of drug abuse and dependence. It should be used cautiously, however, in patients at high risk for developing orthostatic hypotension or cardiac arrhythmias.

Treatment of insomnia in older patients presents another challenge. These patients are at increased risk of adverse drug events secondary to altered pharmacokinetics and polypharmacy, and avoidance of hypnotic medications in

this population is desirable. As mentioned previously, nonpharmacologic therapies such as ingesting a warm beverage, receiving a back massage, and listening to relaxation tapes have proven useful in hospitalized geriatric patients.[10] A study[62] performed in healthy outpatients older than 54 years with chronic insomnia showed behavioral therapy was at least as effective, if not more effective, than pharmacotherapy (temazepam.) The results of this study may not be applicable to the short-term treatment of insomnia in hospitalized older patients with multiple medical conditions; however, they provide an argument for initiating behavioral therapy that may be continued on discharge if deemed appropriate for patients diagnosed with chronic insomnia. When hypnotic medications are administered to geriatric patients, low doses, slow dose titration, and careful monitoring for adverse effects are required.

When prescribing hypnotic agents to hospitalized patients, orders should ideally be written on a daily basis to allow daily evaluation of the need for pharmacologic therapy. As this approach is not very practical, as-needed orders may be written along with nursing education reinforcing the need to limit therapy only to patients who do not feel nonpharmacologic therapy is beneficial. Alternatively, orders may be written for the hypnotic agent to be administered every night at bedtime, yet allow for patient refusal of the medication.

The majority of patients treated for insomnia during hospitalization will not require continued therapy on discharge. If outpatient therapy is necessary during treatment optimization for underlying disorders such as depression, the agent effectively and safely producing patient satisfaction with sleep during hospitalization may be continued for two to four weeks. Patients should be educated regarding nonpharmacologic techniques, and daily use of the hypnotic agent should be discouraged. Potential adverse effects should also be reviewed with the patient. After two to four weeks, the patient should be reevaluated to determine whether continuation of therapy is necessary. A detailed discussion of the treatment of long-term or chronic insomnia is beyond the scope of this article.

Table 4[6,63,64] lists guidelines for dosing of the preferred hypnotic medications, derived from previously published dosing recommendations. Focus should be placed on using the lowest effective dose, particularly in elderly patients.

Summary

Very little information exists regarding the treatment of insomnia in hospitalized patients. Patients with insomnia should undergo a thorough sleep history and physical examination in an effort to identify the etiology of the insomnia. When appropriate, treatment aimed at resolving the identified problem(s) should be tried before sedative–hypnotic medications. When hypnotic therapy is required, the pharmacokinetic and pharmacodynamic properties and adverse effect profile of each medication and patient-specific characteristics should be considered when selecting an agent and dose that will be effective yet produce minimal adverse effects. Intermediate-acting benzodiazepines with no active metabolites (e.g., lorazepam, temazepam) are sensible first-line agents. Zaleplon and zolpidem are likely best used as second-line agents due to their cost relative to that of the benzodiazepines. Trazodone is an alternative for patients with hypercapnea or hypoxemia associated with COPD or other lung diseases. Trazodone may also be a useful alternative for patients with a history of drug abuse or dependence. The administration of antihistamines, tricyclic antidepressants, barbiturates, chloral hydrate, and alternative and herbal therapies is discouraged.

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Table 4. Dosing Recommendations for Hypnotic Medications[6,63,64]

	Patient Age <65		Patient Age ≥65		Hepatic Insufficiency	
Medication	**Starting Dose (mg)**	**Max. Dose (mg)**	**Starting Dose (mg)**	**Max. Dose (mg)**	**Starting Dose (mg)**	**Max. Dose (mg)**
Lorazepam	0.5–1	4	0.25–0.5	1	0.25–0.5	1
Temazepam	15	30	7.5	15	7.5	15
Trazodone	50	300	25–50	100	25–50	100
Zaleplon	5–10	20	5	10	5	5
Zolpidem	5–10	10	5	5	5	5

Max = maximum.

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EXTRACTO

OBJETIVO: Prover recomendaciones para el manejo a corto plazo de insomnio en pacientes hospitalizados. La evaluación de pacientes, modalidades de tratamiento no farmacológicas, y la selección de medicamentos hipnóticos serán revisadas.

FUENTES DE INFORMACIÓN: Artículos de revisión y literatura primaria representativa del conocimiento actual con relación al tratamiento de insomnio fueron identificados a través de una búsqueda en MEDLINE. Términos utilizados en la búsqueda incluyeron insomnio (desórdenes del comienzo y mantenimiento del sueño), benzodiazepinas, zaleplon, zolpidem, y trazodona.

SÍNTESIS: La literatura con relación al manejo de insomnio en pacientes hospitalizados es limitada, por lo tanto, datos pertinentes al tratamiento de pacientes ambulatorios deben ser extrapolados al escenario de hospitalización. Al evaluar insomnio en pacientes hospitalizados, parece razonable obtener un historial y examen físico cuidadoso y completo para identificar potenciales etiologías fundamentales. El tratamiento de easts etiologías fundamentales debe ser considerado. Cuando el uso de un agente sedante-hipnótico es necesario, la selección del medicamento y la dosis deben estar basados en los perfiles farmacocinéticos y de efectos adversos de cada agente. Las características específicas de cada paciente también deben ser consideradas para poder proveer un tratamiento efectivo, minimizando los efectos adversos.

CONCLUSIONES: Los enfoques no farmacológicos para el tratamiento de insomnio deben ser considerados en los pacientes hospitalizados. Cuando se requiere administrar medicamentos sedantes-hipnóticos, el perfil farmacocinético de las benzodiazepinas de acción intermedia (e.g., lorazepam, temazepam) las hace agentes de primera selección. Zaleplon y zolpidem también son agentes hipnóticos atractivos, sin embargo, típicamente son reservados como terapia de segunda selección debido al costo. Trazodona podría ser una alternativa para pacientes que no pueden tomar benzodiazepinas.

Brenda R Morand

RÉSUMÉ

OBJECTIF: Émettre des recommandations pour le traitement de courte durée de l'insomnie des patients hospitalisés. Les modalités non-pharmacologiques et la sélection des agents sédatifs ou hypnotiques seront revues.

SOURCES DE LA LITTÉRATURE: Recherche bibliographique dans la banque de données MEDLINE ayant utilisé les mots-clés suivants: insomnie, benzodiazépines, zaleplon, zolpidem, et trazodone.

RÉSUMÉ: La documentation scientifique sur le traitement de l'insomnie des patients hospitalisés est limitée. Dans un tel contexte, l'approche suggérée par les auteurs est donc d'extrapoler les données recueillies chez les patients ambulatoires aux patients hospitalisés. Lors de l'évaluation de l'insomnie chez un patient hospitalisé, une histoire médicale et un examen physique complets sont nécessaires afin d'identifier une étiologie possible sous-jacente. Lorsque les méthodes non-pharmacologiques ne parviennent pas à maîtriser l'insomnie, l'ajout d'un agent sédatif ou hypnotique peut être requis. Le choix de la médication ainsi que sa dose doivent être basé sur la pharmacocinétique et le profil d'innocuité de chaque agent tout en considérant les caractéristiques spécifiques de l'insomnie du patient.

CONCLUSIONS: Les modalités non-pharmacologiques demeurent l'approche privilégiée pour le traitement de l'insomnie et ce, même en milieu hospitalier. Par contre, lorsqu'un agent sédatif ou hypnotique doit être prescrit, le profil pharmacocinétique des benzodiazépines ayant une action intermédiaire tels que le lorazépam et la témazépam en fait des agents de choix. Le zaleplon et le zolpidem sont aussi des agents hypnotiques intéressants mais devraient être réservés comme un traitement de deuxième intention, principalement dû à leur coût élevé. La trazodone demeure une bonne alternative pour les patients intolérants aux benzodiazépines.

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