Sleep in Hospitalized Medical Patients, Part 2: Behavioral and Pharmacological Management of Sleep Disturbances

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BACKGROUND: As described in Part 1 of this article, multiple factors lead to disrupted sleep in hospitalized medical patients. Recognizing and addressing these factors can help clinicians more effectively manage patients’ sleep complaints.

METHODS: A PubMed search was conducted by cross-referencing the terms “sleep deprivation,” “insomnia,” and “sleep”; “hospitalized,” “acutely ill,” and “critically ill”; and “medication,” “drugs,” “hypnotics,” “benzodiazepines,” and “sedatives.” The search was limited to English-language articles published between 1997 and 2008. Subsequent PubMed searches were performed to clarify the data described in the initial search.

RESULTS: Few articles addressed the topic of the assessment and management of sleep problems in hospitalized medical patients. In Part 2, we propose an evaluation and treatment algorithm that includes recommendations regarding the use of nonpharmacologic and pharmacologic therapies as clinicians consider relevant clinical data. The algorithm is accompanied by 5 tables that include pertinent and practical information to assist clinicians as they manage their inpatients’ sleep complaints.

CONCLUSIONS: Assessment of a sleep complaint should include a review of factors that could exacerbate patients’ sleep. The treatment could then focus on ameliorating these factors, and the judicious use of nonpharmacologic strategies and psychopharmacologic agents. Journal of Hospital Medicine 2009;4:50–59. © 2009 Society of Hospital Medicine.

KEYWORDS: acute illness, assessment, hospitalized medical patient, insomnia, treatment.

In Part 1, we reviewed normal sleep architecture, and discussed the numerous factors that often disrupt the sleep of hospitalized medical patients. Effective management of sleep complaints among acutely ill patients includes a thorough assessment of medical and psychiatric conditions, medications and other psychosocial factors that may be directly or indirectly impairing sleep. In Part 2, we review and introduce an algorithm for assessing and managing sleep complaints in acutely ill hospitalized patients.

ASSessment AND EVALUATION OF SLEEP COMPLAINTS

Assessment and evaluation of a sleep complaint begins with (Figure 1) an initial review of the medical record for documentation of the signs and symptoms of an underlying primary sleep disorder, which may be exacerbated during an acute medical
illness. Common sleep disorders that are often overlooked include obstructive sleep apnea (OSA), restless leg syndrome (RLS), and periodic limb movement disorder (PLMD). Predisposing factors, characteristic clinical features, and differential diagnoses of these disorders are described in Table 1. Obtain a focused history by using questions listed in Table 2 to characterize the onset, duration, frequency, and specific characteristics of the patient's current sleep patterns. Next, establish whether the onset of the patient's sleep complaint began with the time of hospitalization. Subsequent
questions can then focus on factors that may be impairing sleep such as the hospital environment and sleep hygiene behaviors by comparing the patient’s home sleep habits with those during hospitalization. Inquire about the use or abuse of substances such as sedatives, antidepressants, sedatives, antiepileptic drugs (AEDs), and opioids. Ask questions about the presence of pain syndromes and other comorbidities that often impact sleep.
MANAGEMENT OF SLEEP COMPLAINTS

Management of sleep disturbance is multifactorial and consists of nonpharmacologic as well as pharmacologic therapies. A stepwise approach is suggested and begins with nonpharmacologic strategies.

Nonpharmacologic Interventions
Before using sedative/hypnotic agents, address sleep hygiene and other factors that disrupt sleep during a hospitalization such as those listed in Table 3.

Pharmacologic (Sedative/Hypnotic) Interventions
Pharmacologic therapy may be necessary to treat disordered sleep. The ideal sleep aid would reduce sleep latency or time to fall asleep, increase total sleep time (TST), not cause next-day sedation, improve daytime functioning, and minimize the development of tolerance. Unfortunately, no single agent meets all these independent criteria. In the past 10 years, newer benzodiazepines (BzRAs) with shorter half-lives have been shown to be efficacious in reducing sleep latency, but the problem of sleep maintenance without next-day sedation persists. To choose an appropriate sleep agent, evaluate the drug's efficacy, mechanism of action, and side-effect profile. Then, match these characteristics with the patient's clinical condition(s). In patients with comorbid sleep and psychiatric problems, consider using a sedating psychotropic at bedtime to promote sleep.

Non-Food and Drug Administration–Approved (“Off-Label”) Sleep Aids: Psychotropic Medications
Limited data exist on the efficacy of non-Food and Drug Administration (FDA)–approved medications for insomnia, such as antidepressants and atypical antipsychotics (AAPs), and antihistamines; examples of which are listed in Table 4. The administration of antihistamines, barbiturates,
Chloral hydrate, and alternative/herbal therapies has been discouraged, because the benefits rarely outweigh the risks associated with their use. Currently, trazodone is the most commonly prescribed antidepressant for the treatment of insomnia, despite the relative lack of data regarding its use for insomnia.\(^3\) Prescription data suggest that trazodone—at “hypnotic” doses, which are lower than the full “antidepressant” dose—is more commonly prescribed for insomnia rather than for its FDA-approved use for depression.\(^4\) In general, sleep specialists refrain from recommending sedating antidepressants for primary insomnia due to insufficient data regarding efficacy and safety. In addition, trazodone has been associated with arrhythmias in patients with preexisting cardiac conduction system disease. Curry et al.\(^3\) speculated that trazodone is popular among prescribers because, unlike most BzRAs, trazodone does not have a recommended limited duration of use and is perceived as being “safer” than BzRAs. Walsh et al.\(^5\) conducted a randomized double-blind, placebo-controlled trial (n = 589) that compared the hypnotic efficacy and other sleep-associated variables of trazodone (50 mg) and zolpidem (10 mg). During the first week of treatment, the subjects on trazodone or zolpidem decreased their time to fall asleep, or sleep latency, by 22% and 35%, respectively, compared to placebo. Sleep latency was significantly shorter on

### TABLE 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pertinent Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>Somnolence, ↑ appetite, ↑ weight, dry mouth</td>
<td>May be beneficial for comorbid depression and insomnia. Lower doses (&lt;15 mg) increase sedation.</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Residual daytime sedation, headache, orthostatic hypotension, priapism, cardiac arrhythmias</td>
<td>May be beneficial for comorbid depression and insomnia. Not recommended as first-line agent for insomnia. May be an alternative if BzRAs are contraindicated (severe hypercapnia or hypoxemia or history of substance abuse). Tolerance usually develops within 2 weeks. Lower doses (50–100 mg) than when used for depression (~400 mg).</td>
</tr>
<tr>
<td>TCAs</td>
<td>Delirium, ↓ cognition, ↓ seizure threshold, orthostatic hypotension, tachycardia, acquired prolonged QT syndrome, heart block, acute hepatitis</td>
<td></td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl)</td>
<td>Residual daytime sedation, delirium, orthostatic hypotension, ↓ psychomotor function, prolonged QT syndrome, blurred vision, urinary retention</td>
<td>Better than placebo to treat insomnia,(^12) but data is lacking to definitively endorse diphenhydramine for insomnia.(^13) Tolerance to antihistamines develops within a few days. Avoid in patients &gt;60 years old.(^14)</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Drowsiness, dry mouth, dizziness, agitation, ↓ cognitive function</td>
<td>Efficacy as anxiolytic for &gt;4 months use not established. Not FDA-approved for insomnia. Avoid in patients &gt;60 years old, closed-angle glaucoma, prostatic hypertrophy, severe asthma, and COPD.</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Sedation, orthostatic hypotension, hyperglycemia, ↑ appetite, ↑ weight, hyperlipidemia</td>
<td>The most sedating of the atypical antipsychotics, it is frequently used as a sleep aid. Not recommended for insomnia or other sleep problems unless there is a comorbid psychiatric disorder. Dosed lower (25–100 mg) when used for insomnia versus for FDA-approved indications (~600 mg).</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Sedation, hyperglycemia, ↑ appetite, ↑ weight, hyperlipidemia</td>
<td>Of atypical antipsychotics, olanzapine is the most likely to cause metabolic complications. Should not be used solely for insomnia.</td>
</tr>
<tr>
<td><strong>Barbiturates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Oversedation, respiratory depression, nausea, vomiting, diarrhea, drowsiness, ↓ cognitive function, psychotic symptoms (paranoia, hallucinations), vertigo, dizziness, headache</td>
<td>Chloral hydrate has been used for the short-term (&lt;2 weeks) treatment of insomnia, but is currently not FDA-approved for that indication. Additive CNS depression may occur if given with other sedative-hypnotics. Caution in patients with severe cardiac disease. Contraindicated in marked hepatic or renal impairment. Highly lethal in overdose, and should be avoided in patients with risk of suicide.</td>
</tr>
</tbody>
</table>

**Abbreviations**: ↓, decrease; ↑, increase; COPD, chronic obstructive pulmonary disease; TCAs, tricyclic and tetracyclic antidepressants (trimipramine, doxepin, amitriptyline, imipramine, nortriptyline, desipramine).
With chronic use of AAPs, the risks of hyperglycemia, hyperlipidemia, and weight gain outweigh the potential sleep benefits of these agents. AAPs, especially risperidone, may cause extrapyramidal syndrome (EPS). Risperidone, ziprasidone and quetiapine have been associated with prolonged QTc interval, but the relatively low doses of AAPs that are used purely for sedative purposes makes this risk relatively low. If a patient has a history of Parkinsonism or other EPS, risperidone should generally be avoided. If a patient treated with risperidone develops EPS, another AAP should be considered. A reasonable precaution is to obtain a pretreatment 12-lead electrocardiogram. If the QTc is greater than 450 msec, consider using olanzapine rather than ziprasidone, risperidone, or quetiapine. Sedating AAPs include risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel), with the latter 2 being especially sedating. Quetiapine may also cause orthostatic hypotension. The recent practice of using AAPs for delirium has not been reported to be associated with significant safety risks, probably because delirium treatment is typically of short duration under a period of close clinical observation. These agents should not be used indefinitely for insomnia without close monitoring of metabolic, psychiatric, and neurologic status. However, recent data suggest that the risk of serious adverse effects of AAPs may outweigh the potential benefits for the treatment of aggression or agitation in patients with Alzheimer’s disease.

A meta-analysis of randomized placebo-controlled trials of AAP use among dementia patients showed that overall, the use of AAP drugs for periods of less than 8 to 12 weeks was associated with a small increased risk for death compared with placebo. Data indicated that most patients’ behaviors improved substantially during the first 1 to 4 weeks of treatment. In a double-blind, placebo-controlled trial, 421 patients with Alzheimer’s disease and psychosis, aggression or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo. A lower, but significant, proportion of the patients (24%, 16%, 18%, and 5%, respectively) discontinued these medications due to intolerable side effects. Thus, if...
minimal improvement is observed even after 8 weeks of treatment, prescribers should consider discontinuing the AAP. The management of agitation in dementia, particularly in the elderly, calls for an integrative and creative psychopharmacological approach, including the use of antidepressants, nonbenzodiazepine anxiolytics such as buspirone, and mood stabilizers such as divalproex sodium (Depakote) before exposing patients to the risks of AAPs.

Antihistamines are the most commonly used over-the-counter agents for chronic insomnia. Diphenhydramine (Benadryl) has been shown to be better than placebo to treat insomnia, but data is lacking to definitively endorse its use to promote sleep. Diphenhydramine is also limited by the development of tolerance within a few days of daily use. The anticholinergic action of antihistamines may lead to orthostatic hypotension, urinary retention, and may induce delirium in vulnerable patients. Therefore, diphenhydramine should be avoided in hospitalized patients.

Recent data suggest that hydroxyzine, an antihistamine, may be an appropriate sleep aid for patients with hepatic encephalopathy in whom BzRAs are contraindicated. Subjective improvement in sleep was observed in 40% of hydroxyzine-treated patients with hepatic encephalopathy compared to placebo.

Chloral hydrate is one of the Western world’s oldest known sedative-hypnotics and was commonly used as a sleep aid through the 1970s. Chloral hydrate was eventually supplanted by BzRAs, and fell out of favor as a sleep aid due to its relatively high tolerance rate, drug-drug interaction profile, and the high risk of death in an overdose. Doses of 500 to 1000 mg sufficed to promote sleep in most of the hospitalized subjects. More recent data regarding its use for treating insomnia are not available, but chloral hydrate may be an alternative short-term treatment for insomnia in selected hospitalized patients. Because of its high-risk profile, chloral hydrate would be used as a last-resort medication, preferably with input from critical care and/or sleep medicine specialists.

FDA-Approved Sleep Aids

As shown in Table 5, the FDA has approved 5 classes of medications for the treatment of insomnia: benzodiazepine gamma-aminobutyric acid (GABA)\textsubscript{A} receptor agonists (BzRAs), nonbenzodiazepine GABA\textsubscript{A} receptor agonists (non-BzRAs), and melatonin-receptor agonists. BzRAs include estazolam (ProSom), flurazepam (Dalmene), quazepam (Doral), temazepam (Restoril), and triazolam (Halcion). Though BzRAs decrease sleep latency, increase TST, and decrease slow wave or deep sleep, they also have adverse side effects such as daytime sedation, anterograde amnesia, cognitive impairment, motor incoordination, dependence, tolerance, and rebound insomnia. Because of these side effects, BzRAs should be limited to generally healthy, young (ie, <45 years old) patients who are expected to have brief hospital stays.

Efficacy and safety studies have generally been limited to healthy, younger individuals without a history of primary sleep disorder. Potential adverse effects of BzRAs may become even more pronounced in hospitalized medical patients due to older age, acute illness, cointeraction drugs, and multidrug regimens. Although BzRAs are FDA-approved for the treatment of insomnia, flurazepam and quazepam should generally be avoided in hospitalized patients. These agents’ long half-lives increase the risk of drug-drug interactions and adverse events such as respiratory depression, cognitive decline, and delirium in acutely ill patients. For similar reasons, other long-acting BzRAs such as clonazepam (Klonopin) and diazepam (Valium) should also not be used to treat insomnia in hospitalized patients. An exception to this is a patient with RLS, in which clonazepam is an approved treatment. However, now that ropinirole HCl (Requip) is FDA-approved for RLS, BzARs may be able to be avoided. Lorazepam (Ativan), due to its relatively short half-life and its anxiolytic property, is frequently used to treat insomnia in hospitalized medical patients. Start with the lowest dose possible (eg, 0.5 mg) as a one-time-only order, or on a “as needed” basis for \(\leq 3\) days. Alprazolam (Xanax), a potent, fast-acting BzRA with a relatively short half-life, has developed a reputation as being notoriously addictive, and experts feel alprazolam has similar potential for withdrawal and rebound.

The use of BzRAs should be minimized in all patients, and avoided in the elderly or those with a particularly high risk for delirium (eg, traumatic brain injury, stroke, multiple new medications). All BzRAs should be avoided in patients with a prior history of sedative-hypnotic and/or alcohol dependence unless medically indicated, such as in
alcohol withdrawal. Refrain from ordering nightly scheduled BzRAs without a specific time limit to ensure that sedative-hypnotic use is closely monitored.

For the past 2 decades, physicians have been advised against using long-acting BzRAs in the elderly (>65 years old) due to the increased risks of hip fractures, falls, motor vehicle accidents, daytime sedation, and adverse cognitive events such as delirium. A large 5-year prospective study in Quebec found that the risk of injury varied by the BzRA, and was independent of half-life. Importantly, the risk of injury was dose-dependent: the higher the dose of oxazepam, flurazepam, or chlordiazepoxide, the higher the risk of injury in the elderly.

Non-BzRAs seem to have a superior side-effect profile when compared to BzRAs, but should also be used with caution in the elderly. Non-BzRAs include eszopiclone (Lunesta), zaleplon (Sonata), zolpidem (Ambien), and zolpidem extended-release. The number of comparison studies is limited, but the available data reveal that: (1) zolpidem (Ambien) may be better than temazepam (Restoril) in terms of sleep latency and quality; and (2) zaleplon (Sonata) may lead to a shorter sleep latency than zolpidem (Ambien), but the latter is associated with longer sleep duration.

TABLE 5
Food and Drug Administration–Approved Drugs for Insomnia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Adult Dose (mg)</th>
<th>Half-Life (hours)*</th>
<th>Onset (minutes)</th>
<th>Peak Effect (hours)</th>
<th>Major Effects/Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BzRAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam (Prosom)</td>
<td>1–2</td>
<td>10–24</td>
<td>60</td>
<td>0.5–1.5</td>
<td>Caution in elderly patients. Tolerance to BzRAs develop to the sedative, hypnotic, and anticonvulsant effects.</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>15–30</td>
<td>47–100</td>
<td>15–20</td>
<td>3–6</td>
<td>Short-term (7–10 days) treatment for frequent arousals, early morning awakening. Not as useful for sleep onset. Avoid in patients with OSA. Caution in elderly patients, liver disease. High doses can cause respiratory depression.</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>7.5–15</td>
<td>25–114</td>
<td>1.5</td>
<td></td>
<td>In general, avoid in hospitalized medical patients, especially elderly patients.</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>15–30</td>
<td>6–16</td>
<td>2–3</td>
<td></td>
<td>In general, avoid in hospitalized medical patients, especially elderly patients.</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>0.125–0.25</td>
<td>1.5–5.5</td>
<td>15–30</td>
<td>1.7–5</td>
<td>Short-term (7–10 days) treatment. Maximum dose is 0.5 mg.</td>
</tr>
<tr>
<td>Non-BzRAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>2–3</td>
<td>6–9</td>
<td>1</td>
<td></td>
<td>In elderly: difficulty falling asleep, then initial: 1 mg; maximum 2 mg. Difficulty staying asleep: 2 mg. Rapid onset; should be in bed when taking medication. For faster sleep onset, do not ingest with high-fat foods. No tolerance after 6 months.</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>5–20</td>
<td>1</td>
<td>Rapid</td>
<td>1</td>
<td>Short-term (7–10 days) treatment for falling asleep and/or next-day wakefulness is crucial (eg, shift workers).</td>
</tr>
<tr>
<td>Zopiclone (Imovane)</td>
<td>5–15</td>
<td>3.8–6.5 (5–10 in elderly)</td>
<td>30</td>
<td>&lt;2</td>
<td>Transient and short-term (7–10 days) treatment.</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>5–20</td>
<td>1.4–4.5</td>
<td>30</td>
<td>2</td>
<td>Short-term (7–10 days) treatment for sleep onset and maintenance. Rapid onset; should be in bed when taking medication. For faster sleep onset, do not ingest with food. No tolerance after 50 weeks.</td>
</tr>
<tr>
<td>Melatonin agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelton (Rozerem)</td>
<td>8</td>
<td>1–2</td>
<td>30</td>
<td>1–1.5</td>
<td>For sleep onset. For faster sleep onset, do not ingest with high-fat foods. No tolerance. Caution in severe respiratory impairment.</td>
</tr>
</tbody>
</table>

Abbreviations: ↑, increase; ↓, decrease; BzRAs, benzodiazepines; Non-BzRAs, non-benzodiazepines; OSA, obstructive sleep apnea; SWS, slow wave sleep; T½, half-life of TST; TST, total sleep time.
Non-BzRAs have less next-day sedation, psychomotor dysfunction, tolerance/withdrawal, and rapid-eye-movement (REM) sleep rebound; and lower abuse potential than BzRAs.27

The most commonly prescribed hypnotic, zolpidem has a short half-life, and seems to reduce sleep latency with minimal residual side effects when compared to BzRAs. The results of a recent multicenter, randomized, double-blind, placebo-controlled trial indicated that zolpidem extended-release may be efficacious for up to 6 months in outpatients with chronic insomnia.28

The sole melatonin-receptor agonist, ramelteon (Rozerem), also reduces time to fall asleep without next-day psychomotor and memory effects.29 Ramelteon is believed to target receptors melatonin 1 and 2 receptors located in the brain’s suprachiasmatic nucleus to stabilize circadian rhythms and stabilize the sleep-wake cycle.30

CONCLUSION
Hospitalization is often associated with disrupted sleep, which can affect recovery from illness. Understanding the major factors that impair sleep during hospitalization allows clinicians to systemically evaluate and treat sleep problems. More than just prescribing a sedative/hypnotic, the treatment for sleep disruption includes addressing sleep hygiene and hospital environment issues, identifying medications that could disrupt sleep, and treating specific syndromes that impair sleep. We suggest a practical algorithm to guide clinical assessment, treatment options, and selection of appropriate sleep medications. Critical to optimizing recovery from illness, sleep may be considered “the sixth vital sign,” and should be part of the routine evaluation of every hospitalized patient.

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