Managing Sleepiness After Traumatic Brain Injury

CASE SCENARIO

Sleepiness is common in patients who have sustained traumatic brain injuries (TBI). Pharmacologic intervention may be required to help address sleepiness, because problems with sleep regulation have been described in this population. But it is not always appropriate to address sleepiness by initiating such medications, because there are many reasons why a patient may exhibit sleepiness after TBI. In addition, medications commonly used to help with sleep may not necessarily be benign or have the desired outcome. There are no clear guidelines that help clinicians determine when it is appropriate to start medications to enhance sleep. This case scenario and the following point/counterpoint discussion addresses this common problem.

A 48-year-old man has been on an inpatient TBI unit for 2 days. He was injured 7 days before his rehabilitation admission as a result of a head-on motor vehicle collision. He was an unrestrained driver and sustained right temporal and bifrontal contusions. The initial Glasgow Coma Scale score was 11. Neurosurgical intervention was not required. He received a 7-day course of phenytoin for seizure prophylaxis. In addition to his TBI, he sustained a left fibula fracture that was treated without surgery. On admission, he was moderately obese and in no acute distress. He was sleepy but arousable, was able to answer simple biographical questions, and was oriented to self only. Posttraumatic amnesia has persisted. He is impulsive and demonstrates little insight regarding his deficits. He also had poor balance, so he has required 1:1 supervision throughout the day and night since admission. His medical history is positive for hypertension. Current medications include subcutaneous heparin for deep vein thrombosis prophylaxis, metoclopramide, famotidine, and metoprolol, as well as acetaminophen for mild pain and oxycodone for moderate-to-severe pain as needed. Admission laboratory studies included complete blood cell count and electrolytes, both within normal limits. The rehabilitation team is reporting that he has difficulty staying awake during the day and that this is hampering his ability to benefit from therapy. He also states that he is having trouble sleeping. The team is asking that you start a medication to help with sleep. What is your decision?

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Brian Greenwald, MD, Responds

Arousal impairment, fatigue, and sleep disorders are all common problems after traumatic brain injury (TBI). Arousal impairments vary from coma to difficulty maintaining consistent wakefulness. The presence of sleep impairment early after TBI may be as high as 70% [1]. In a study of patients with mild-to-moderate TBI, 57% of patients had fatigue at 1 month after injury [2].

Makley et al [3], in a rehabilitation unit, evaluated the prevalence of sleep disturbance in patients with closed head injury. The nurses observed the patients overnight. The patients were considered to have disrupted nighttime sleep if they had at least 3 individual hours or 2 consecutive hours rated as awake. Sixty-eight percent of patients had aberrations of nighttime sleep. No significant differences were seen in the Glasgow Coma Scale score or age of the affected and unaffected groups. The patients with disturbed sleep had significantly longer stays in the trauma center and rehabilitation center.

Before considering any medication for arousal, whether it be to improve sleep at night or a stimulant during the day, a

PM&R
1934-1482/11/$36.00
Printed in U.S.A.

Vol. 3, 480-485, May 2011
DOI: 10.1016/j.pmrj.2011.04.010

review of current medications is critical. There are many commonly used medications that have the adverse effect of drowsiness, including anticonvulsants, antidepressants, antihistamines, and antihypertensives. In this case, metoclopramide is well known to cause sleepiness. Its primary action is through dopamine blockade and is indicated as an antiemetic. Use of this medication scheduled throughout the 24-hour day can worsen drowsiness.

Opioids, for example, oxycodone, should be use cautiously because they can cause drowsiness and confusion. Using opioids on an "as needed" basis also can be problematic in this confused patient who may unknowingly demonstrate agitation as a way of expressing pain. Painful conditions that commonly occur after TBI include headaches, pressure sores, constipation, fractures, and other musculoskeletal injuries. For fracture-related pain, standing doses of nonsteroidal anti-inflammatory medications and/or acetaminophen can be considered, with close monitoring of pain levels and behaviors.

Medical comorbidities also need to be explored as possible causes of insomnia. Endocrine, cardiac, pulmonary, and neurologic (ie, seizures) conditions are all common comorbidities and should not be overlooked as possible causes of insomnia. Pharmacologic treatments used ostensibly to improve sleep will effectively sedate the patient but without addressing these medical comorbidities.

In contrast to the medications that can cause daytime sleepiness, there are a host of medications commonly used in the acute rehabilitation setting that can cause impaired sleep. Common examples include neurostimulants (eg, methylphenidate, modafinil, amantadine), and β-2 agonists (eg, albuterol). A working knowledge of the pharmacokinetics of these medications is necessary. Understanding the half-life of these medications will help determine how close to bedtime they can be used.

The environment also is a key consideration in ensuring a good night's sleep for our patient whether in the rehabilitation unit or the home setting. In the rehabilitation unit, the sleep habits, medical needs, and noise created by a roommate are a common problem. The need to take vital signs and administer tube feedings or medications at night also should be evaluated. These potentially modifiable environmental problems should not typically be the rationale to sedate a patient with medications.

Rao et al [4] evaluated the prevalence of sleep disturbances in patients within 3 months of having a TBI. The subjects also were assessed for anxiety, depression, medical comorbidity, and severity of TBI. New onset anxiety disorder with generalized anxiety features that developed for the first time after the TBI was the most-consistent correlate of sleep disturbance. Mood disorder with a major depressive-like episode that developed for the first time after TBI also appeared to be related to sleep problems, but the relationship was not as consistent. Severity of TBI was not a significant risk factor for sleep disturbance. This study underscored the importance of the evaluation of psychiatric disturbance in persons with sleep disturbance after TBI.

After careful consideration of possible causes of daytime sleepiness, if a sleep disorder is considered the primary or most likely cause, careful consideration needs to be given to determine the best course of treatment. In the patient population of chronic TBIs, approximately 46% of patients with TBI have a sleep disorder that requires nocturnal polysomnography and mean sleep latency testing to determine a diagnosis. These disorders include sleep apnea, posttraumatic hypersomnia, narcolepsy, and periodic limb movements [5]. Sedative medications are not effective in treating these disorders and, in some cases, can exacerbate the problem.

Webster et al [6] evaluated subjects admitted to an inpatient rehabilitation unit who were less than 3 months after injury with a Ranchos Los Amigos Scale level of 3 or higher. This study evaluated the frequency and nature of sleep-related breathing disorders in adults with TBI. All the subjects had overnight sleep studies. Evidence of sleep apnea was found in 36% of the subjects. Sleep-related breathing disorders were primarily central, although obstructive sleep apneas (OSA) also were noted. No correlation was found between the occurrence of significant sleep apnea and measurements of TBI severity or other demographic variables. Wilde et al [7] evaluated neuropsychological test performances of patients with TBI and with OSA compared with those who did not have OSA. The diagnosis of OSA was based on standard criteria by using nocturnal polysomnography. OSA was associated with more impairment of sustained attention and memory in patients with TBI. Wilde et al [7] hypothesized that early identification and treatment of OSA may improve cognitive, and thus potentially functional, outcomes of patients with TBI. Again, medications commonly used to improve sleep are not appropriate for this sleep disorder.

Castriotta et al [8] evaluated the effectiveness of treating sleep disorders in adults who were more than 3 months after TBI. These treatments include continuous positive airway pressure used for OSA, modafinil for narcolepsy and posttraumatic hypersomnia, and pramipexole for periodic leg movements during sleep. Polysomnography and measurements of neuropsychologic function were used to determine efficacy. Despite resolution of polysomnographic changes in each of these disorders with appropriate treatments, sleepiness and neuropsychologic function did not improve.

Prescription of medications to treat insomnia acutely after TBI is a common practice. Yet, there are no standards of care or widely accepted guidelines regarding the use of medication for this problem. The literature base to establish the efficacy and safety of medications that are used to assist with sleep is nearly nonexistent. Furthermore, individuals with TBI may be more sensitive to these medications than other non-brain injured

populations due to changes in brain chemistry and alterations in blood-brain barrier permeability [9,10].

Pharmacologic treatment of insomnia after TBI often includes medications that are known to have adverse effects. Goldstein [11] found that 72% of patients were prescribed medications that could interfere with recovery. Mysiw at el [12] found that 67% of patients with TBI in an inpatient rehabilitation unit were receiving benzodiazepines. The paradoxical effect of agitation with the use of benzodiazepines has been well described. Animal studies reported that benzodiazepines might slow or decrease recovery [13]. This class of primarily long-acting medications can result in decreased coordination, sedation, impairment of memory, and consequently, increased prevalence of falls [14].

The "z-drugs" (ie, zopiclone, zaleplon, and zolpidem) are more selective than the benzodiazepines for the γ-aminobutyric acid ($GABA_A$) receptor 1 subtype and, therefore, are believed to have fewer adverse effects. The half-life of these drugs also is shorter than most of the benzodiazepines, which decreases the risk of a "hangover" the next day. These medications are active in the first hours after administration, therefore, adverse effects on memory and coordination can be expected, and, if a patient is awoken while the agent is still active, then unintended behaviors and risk of fall can be seen. The research on the short- and long-term effects of this class of commonly prescribed sleep agents has primarily been performed in the non-brain injured population and should be used cautiously in patients with TBI.

Trazodone is an antidepressant that is commonly used in an off-label fashion for the treatment of insomnia. Reviews of clinical practice report that it is among the most commonly used medications for insomnia for patients with TBI [15]. Despite its popularity, there are few clinical trials that support the effectiveness of trazodone as a sleep medication in the non-TBI population. More pertinently, there are no clinical trials of trazodone that evaluated the effectiveness of trazodone for the treatment of insomnia or potential cognitive adverse effects in patients with TBI.

Optimal treatment of daytime sleepiness and sleep impairment after TBI first requires a comprehensive review of comorbidities, environment, and current treatments. It is important to recognize the large group of patients who, soon after TBI, have sleep disorders that require evaluation with polysomnography and who should not be treated with sedatives. When making the decision to start a medication to treat insomnia, careful consideration must be taken to limit possible short- and long-term negative consequences to recovery. Indiscriminately starting a medication to sedate this patient at night may please the staff but may pose a risk for this patient. It is simply inappropriate to give a medication when we do not know what we are treating.

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Lisa A. Lombard, MD, Responds

This case scenario presents an all too common scenario seen in the rehabilitation of persons with traumatic brain injury (TBI). In a study of 31 consecutive admissions to a brain injury rehabilitation unit, 21 patients had sleep aberrations. Those patients with sleep disturbance were found to have longer lengths of stay both in acute care as well as in inpatient rehabilitation [1].

Many acute care factors, such as pain issues, ambient noise, drug withdrawal, and disturbed day-night cycles from the intensive care unit stay, can contribute to the sleep

disturbance. One could argue that merely treating external causes will result in full treatment of the sleep disturbance. However, it seems that this population continues to have severe sleep disturbance even long after rehabilitation; a report by Cohen et al [2] noted that 51.9% of persons with TBI 2-3 years after their injury had disturbed sleep. This study also noted that the variety of sleep disorders changed over time as well; patients with acutely injured TBI more frequently had disorders in initiating and maintaining sleep, whereas, those with chronic injuries were more commonly mentioning disorders of excessive somnolence.

Anyone who has been a medical intern or a new parent has experienced the fatigue, poor short-term memory, and impaired attention that sleep deprivation can cause. In persons with brain injury, these affects can be amplified. In a study of 87 outpatients with TBI, sleep disturbance accounted for 14% of the variance in performance in cognitive measurements beyond that was accounted for by injury severity and gender [3]. Prolonged sleep deprivation and delirium share many similar characteristics, and one can accentuate the other [4]. This case in particular shows the ramifications of poor sleep and how it can adversely affect the patient's participation in rehabilitation.

In recent years, there has been increased awareness of endocrine abnormalities after TBI [5]. Many of the clinical manifestations associated with endocrine deficiencies mimic physical and cognitive deficits seen after TBI [6]. There also are well-known interactions between sleep and hormone secretion, which, if uncorrected, may result in similar deficits [7]. Pharmacologic interventions to improve sleep also have been shown to increase secretion of sleep cycle related hormones [8]. Similarly, metabolic function may be altered with sleep deficiencies, which compound problems that patients with TBI may already be experiencing [9].

Because physiatrists are under greater pressure from third-party payers to decrease acute rehabilitation lengths of stay, ensuring that patients have adequate sleep-cycle regulation early is essential to make the most gains during their limited inpatient time. In addition, because of this patient's impulsivity, he has a 1:1 nursing staff with him all shifts, which is a tremendous burden in finances and manpower for a nursing unit. If he is sleeping soundly throughout the night, then the night shift 1:1 staff could be eliminated and thus reduce the cost of his stay. If he continues to have issues with insomnia and nighttime impulsivity at the time of discharge, then this might prove to be too significant a burden of care for his family and may jeopardize his ability to be discharged to the community. Early aggressive treatment of this patient's sleep impairment will have a significantly positive impact on his rehabilitation stay as well as his discharge.

The patient has gone through a basic laboratory workup, which ensures that there are no metabolic causes for his sleep disturbance (eg, infection or severe hyponatremia). He also is on several medications, including metoclopramide, metoprolol, and oxycodone, that may cause daytime drowsiness. Minimizing these medications or changing to less-sedating alternatives, as one is able, will assist somewhat with his issues. However, I do not believe that these measures alone will fix the sleep disturbance. Given the severity of his sleep problems and its current impact on his ability to participate with therapies, it would be wise to consider pharmacologic treatment.

Before decisions are made regarding the initiation of a medication for sleep disturbance, it is important to try to identify the potential cause (if possible), the pattern of disturbance, and factors that might worsen the issue. Blindly choosing any of the following medications without these considerations might lead to a less than optimal result. In addition, having objective measurements of sleep, such as with an hourly sleep log performed by the nursing staff, also will help track patterns of sleep disturbance and effectiveness of treatment. Particular behaviors at night will dictate specific medications.

If the patient were aggressive and difficult to redirect at nighttime, then mood stabilizers, such as valproic acid, may be considered. Severe behavioral disturbance may lead clinicians to use atypical antipsychotics. However, given the potential slowing of neurorecovery with these agents, these agents should be used sparingly and as a bridge to other options. Restless leg syndrome can result in sleep deprivation and would best be treated with dopamine agonists.

Antihistamines, for example, diphenhydramine, are commonly used as over-the-counter sleeping agents in the general population. Because this class of medication has significant anticholinergic adverse effects, it should be avoided in persons with neurocognitive deficits. Benzodiazepines also are often used as first-line agents for insomnia in the community. These agents can cause memory loss (in fact, they often are used for conscious sedation during procedures), and, because this patient is emerging from posttraumatic amnesia, suppressing recall would be counterproductive. In addition, these agents are often associated with a "hangover" effect that might further impair this patient's wakefulness in therapies [10].

Sedative hypnotics act on the $GABA_A$ receptor 1 subtype and are thought to have fewer adverse effects than benzodiazepines [11]. Several options in this class, including zolpidem, have relatively short half-lives, which give the potential for less "hangover" effects than benzodiazepines [12]. As a result, this class might be effective in treating the disorders in initiating and maintaining sleep variety of sleep disturbance. However, this class of medications includes warnings related to hallucinations, decreased inhibition, and somnambulation, and in engaging in activities without later memory of the event(s) [13]; for this reason, I recommend that they be used with great caution in those patients still in posttraumatic amnesia.

Melatonin, as a naturally occurring hormone, can be an appealing choice because its adverse effects are significantly less than with other pharmaceutical treatments. It has been

shown to reduce sleep latency and increase sleep efficiency. In addition, it appears that melatonin levels in persons with severe TBI are suppressed, so it may be that this is one of the causes of sleep disorders in this population [14]. Ramelteon is a synthetic version of melatonin that is available and has been shown to decrease sleep latency, but it can take several days for maximum effect, which would be an unacceptably long onset of action in this circumstance. In my practice, I have only seen minimal results from synthetic melatonin.

In comparison with placebo, trazodone (a triazolopyridine antidepressant) has been shown to improve sleep latency and time asleep [15]. The effective dose for sleep regulation (50-150 mg) is far below its antidepressant dosage, therefore, lowering risks of adverse effects. It does not incur the anticholinergic adverse effects of tricyclic antidepressants. It remains one of my top choices of sleep medications for persons with TBI and disorders in initiating and maintaining sleep.

In summary, this patient is suffering from his lack of sleep regulation. Not addressing this issue aggressively with medications could jeopardize his health, cognition, and potentially his outcome in rehabilitation.

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Brian Greenwald, MD, Rebuts

Dr Lombard and I clearly agree on the frequency of the short- and long-term sleep problems that patients with TBI face. What surveys about the prevalence of sleep disorders miss is the potential for a sleep disorder that may not respond to sedatives. Much of the sleep research literature has found that sleep disorders such as sleep apnea and restless leg syndrome are very common after TBI. Use of sedatives in persons with one of these sleep disorders will not help and may even worsen the problem. Remember, we are not dealing with a normal brain in patients with TBI and that the experience of an "intern" is not equivalent to the structural and chemical changes that have occurred after brain injury that cause sleep disturbance and fatigue.

Castriotta [1] found that, even after effectively normalizing the polysomnographic changes, sleepiness and neuropsychologic function did not improve. Sedating the person overnight may not be the answer to improving fatigue or neuropsychologic function. Many of the sedatives commonly used have the potential of increasing sedation and worsening neuropsychologic function. I agree with Dr Lombard that sedating a patient overnight may decrease staffing costs but at what costs to the patient?

Although it is easy to reflexively order medications, starting with a differential diagnosis approach to the evaluation of sleep disorders and fatigue will give one the best outcome. Start by considering the environment. Is it conducive to the patient falling asleep? What can be done to create a conducive environment? Review the list of current medications. Is there something that this patient is taking that can impair his or her sleep quality and quantity? Is the patient on any sedatives that will impair his or her daytime arousal? It is so much better to decrease the number of medications that a patient is taking than to find excuses to add medications.

Soon after brain injury, there are many comorbidities that can cause sleep impairment. Pain from a wide variety of sources is very high on the list. Do not forget how often bone and nerve injuries are missed. Hydrocephalus, seizures, in-

fections, wounds, pulmonary disorders, cardiac disorders, and endocrine disorders all need to be considered and investigated [2]. Impaired sleep may just be a symptom of one of these disorders, not the primary problem. Furthermore, these conditions could lead to symptoms that appear to be related to impaired sleep but that are not.

If all the potential causes of insomnia are ruled out, then treatment can be considered. Cognitive behavioral therapy is becoming one of the leading treatments for insomnia in the general population. Acupuncture also has been studied in the TBI population and has been used effectively. Sedatives have a place in the treatment of insomnia after TBI. There is a dearth of literature to guide a practioner on the best agent to use. I agree with Dr Lombard that, in my experience, trazodone at low doses appears effective and safe, even though there is no evidence in the TBI literature to support its use.

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Lisa A. Lombard, MD, Rebuts

Dr Greenwald has done an excellent job describing the assessment and nonpharmacologic management of sleep in persons with TBI, however, he missed the big picture of this patient's care.

He lists factors that may cause or exacerbate sleep disorder from environmental disturbances to pain; on a practical basis, these factors could be assessed rather rapidly, and, although there might be factors that are contributing to the sleep problem, given the frequency of sleep issues in persons with TBI indicated by both of us, even after removing some of the extraneous factors, we will likely still be left with a patient who is not sleeping.

Dr Greenwald also mentioned anxiety correlating with sleep disturbance. The presence of one issue does not preclude the treatment of the other. As a matter of fact, one might be able to treat both problems; a recent article indicates that treatment of persons with major depression with agomelatine, a combination melatonergic receptor agonist and $5HT_{2C}$ receptor antagonist, can be very efficacious. The investigator cites an improvement in circadian rhythms as the possible mechanism of improvement [1]. Perhaps treating this patient's sleep disorder may help underlying symptoms of depression and/or anxiety.

Dr Greenwald describes OSA as a possible cause; although this condition does occur in persons with TBI, the full workup would require an extensive assessment in a sleep laboratory. The vast majority of rehabilitation inpatients do not have access to such tests. Even if OSA were diagnosed, trying to get a patient with TBI who is confused and restless to comply with a new continuous positive airway pressure mask would be an exercise in futility. As with any person with TBI, it is worthwhile to "start low and go slow" with the dosing of the sleeping agents to make sure that the breathing drive is not compromised in a person suspected of having OSA.

Finally, Dr Greenwald mentions the lack of standards of care for the pharmacologic treatment of TBI-related sleep disorders; unfortunately this is the case with many treatments we give our patients. Just because there is no "standard of care" for the treatment of severe disorders of consciousness, hyperadrenergic state, or posttraumatic agitation, does not mean that I will refuse to treat patients who come under my care with those issues.

It is still clear to me that judicious selection and dosing of a sleep aid will result in a comfortable well-rested patient, happier staff, and a more-effective inpatient rehabilitation stay.

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