Sleep Disturbances Following Traumatic Brain Injury

*Vani Rao, MD**
Pamela Rollings, MD

Address
*Department of Psychiatry and Behavioral Sciences,
The Neuropsychiatry and Memory Group Service of Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287, USA.
E-mail: vrao@mail.jhmi.edu

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Opinion statement

- Sleep disorders commonly complicate the course following traumatic brain injury (TBI).
- Insomnia, excessive daytime somnolence and alteration of the sleep-wake schedule are common disturbances that affect the course of recovery and prognosis in TBI survivors.
- Few studies, however, have looked at the diagnosis and management of these disturbances in TBI. Early treatment of sleep disorders must be considered an integral part of the rehabilitation process. Recognition and management of comorbid medical or surgical diseases, assessment and treatment of associated psychiatric disorders, and awareness of other psychosocial stressors are mandatory steps in the management of sleep disturbances following TBI. In addition to pharmacologic therapy, nonpharmacologic approaches such as diet, environmental modification, and behavioral interventions are essential components in the management of sleep disturbances in TBI.
- Based on the evidence that sleep disturbances impact rehabilitation in TBI patients we support the need for ongoing studies in this area.

Introduction

Sleep is a complex, vital, and active process whose functions are yet unclear [1•]. It is regulated by homeostatic (a process that determines the amount of prior sleeping and waking), circadian mechanisms (a process that organizes sleep and waking over 24 hours), and ultradian (a process within sleep that controls the two different sleep states). A number of centers located mainly in the brain stem control sleep. Serotonin and acetylcholine are the main neurotransmittors involved in sleep, although other hormones and endogenous products such as dopamine norepinephrine, and substances S and C also play important roles. Sleep consists of two distinct states that affect an individual's physiologic function and behavior. The two sleep states include rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. The reader is encouraged to read any standard textbook on sleep disorders for more information on normal sleep architecture. Roth and Roehrs [1•] have also eloquently described sleep organization and regulation in their review paper, which readers may find useful.

Traumatic brain injury is associated with a variety of neuropsychiatric sequelae [2]. Sleep disturbances are very common following TBI and range in frequency from 36% to 70% [3,4]. The impact of brain injury on the sleep-wake schedule can be primarily related to 1) the injury itself, 2) secondary to the neuropsychiatric conditions associated with TBI, and 3) the pharmacologic management of the injury or its consequences [5••]

Insomnia, hypersomnia, and disorders of sleep-wake schedule are common complaints following TBI. Patients with TBI complicated by sleep disturbances have more communicative and cognitive problems, mood and behavioral disturbances such as depression, anxiety, apathy, and aggression, and poor employment history [5••]. Sleep disturbances are increasingly recognized as having a major impact on the course of

recovery from TBI. However, despite the ubiquity of this problem, there is very little objective data on the prevalence, clinical features, types of sleep problems, relationship between sleep disorders and other psychiatric problems, and treatment of these conditions.

The authors of this paper will discuss the three commonly reported conditions—insomnia, hypersomnia, and sleep-wake schedule disturbance. An approach to management of each of these conditions will be briefly described under these sections, but will be described in greater detail under the Treatment section. Parasomnias (undesirable motor and behavioral events that occur during sleep) are probably present in TBI subjects, but systematic studies indicating their prevalence and clinical features are scarce

INSOMNIA

Insomnia may be defined as difficulty in initiating or maintaining sleep for at least 1 month, associated with daytime fatigue or impaired daytime functioning [6].

Cohen *et al.* [7] reported that immediately following TBI, early and middle insomnias are common complaints. In a study of 22 hospitalized patients who had sustained a TBI over the last 3 to 5 months, 81% complained of difficulty in falling asleep and maintaining sleep. Mann *et al.* [8], in a prospective study of 50 consecutive postacute TBI patients, diagnosed insomnia in 30% using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria. Some researchers have suggested that sleep disturbances in the acute phase may be secondary to the biologic effects of brain damage and environmental conditions, whereas in the chronic phase it is probably related to other psychiatric disease and psychosocial stressors [7]. Fichtenberg *et al.* [9••], in a study of 91 consecutive brain-injured patients admitted to an outpatient rehabilitation center, noted no association between insomnia and gender, education, age, and time since injury, but noted a positive correlation between insomnia and depression and history of mild brain injuries. The presence of pain has also been found to increase the rate of insomnia, approximately two-fold, with sleep maintenance difficulty being the most common complaint [10]. However, other researchers have not found the same robust relationship between pain and insomnia [7].

Treatment of insomnia includes the following: 1) evaluation and treatment of other comorbid medical and psychiatric conditions; 2) general interventions such as sleep hygiene measures, relaxation exercises, and sleep restriction therapies; and 3) specific measures such as use of hypnotics judiciously and with caution for the treatment of transient insomnia. Patients with chronic insomnia or those in whom depression coexists with insomnia would benefit from sedative antidepressants.

HYPERSOMNIA

Hypersomnia may be defined as excessive sleepiness with either prolonged sleep episodes or daytime sleep episodes (somnolence) that occur daily for at least 1 month.

Hypersomnia is more commonly seen in patients for months or years after brain injury. Cohen *et al.* [7] reported a prevalence of 73% in patients who had sustained TBI 2 to 3 years previously. Increased mood and behavioral disturbances and increased unemployment rate were noted in these patients when compared with a similar group of patients with TBI without sleep disturbances [7]. In another study of 184 patients referred to a sleep clinic about 15 months after head trauma, impaired daytime functioning was observed in 98% of patients who complained of excessive daytime somnolence [11••]. Factors associated with hypersomnia, in this study included, prolonged coma of greater than 24 hours, head fracture, pain and some kind of neurosurgical intervention post-trauma. Eight of the 184 patients who were "subjectively sleepy," but had normal multiple sleep latency test (MSLT) scores were found to be apathetic. Guilleminault *et al.* [11••] described this condition as "psuedohypersomnia," and cautioned that this disabling condition should be differentiated from malingering.

Treatment of hypersomnia includes the following: 1) evaluation and management of comorbid conditions; 2) general sleep hygiene measures; and 3) specific measures including use of stimulant drugs such as amphetamines or nonsedating antidepressants such as serotonin-specific reuptake inhibitors. However, there are no clinical data available in the literature to support the use of these agents for hypersomnia.

SLEEP-WAKE SCHEDULE DISTURBANCE

Sleep-wake schedule disturbance is defined as the displacement of sleep from its original circadian pattern [6]. Patients who suffer from this disorder are unable to go to sleep or stay awake at a desired clock time. However, when they do fall asleep, both the duration and pattern of sleep are normal. Several varieties of this disorder are seen including delayed-phase, advanced, and disorganized types. Of these, the delayed-phase type has been most commonly reported [12,13]. The characteristic feature is inability to fall asleep until early hours of the morning followed by normal sleep. Schreiber *et al.* [14] analyzed the polysomnographic (PSG) and actigraphic records on 15 mild TBI patients who were all neurologically intact. All of them had normal brain CT scans. None had past history of psychiatric illness or sleep apnea syndrome. More than half of these patients were found to have delayed sleep-phase syndrome and the rest disorganized-phase type. The etiology of this condition is unclear, but is considered to be secondary to damage to the suprachiasmatic nucleus of the hypothalamus, which is considered to be the site of the human circadian clock

[10,15]. Awareness of sleep-wake schedule disturbances is important because they could otherwise be easily overlooked as symptoms of the more common, but controversial condition, the postconcussive syndrome. Treatment of this condition is mainly nonpharmacologic and includes 1) sleep hygiene measures, 2) phototherapy, and 3) chronotherapy. Medications such as sedative or hypnotics, vitamin B12, and melatonin have also been used with only limited success [12, Class III].

EVALUATION OF SLEEP DISTURBANCES IN TRAUMATIC BRAIN INJURY

Table 1 outlines the assessment and treatments of sleep disturbances in TBI. Obtaining a careful history from the patient and from collateral informants with the consent of the patient is the most essential step in the evaluation of these patients. Specific questions include the following: 1) sleep duration and pattern prior to the head injury; 2) sleep duration and pattern following head injury; 3) past psychiatric history and evaluation for coexisting psychiatric illness; 4) current medications and medical history; and 5) substance abuse history.

Ancillary sources of information include encouraging patients to maintain sleep logs and psychometric testing. Appropriate laboratory tests such as blood work and cardiac or pulmonary function tests should also be performed to exclude any suspected medical disorders. Also brain scan should be obtained to diagnose structural lesions. Essential tests to diagnose the nature of sleep dysfunction include overnight PSG, MSLT, and Actigraphy.

Table 1. Principles of assessment and treatment of sleep disturbances in traumatic brain injury

Assessment
Obtain history from patient and collateral informants
Physical and neurologic examination
Blood work to rule out other medical illnesses
Brain scan (CT or MRI) to evaluate structural lesions
Specific sleep studies—PSG, MSLT, Actigraph
Treatment
Treat coexisting psychiatric disorders
Treat underlying medical diseases
Treat sleep disturbances
Sleep hygiene measures
Environmental maipulations
Behavioral therapies
Pharmacologic measures
Sedatives or hypnotics
Antidepressants
Antipsychotics
Anticonvulsants
Melatonin

MSLT—multiple sleep latency test; PSG—polysomnographic.

Treatment

- Management of sleep disturbances associated with TBI include behavioral interventions and environmental modifications in conjunction with pharmacologic intervention [16].
- Pharmacologic interventions must target the sleep disturbances, any coexisting psychiatric disorders, as well as recognizing the deleterious effects pharmacologic agents have on the sleep-wake cycle.
- Few studies have reviewed pharmacologic management of sleep disturbances specifically in TBI patients. The experience in the management of sleep disturbances in TBI is based on prior knowledge of pharmacologic intervention in sleep disturbances in general.
- Patients should be educated regarding healthy sleep practices.
- Consumption of caffeine, alcohol and nicotine should be minimized or avoided.
- Medications that adversely affect sleep or breathing should be minimized or avoided.
- Daytime naps should be avoided, and patients should be encouraged to maintain regular sleep schedules.
- Associated medical conditions that interfere with sleep such as pain and frequency of micturition should be adequately treated.

Pharmacologic treatment

- The following general principles should be adhered in the management of sleep disturbances associated with TBI [17], including: 1) treat underlying psychiatric or medical conditions; 2) brain-injured patients often require much lower dosages than non-brain-injured patients. Hence, always start at the lowest dosages and gently increase the dose; 3) encourage daytime functioning (treatment of sleep disorders should not interfere with daytime productivity); and 4) continue to encourage good sleep hygiene practices throughout the course of treatment.
- There are only very few studies available in the literature documenting pharmacologic treatment of sleep disturbances in TBI. The different medications discussed in this paper are from the authors' clinical experience and the information available on the treatment of psychiatric disorders and sleep disturbances in general [18].

Sedatives and hypnotics—benzodiazepines

- Benzodiazepines should be used only in patients with insomnia of short duration or transient insomnia. Even in these patients, it should be used cautiously and avoided in those with sleep apnea, pulmonary, and hepatic or renal diseases. It should not be used for more than 3 consecutive weeks, because of the risk of dependence. Use of benzodiazeoine soon after TBI may interfere with neuronal recovery. The mechanism of action of benzodiazepines in the treatment of insomnia is unclear, although there is a subjective improvement in the quality and quantity of sleep and some objective improvement in PSG studies [19•, Class III]. The most commonly used benzodiazepines in the treatment of insomnia include lorazepam, temazepam, clonazepam, and diazepam.

Lorazepam

Standard dosage	0.5 to 2 mg at bedtime.
Contraindications	Sleep apnea, hepatic impairment, pulmonary disease, porphyria, and myasthenia gravis. Patients should be advised not to operate heavy machines or drive while on benzodiazepines. It should be used with caution in the elderly. Avoid in pregnancy and nursing mothers.
Main drug interactions	Decreased absorption of benzodiazepines with antacids. Concomitant use of antihistamines, alcohol, barbiturates, and cyclic antidepressants can enhance central nervous system depression. Drugs such as cimitedine, disulfiram, erythromycin, fluoxetine, estrogens, and isoniazid can increase benzodiazepine levels, and carbamazepam can decrease benzodiazepine levels.
Main side effects	Rebound insomnia, amnesia, paradoxical aggression, and falls.
Cost/cost effectiveness	30 tablets of 0.5-mg tablets costs $11.87 and 2-mg tablets costs $20.87.

Temazepam

Standard dosage	7.5 to 30 mg at bedtime.
Contraindications	Similar to lorazepam.
Main drug interactions	Similar to lorazepam.
Main side effects	Similar to lorazepam.
Cost/cost effectiveness	30 tablets of 7.5 mg costs $13.87 and 30 mg costs $9.87.

Clonazepam

Standard dosage	0.25 to 2 mg at bedtime.
Contraindications	Similar to lorazepam.
Main drug interactions	Similar to lorazepam.
Main side effects	Dizziness, falls, impaired motor performance, and cognitive impairment.
Cost/cost effectiveness	30 tablets of 0.5 mg costs $5.87 and 2 mg costs $9.87.

Diazepam

Standard dosage	2 to 10 mg at bedtime.
Contraindications	Similar to lorazepam.
Main drug interactions	Similar to lorazepam.
Main side effects	Similar to clonazepam.
Cost/cost effectiveness	30 tablets of 2 mg costs $3.87 and 10 mg costs $3.87.

Sedative and hypnotics—nonbenzodiazepines

- Zolpidem and zaleplon are a new class of nonbenzodiazepines that are structurally dissimilar to the benzodiazepines, but mediate their action through the benzodiazepine receptor complex with more selectivity to the type I receptors that are involved in the mediation of sleep [20,21, Class III]. They are thus less likely to produce cognitive side effects. They also have short serum half-lives, and are at less risk of causing excessive daytime drowsiness.

Zolpidem

Standard dosage	5 to 10 mg at bedtime.
Contraindications	Similar to lorazepam.
Main drug interactions	Information is limited.
Main side effects	Anterograde amnesia, rebound insomnia, anxiety, nausea, vomiting, and dysphoric reactions.
Cost/cost effectiveness	A 30-day supply of 5-mg tablets costs $60.00 and 10 mg costs $75.00.

Zaleplon

Standard dosage	5 to 10 mg at bedtime.
Contraindications	Similar to lorazepam.
Main drug interactions	As zaleplon is metabolized through the P4503A4 cytochrome enzymes, caution should be used when drugs that are degraded through the same enzymes (fluoxetine, sertraline, fluvoxamine, and nefazadone) are concomitantly administered [22].
Main side effects	Limited information. Less likely to produce psychomotor impairment.
Cost/cost effectiveness	A 30-day supply of 5-mg tablets costs $60.00 and 10-mg tablets costs $75.00.

Tricyclic antidepressants

- Antidepressants are most useful in the treatment of insomnia, when it is associated with depression. Theoretically, tricyclic antidepressants (TCAs) may be useful in the treatment of insomnia because of their antihistamine and anticholinergic properties. However, no studies are available on the use of TCAs in brain-injured patients with insomnia, though a modest response rate (30% with amitriptyline and 60% with with desipramine) has been observed in post-TBI depression [23–25]. Both of these medications have a therapeutic window for depression. For the treatment of insomnia, lower doses can be used.

Amitriptyline

Standard dosage	25 to 150 mg at bedtime.
Contraindications	Conduction heart defects, narrow angle glaucoma, prostatic hypertrophy, and postacute myocardial infarction. Avoid use in seizure disorders, because it can lower seizure threshold. Also avoid during pregnancy and lactation.
Main drug interactions	Blocks antihypertensive effects of beta-blockers and clonidine, and causes serious cardiovascular side effects when used with sympathomimetics. Birth control pills decrease tricyclic levels through induction of hepatic enzymes.
Main side effects	Dry mouth, constipation, blurred vision, urinary retention, orthostasis, weight gain, sedation, confusion, and cardiac conduction defects.
Cost/cost effectiveness	30 tablets at 25 mg costs $3.70 and at 150 mg costs $7.87.

Nortriptyline

Standard dosage	10 to 150 mg at bedtime.
Contraindications	Similar to amitriptyline.
Main drug interaction	Similar to amitriptyline.
Main side effects	Similar to amitriptyline, but less severe.
Cost/cost effectiveness	30 tablets of 10 mg costs $6.87 and 75 mg costs $21.87.

Selective serotonin reuptake inhibitors

- Selective serotonin reuptake inhibitors (SSRIs) have been useful in the treatment of post-TBI depression [24,25, Class III]. However, no reports are available on the use of SSRIs in the treatment of sleep disturbances in TBI. Of all the different types of SSRIs, paroxetine is most sedating and thus may be useful in the treatment of insomnia [26,27, Class III].

Paroxetine

Standard dosage	10 to 40 mg per day.
Contraindications	Concomitant use of monamine oxidase inhibitors (MAOI) can cause serotonin syndrome with fatal consequences.
Main drug interactions	Potent inhibitor of CYP2D6 and cytochrome P450 enzymes. Hence, may cause increased levels of drugs (*eg,* cimetidine, warfarin, theophylline, benzodiazepines, clozapine, and digoxin) that are metabolized through this system.
Main side effects	Gastrointestinal (nausea, vomiting, and diarrhea) side effects and sexual dysfunction are common.
Cost/cost effectiveness	30 10-mg tablets costs $75.51 and 20-mg tablets costs $72.89.

Trazadone

	Trazadone is a sedative antidepressant that inhibits serotonin reuptake. It has been useful in the treatment of post-TBI depression [28, Class III]. The authors of this paper have found it very useful in the treatment of post-TBI insomnia.
Standard dosage	50 to 400 mg.
Contraindications	Concomitant use of MAOIs. Avoid in pregnant and nursing women.
Main drug interactions	Fluoxetine increase concentration of trazadone and the latter increases the levels of phenytoin and digoxin. Antihypertensives when used with trazadone can cause hypotension.
Main side effects	Ortostasis, dizziness, headaches, and priapism.
Cost/cost effectiveness	30 tablets of 50 mg costs $5.87.

Antipsychotics

- Typical antipsychotics such as haloperidol should be avoided as they have shown to impair neuronal recovery [29]. Schreiber *et al.* [30•, Class III], described a brain-injured patient with sever insomnia and daytime fatigue, and paranoid and jealousy delusions who responded dramatically to 2 mg of risperidone. However all symptoms re-emerged secondary to medication noncompliance. Patient was later started on fluphenazine decanoate (6.25 mg every 2 weeks) with stabilization of psychotic symptoms but not insomnia. The novel psychopharmalogic effects of risperidone (D2 antagonism, serotonergic activity, antihistamine activity, and possible opioid system involvement) have been postulated to be responsible for the alleviation of a variety of symptoms.

Risperidone

Standard dosage	0.25 to 6 mg per day.
Contraindications	Avoid in nursing mothers.
Main drug interaction	Can cause increased drowsiness when used with other central nervous system depressants.
Main side effects	Extrapyramidal side effects in doses greater than 6 mg per day. Other common side effects include dry mouth, constipation, and weight gain
Cost/cost effectiveness	30 0.5-mg tablets costs $76.50 and 1-mg tablets cost $69.30.

Anticonvulsants

- Anticonvulsants such as gabapentin are useful in the treatment of chronic pain. Mellick and Mellick [31, Class III] performed an open-label trial with gabapentin on six patients with severe reflex sympathetic dystrophy. All patients reported to both an improvement in pain and quality and duration of sleep with minimal nocturnal awakenings. In another study on healthy young adults, an increase in slow wave sleep and whole blood serotonin was found after administration of gabapentin [32, Class III]. As already discussed, TBI subjects have more pain complaints, and pain is often associated with insomnia. Even though studies in TBI patients are not available, it is conceivable that this drug could be used for the treatment of sleep disturbances in these patients

Gabapentin

Standard dosage	100 to 3600 mg per day. The authors recommend starting at 100 mg at bedtime and gradually increasing the dose if necessary to 300 to 600 mg twice or three times a day. Maximum dose is 3600 mg per day.
Contraindications	Avoid in nursing mothers. Avoid in patients with previous hypersensitivity reactions to the drug.
Main drug interactions	Not appreciably metabolized by the liver, therefore few drug-to-drug interactions.
Main side effects	Somnolence, ataxia, fatigue nausea, and dizziness.
Cost/cost effectiveness	30 100-mg tablets costs $12.87 and 800-mg tablets costs $71.87.

Psychostimulants

- Psychostimulants have been used to treat impaired arousal and inattention in TBI patients [33, Class III] and hypersomnia in the general population [6, Class III]. However, studies on treatment of hypersomnia in TBI are not available. Methylphenidate and dextroamphetamine are the commonly used agents.

Methylphenidate and dextroamphetamine

Standard dosage	5 to 60 mg per day.
Contraindications	Severe hypertension and cardiovascular disease. Avoid in patients with history of substance abuse, and in those on MAOIs.
Main drug interactions	Increased levels of TCAs, warfarin, phenytoin, primidone, and phenobarbital are found, when co-administered with sympathomimetics, to be secondary to decrease metabolism of these drugs.
Main side effects	Headache, tachycardia, restlessness, and mild increase in blood pressure.
Cost/cost effectiveness	30 5-mg tablets of methylphenidate costs $10.87 and 30 5-mg dextroamphetamine tablets costs $13.87.

Melatonin

	Melatonin is a metabolite of serotonin produced in the pineal gland. It is produced during darkness and suppressed by exposure to light. It is secreted into the bloodstream and binds to several receptors. The suprachiasmatic nucleus in the hypothalamus, which is believed to mediate the circadian rhythm, is rich in melatonin receptors. It is believed that melatonin plays a crucial role in maintaining the body's internal clock and synchronizes the body's sleep-wake cycle with the environment [5]. Melatonin has found to be useful in improving sleep time, efficiency, NREM sleep, and REM latency [18, Class III].
Standard dosage	Therapeutic dose of melatonin has not been determined. Its manufacture is not regulated by government agencies, purity of the agent is unknown and standardized preparations are not available [18].
Contraindications	Heart disease, atherosclerosis, and stroke, secondary to vascular constriction effects of melatonin. Possibly inhibits fertility.
Main drug interactions	Fluoxetine decreases melatonin levels and TCAs and fluoxamine increases melatonin concentrations, when administered concurrently.
Main side effects	Limited information. Drowsiness
Cost/cost effectiveness	A 30-day supply of 1.5-mg tablets costs $3.00.

Other drugs

- Antihistamines are generally not very useful in the treatment of chronic insomnia, secondary to their marked anticholinergic side effects. There are no data on the usefulness of other sedating antidepressants, such as mirtazapine and nefazodone, in the treatment of sleep disturbances in TBI. However, clinical experience reveals that these agents are useful in the treatment of insomnia in TBI patients even when not associated with depression.

Other treatments

Psychotherapy and behavioral therapy

- Psychotherapy (individual or group) may be useful for the treatment of sleep disturbances when associated with mood or other emotional problems [34, Class III].
- Behavioral therapies such as progressive deep muscle relaxation, stimulus control, and sleep reduction have been found to be useful in reducing sleep latency and middle insomnia [17,34, Class III]. Disadvantages of these therapies include physician unfamiliarity and lack of a standardized method to administer these therapies [17].

Phototherapy

- Phototherapy has been found to be useful in the treatment of circadian rhythm disorders. Exposure to bright light at strategic times of the sleep-wake cycle results in a shift of the underlying biologic rhythm [5]. However, the actual mechanism of action of phototherapy is uncertain. Brain-damaged (non-TBI) children with sleep problems have been found to respond well to bright light therapy [35, Class III].
- It is generally accepted that exposure to light in the morning results in a phase advance, and exposure in the evening results in phase delay [18]. Therefore, the timing of light exposure depends on the diagnosis and response of the individual.
- Full spectrum bright light (2500 lux) that is about 200 times brighter than ordinary indoor lighting is used. The actual duration is unknown, but usually varies from 30 minutes to 2 to 3 hours. Distance from the light is important in determining the brightness. Patients with eye problems should consult an ophthalmologist before starting light treatment. Similarly patients who are photosensitive or are on drugs that increase photosensitivity should avoid light therapy.
- Side effects include headache, eyestrain, early sleep onset, and precipitation of mania in patients with bipolar disorder.

Chronotherapy

- Chronotherapy involves delaying or advancing sleep onset by a few hours every day until the desired sleep-onset time is obtained. After this the patient is advised to strictly adhere to the new sleep schedule [5, Class III].
- This form of treatment requires motivation and determination on the part of the part of the patient to not only to get to the "new" sleep schedule, but also to maintain it thereafter.
- Even though this method of treatment has been known for several years, there is paucity of literature on the effectiveness of this treatment.

Emerging therapies

- Review of literature indicates that although sleep disturbances are common in TBI patients, there is very little objective data on the varieties and treatment of these disorders. Hence, more research is necessary as identification and prompt treatment of sleep disturbances in TBI will not only alleviate suffering in the patient and family but will also help with effective rehabilitation.
- The neuropharmacology of the new nonbenzodiazepine agent, zaleplon, is being explored further to determine its hypnotic effect and adverse effects. There is a suggestion that it can be effectively used as a hypnotic, even with middle-of-the-night dosing, without the adverse effects of anterograde amnesia and psychomotor impairment [21, Class III].
- Better management of sleep disturbances requires better understanding of the pathogenesis. Abnormal coticotropin-releasing factor (CRF) regulation has been postulated to play a major role in primary imsomnia. Some research workers have postulated that hyperactivity of the CRF neurons produces sleep disruption, physiologic hyperarousal, and major depression [36••]. If this could be confirmed, CRF antagonists may play an important role in the treatment of both mood and sleep disorders.

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