

Excessive Sleepiness after Brain Injury

Introduction

The areas controlling sleep and wakefulness in the brain are widely distributed so it is not surprising that brain injuries can disturb sleep in many ways. While many aspects of brain injury have been well researched, there is remarkably little information regarding sleep disorders, the mechanisms of changes in sleep/wake patterns or the factors that determine the prognosis of the sleep disorder.

Physiological mechanisms of sleep/wake control (Figure 1)

There are three control systems,¹ all of which can be damaged by brain injuries.

- a) Homeostatic drive to sleep. The drive to enter sleep increases exponentially with the duration since the end of the previous sleep episode and declines exponentially once sleep is initiated. The most important sleep-promoting centre is the ventrolateral pre-optic nucleus (VLPO) in the anterior hypothalamus.² This inhibits all the main arousal systems especially those in the brain stem such as the locus coeruleus and raphe nuclei, which form part of the ascending reticular activating system, and the tuberomammillary nuclei in the hypothalamus.
- b) Circadian rhythms. These are generated in the suprachiasmatic nuclei which are responsible for the intrinsic circadian rhythm of around 24.2 hours. This entrains several important systems including sleep/wake control, temperature, feeding, motor behaviour and endocrine function to the local environmental time. Exposure to light fine tunes the circadian rhythms and is sensed, not by rods and cones, but by the retinal ganglion cells. Information from these passes especially to the suprachiasmatic nuclei which connect to the pineal gland. In the absence of light this secretes melatonin which promotes sleep.
- c) Adaptive drive. This includes a variety of mechanisms that adapt sleep and wakefulness to the external environment independently of the homeostatic and circadian drives. They include behavioural responses, psychological aspects and reflex factors, including the influence of exertion and temperature on sleep and wakefulness.

Excessive daytime sleepiness after brain injuries

Excessive daytime sleepiness is a common result of brain injuries but can have several causes.

- a) Post traumatic hypersomnia. This is thought to be due to widespread damage to the sleep/wake control mechanisms. The initial coma is often followed by a stage of continuous sleepiness with a reduction of REM sleep which is interrupted by increasingly frequent awakenings. Improvement in cognitive function is associated with an increase in the duration of REM sleep after the injury although there is usually poor dream recall. NREM sleep and REM sleep may be poorly differentiated which makes accurate sleep staging difficult. The excessive daytime sleepiness may continue to improve for around a year but recovery may be incomplete. There is often a prolonged nocturnal sleep episode together with frequent and prolonged naps during the day and subalertness between these.³ The clinical features of this post traumatic hypersomnia are similar to those of idiopathic hypersomnia apart from the history of a brain injury.

- b) Sleep apnoeas. Obstructive sleep apnoeas are frequently seen after brain injuries^{4,5} but there is little evidence to indicate whether they result from the brain injury or were present before the incident and only diagnosed afterwards. Secondary effects of the brain injury such as weight gain may predispose to obstructive sleep apnoeas. Central sleep apnoeas may be induced by damage to respiratory control mechanisms but little is known of their prevalence after brain injuries.
- c) Narcolepsy. Narcolepsy is occasionally associated with brain injuries. Loss of consciousness at the time of the injury is usual but not invariable. Narcolepsy may follow injuries to any part of the head and usually appears immediately afterwards or within a few weeks or months.⁶ The characteristic HLA type (DQB1*0602) is present in only around 50% of those with post-traumatic narcolepsy⁷ whereas it is found in around 95% of Caucasians with idiopathic narcolepsy. While post traumatic narcolepsy might be due to direct injury to the structures controlling REM sleep, it may also result from damage to the blood/brain barrier or to an inflammatory response within the pons or hypothalamus.
- d) Kleine-Levin syndrome. This syndrome usually occurs in adolescence or early adult life and is more common in males than females. It is characterised by episodic daytime sleepiness which is often severe and associated with a voracious non-selective appetite (megaphagia) and, in around 25% of patients, sexual disinhibition. Psychological changes such as anxiety, depression, confusion and hallucinations are also seen. These features are probably the result of fluctuating hypothalamic inflammation which follows the brain injury.⁸ The condition usually runs a fluctuating course with a tendency to gradual improvement.
- e) Periodic limb movements in sleep. These have been associated with brain injuries but, like obstructive sleep apnoeas⁹ they may have been present before the accident but unrecognised.
- f) Circadian rhythm disorders. Brain injuries can disrupt the circadian control of sleep. A delayed sleep phase syndrome is seen after neck and also brain injuries probably due to damage to the tortuous pathway between the suprachiasmatic nuclei through the cervical spinal cord



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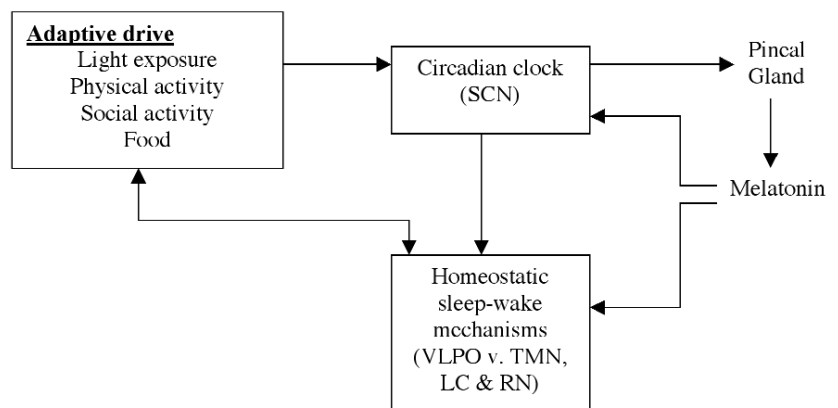


Figure 1: Mechanisms of sleep-wake control. SCN, suprachiasmatic nuclei, VLPO, ventrolateral preoptic nuclei, TMN, tuberomammillary nuclei, LC, locus coeruleus, RN, raphe nuclei.

to the pineal gland.¹⁰ Impairment in vision after brain injuries frequently leads to a non-24 hour sleep/wake rhythm because of the failure of light to entrain the circadian rhythm. This becomes independent of the environment (free running) so that its relationship to the environment changes slightly each day.¹¹ At one point in the cycle the two may be in phase but the sleep rhythm then moves progressively forward leading initially to a delayed sleep phase and then through a period when there is insomnia at night and sleepiness during the day to an advanced sleep phase pattern before temporarily returning to synchrony with the environment again.

- g) Drugs. Drugs used to treat, for instance, epilepsy or psychiatric disorders following brain injuries may cause sedation.

Treatment

- a) Sleep hygiene. Maladaptive behaviour patterns are common in those with sleep disorders following brain injury. The loss of physical activity and exposure to bright light promotes subalertness during the day and impairs sleep at night. Excessive caffeine intake in the evenings and irregular sleep/wake schedules often contribute. Routines imposed in residential and nursing homes and similar institutions may also worsen sleepiness during the day and lead to insomnia at night and agitation.

- b) Drugs. Treatment of excessive daytime sleepiness should be targeted at the cause of the symptoms. Periodic limb movements, for instance, may respond to a dopaminergic agent and a non 24-hour sleep/wake rhythm due to visual impairment can usually be corrected by 0.5mg melatonin at around 9pm, which entrains the circadian rhythms.

Several of the older stimulant medications such as selegiline and amantadine have been used but with little success. Amphetamines, particularly dexamphetamine, are more effective but are generalised central nervous system stimulants with important side effects.

The most effective wakefulness promoting drug is modafinil (Table 1). This is chemically unrelated to the amphetamines and is currently licensed for treatment of excessive daytime sleepiness due to chronic pathological conditions.¹² Its peak blood level is reached within 2-3 hours and it has a half life of 10-15 hours. It is metabolised in the liver and the initial dose of 100-200mg daily often needs to be increased to 400mg daily and occasionally beyond this. Around two-thirds of the dose should be given on waking and one-third in the middle of the day. It increases the activity of the histaminergic neurones in the tuberomammillary nuclei¹³ which promote wakefulness, and inhibits the VLPO. Its main side-effects are headaches, nausea and dry mouth

Table 1. Comparison of amphetamines and modafinil. Reproduced with permission'

	Amphetamines	Modafinil
<i>Efficacy</i>	+	+
<i>Duration of action</i>	Short	Long
<i>Specificity of action</i>	Low	High
<i>Dependency</i>	Moderate risk	Low risk
<i>Withdrawal symptoms</i>	Common	Absent
<i>Tolerance</i>	30% narcoleptics	Unknown
<i>Side-effects</i>	Multiple, often serious	Few, mild
<i>Contraindications</i>	Multiple	Few
<i>Drug interactions</i>	Occasional	Rare
<i>Effects of overdose</i>	May be fatal	Insomnia

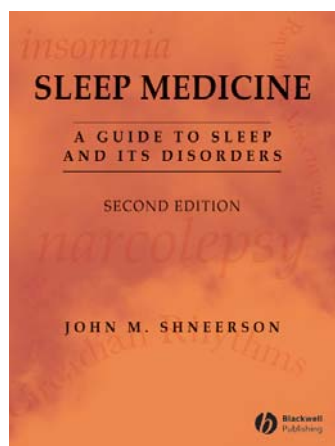
but it is usually well tolerated. Mental hyperactivity, anxiety and nervousness occur with high doses. Tolerance has not been documented and it has little potential for dependency. It can be used if necessary in combination with amphetamines and related drugs.

Conclusions

Excessive sleepiness frequently impedes rehabilitation after brain injuries but often remains unrecognised or underestimated. It can be due to a variety of specific sleep disorders and its causes should be carefully analysed. While sleep hygiene may be of help drug therapy may need to be added to treat specific disorders such as periodic limb movements in sleep. A wakefulness promoting drug is, however, often required and modafinil has several advantages over the older central nervous system stimulants.

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By John Shneerson

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