Emerging Therapeutics in Sleep

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The development of new therapeutics for sleep disorders is increasingly dependent upon understanding the basic brain circuitry that underlies sleep–wake regulation, and how it may be pharmacologically manipulated. In this review, we consider the pathophysiological basis of major sleep disorders that often are seen by neurologists, including excessive daytime sleepiness, insomnia, narcolepsy, rapid eye movement sleep behavior disorder, and restless legs syndrome, as well as circadian disorders, and we review the current and potential future therapeutic approaches.

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Sleep is clearly a brain process, and disorders of sleep represent dysfunction in that brain process. Despite this, neurology has been slow to take ownership of sleep disorders, and the field is shared with psychiatry, pulmonary medicine, and even otolaryngology. Although these other specialties offer unique expertise that certainly improves the lives of many patients with sleep disorders, understanding the disorders requires a neurological perspective, and improvements in therapy should emerge from that understanding.

There are 4 main areas in which sleep disorders intersect with neurology:

1. Excessive daytime sleepiness (EDS) in the presence of adequate nighttime sleep is due to impairment of the normal arousal systems in the brain. This impairment can either be due to neurodegenerative disorders (eg, narcolepsy, Parkinson disease),[1–3] or it can be caused by metabolic or inflammatory disorders that globally affect the brain. To these must be added disorders that cause EDS by preventing adequate nighttime sleep, although the patient may not be aware that this is occurring. This group includes central and obstructive sleep apnea, periodic limb movements of sleep, and parasomnias that may disrupt sleep in a way that is not apparent to the sleeper.[4–6] The consequences of EDS can range from annoying (falling asleep in a social setting), to disabling (falling asleep in class or while at work), to disastrous (falling asleep while driving or operating heavy machinery). One large population study showed that about 25% of adults have subjective sleepiness as measured by the Epworth Sleepiness Scale as well as objective evidence of sleepiness as measured by the Multiple Sleep Latency Test.[7] The prevalence of sleepiness is much greater in patients with specific neurological diseases.
2. The term *insomnia* refers to the inability to obtain sufficient sleep despite an adequate opportunity, resulting in daytime functional impairment.[8] Although such patients also may have EDS, the root of the problem lays in the inability of the patient to fall asleep or to maintain sleep for enough time to feel rested on arising. Insomnia may be chronic or it may occur intermittently, often at times of increased behavioral stress. Insomnia is the most common sleep complaint, with chronic insomnia affecting about 10% of the population and occasional insomnia affecting most people at some point in their lives. It may be primary, in which case insomnia is the sole disorder, or it may be comorbid with major psychiatric disorders, including depression, mania, schizophrenia, and various anxiety or stress disorders. In the latter setting, insomnia is generally treated by psychiatrists. However, neurologists will encounter insomnia in patients with primary neurological degenerative disorders, ranging from Parkinson disease to rare prion disorders such as fatal familial insomnia.
3. Parasomnias are disorders in which there is abnormal motor activity, behavior, or perceptions during sleep

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or the entry into or emergence from sleep.[6] The motor phenomena and behaviors range from periodic leg movements of sleep to sleepwalking (or eating or driving) to rapid eye movement (REM) sleep behavior disorder (RBD), and the perceptions include restless legs syndrome (RLS), night terrors, and hypnagogic hallucinations. Although individually these are relatively uncommon disorders, specific parasomnias are often seen in neurological diseases such as narcolepsy or Parkinson disease.

4. Sleep disorders may also interact with neurological disease. In our Cognitive Neurology Unit, the most common treatable cause of dementia is obstructive sleep apnea (OSA). OSA causes sleep fragmentation and sleep loss, which impair performance on cognitive testing. With poor sleep, patients with minimal cognitive impairment may be pushed over the edge into frank dementia,[9] and restoring normal sleep may dramatically improve cognition. Conversely, the occurrence of cognitive impairment in patients with OSA may be an early marker for a neurodegenerative dementing condition, in the same way that delirium during a hospital admission predisposes to developing dementia.[10] Another sleep disorder that may be a harbinger of neurological disease is idiopathic RBD. About half such patients will develop a synucleinopathy (Parkinson disease, Lewy body dementia, or multiple systems atrophy) by 12 to 14 years after diagnosis of RBD, and at least 80% within 20 to 25 years.[11]

Current Understanding of Sleep Neurobiology

Understanding the brain circuitry responsible for sleep is critical to understanding sleep disorders and their potential therapies.

Wakefulness is driven by the ascending arousal system, which consists of cholinergic (pedunculopontine and laterodorsal tegmental), monoaminergic (noradrenergic locus coeruleus, serotoninergic dorsal and median raphe nuclei, dopaminergic midbrain periaqueductal gray, and histaminergic tuberomammillary), and glutamatergic (parabrachial and precoeruleus) neurons in the upper brainstem.[12] Drugs that cross the blood–brain barrier and acutely inhibit the actions of these various arousal systems (eg, muscarinic antagonists, antihistamines, or clonidine) cause sleepiness. Conversely, most of the drugs that increase arousal, including amphetamines, methylphenidate, and modafinil, enhance dopamine signaling, as shown by their reduced efficacy in mice that lack the dopamine transporter. Neurons in the lateral hypothalamus that produce the orexin (also called hypocretin) neuropeptides also promote wakefulness, in part by directly activating the cerebral cortex and in part by stimulating the upper brainstem arousal neurons. Loss of the orexin neurons causes narcolepsy with cataplexy.[1,2] Finally, basal forebrain cholinergic and γ-aminobutyric acidergic (GABAergic) neurons project to the cerebral cortex, where cholinergic inputs activate pyramidal cells and GABAergic inputs inhibit inhibitory interneurons.

Sleepiness is thought to be caused by buildup of somnogenic molecules in the brain such as adenosine. Caffeine blocks the adenosine A1 and A2a receptors, and mice that lack the A2a receptors do not show the hyperactivity caused by caffeine.[13] Sleep itself is an active process that is promoted by neurons that inhibit the arousal systems. The ventrolateral and median preoptic nuclei, in the rostral hypothalamus, are more active during sleep, and use GABA and galanin as inhibitor neurotransmitters to reduce activity in many components of the arousal system.[12] Neurons in the parafacial zone of the medulla also promote sleep, apparently by using GABA to inhibit the parabrachial arousal neurons.[14]

REM sleep is also an active process that requires the activation of a population of REM-active neurons in the upper pons, mainly in the sublaterodorsal nucleus.[15,16] These glutamatergic neurons provide descending inputs to the medulla and spinal cord, where they activate GABAergic and glycinergic inhibitory interneurons that hyperpolarize motor neurons and cause muscle atonia during REM sleep. Other ascending projections from the sublaterodorsal nucleus, as well as from the parabrachial nucleus, precoeruleus area, and pedunculopontine and laterodorsal tegmental nuclei, are thought to activate forebrain components of REM sleep, such as electroencephalographic desynchronization, hippocampal theta activity, and dreaming.[12]

Sleep state stability is enforced in the brain by systems of mutually inhibitory connections. For example, the ventrolateral preoptic nucleus inhibits most of the components of the ascending arousal system, and it in turn receives inhibitory afferents from many of the same arousal cell groups. This mutual inhibition forms the conditions for a "flip-flop switch," a concept from electrical engineering, in which turning on either side of a circuit turns off the other side.[12] The result is that the circuit is stable in either end state, but is unstable in intermediate states, and rapidly is forced in either one direction or the other. Similarly, transitions into sleep or wakefulness occur relatively rapidly, and transition states occupy only a small percentage of the day. A similar switch for transitions between non-REM and REM sleep has been proposed.[15] Orexin peptides play a role in

stabilizing both switches. Thus, in individuals with normal orexin signaling, it is nearly impossible to go from waking into REM sleep. Conversely, in patients with narcolepsy who lack orexin neurons, there are frequent and unwanted transitions between wake and sleep, and from wake to fragments of REM sleep, such as cataplexy, which is probably very similar to the atonia of REM sleep.

Currently Available Therapies

For many patients with EDS, the best approach is to treat the underlying disorder that produces poor quality or insufficient sleep. Many patients with EDS have unrecognized sleep apnea, which can often be treated effectively with continuous positive airway pressure or other approaches.[4] RLS and periodic limb movements can disturb sleep, and their treatment is discussed below. Other patients may simply need more sleep, and behavioral suggestions are often helpful.

For other patients, especially those with narcolepsy or other neurological causes of EDS, symptomatic treatment of their sleepiness is usually required.[1,2] Traditional stimulant drugs, such as amphetamines and methylphenidate, are frequently very effective. Modafinil and armodafinil (the active R-enantiomer of modafinil) are also first-line agents, as they are less likely to produce side effects and have less abuse potential than the amphetamines. Some patients find modafinil less potent than amphetamines, so amphetamines are often a good choice for patients with severe EDS. Both the amphetamines and modafinil likely promote wake by interfering with the dopamine reuptake transporter, producing higher synaptic concentrations of dopamine that help promote wakefulness.

Most other symptoms of narcolepsy are treated with medications that suppress REM sleep. Cataplexy can be substantially reduced by drugs that block reuptake of norepinephrine and serotonin, including classic tricyclic antidepressants such as clomipramine, and more modern ones such as venlafaxine. Sodium oxybate produces very deep and consolidated sleep and is often very effective at reducing both EDS and cataplexy.

Insomnia is typically treated with a combination of sleep hygiene and cognitive behavioral therapy, as well as sedative medications.[8] Most medications for insomnia either block the actions of the ascending arousal system (eg, antihistamines, sedating antidepressants with antihistamine or anticholinergic properties), or they enhance $GABA_A$ signaling, which inactivates the arousal system and its targets, in part by enhancing the ability of the ventrolateral preoptic nucleus to turn off the arousal system.[17,18] This latter group of drugs includes an enormous array of sedative-hypnotics, ranging from 19th century medications (ethanol, chloral hydrate), to 20th century medications (barbiturates, benzodiazepines), to more recently developed medications that bind to subsets of $GABA_A$ receptors and thus have fewer side effects, such as zolpidem and eszopiclone.[19]

Circadian rhythm disorders often contribute to insomnia, especially in shift workers whose internal sleep cycle is out of synchrony with their designated sleep time or in those with circadian phase delay who have a tendency to stay up late at night and then sleep late in the morning.[20,21] Circadian rhythms are regulated by the suprachiasmatic nucleus (SCN), and melatonin can help adjust the phase of these rhythms by acting directly on SCN pacemaker neurons. Melatonin itself or a melatonin agonist such as ramelteon taken before the intended bedtime is often a good choice in these patients.[22] In addition, bright lights at the onset of the desired wake phase can be used to reset the SCN, which may improve wake-time alertness in patients with circadian sleep phase disorders or in shift workers.[23,24]

Certain movement disorders such as RLS and periodic limb movements of sleep are often treated with dopamine D2 agonists such as pramipexole or ropinirole.[5,25] Calcium channel $\alpha 2\text{-}\delta$ drugs such as gabapentin and pregabalin are also effective, especially in patients in whom these disorders are aggravated by an underlying neuropathy or myelopathy. Benzodiazepines and opiates are good second-line choices.

The pathophysiology of parasomnias is highly varied, and so each is treated with specific medications.[6] REM behavior disorder is generally treated with low-dose clonazepam, and melatonin is a good second-line agent. Conversely, sleepwalking and night terrors, which tend to occur during the deepest stages of non-REM (NREM) sleep, are sometimes treated with tricyclic antidepressants, such as amitriptyline, which suppress deep NREM sleep.

Therapeutic Pipeline in 2013

The most active area for drug development in sleep remains therapies for insomnia. The orexin peptides promote wakefulness, and several pharmaceutical companies are developing orexin receptor antagonists that should improve insomnia. The orexin peptides bind to 2 G protein-coupled receptors, OX1R and OX2R. Signaling through the OX2R may play the greater role in promoting arousal, as mice lacking just OX1R have no evidence of sleepiness, whereas mice lacking OX2R are moderately sleepy. Blockade of orexin signaling is appealing, as this should mainly reduce arousal, whereas benzodiazepines and related drugs act at $GABA_A$ receptors throughout the brain, sometime resulting in impaired cognition,

amnesia, and ataxia.[26,27] Orexin antagonists should also have less potential for addiction and should not cause respiratory depression. This class of drugs may benefit a variety of patients with insomnia, but they may be especially appealing in elderly individuals and in patients with neurological disorders, in whom drugs acting through $GABA_A$ receptors could be problematic.

Merck is currently awaiting US Food and Drug Administration (FDA) approval of suvorexant, a dual orexin receptor antagonist. In very large trials lasting up to 1 year, suvorexant improved both objective and subjective measures of sleep quality including sleep efficiency (percentage of time in bed spent asleep), latency to sleep onset, and amount of wakefulness after sleep onset.[27–30] Suvorexant appears generally well tolerated, although some patients report sleepiness in the morning, perhaps due to the compound's long half-life. In addition to promoting wakefulness, the orexins suppress REM sleep, and suvorexant showed some evidence for disinhibition of REM sleep; specifically, it shortened the latency to REM sleep, and rare patients reported hypnagogic hallucinations or sleep paralysis. An early concern, that blocking orexin receptors would induce cataplexy, has not been borne out in trials so far. Suvorexant received a generally favorable review by an FDA advisory committee, although the FDA suggested it be used at low doses because of concerns about possible morning sedation.

RLS often responds well to dopamine D2 agonists, but these can produce a worsening of symptoms known as augmentation, and other options may be needed. In a recent 12-week study of 304 patients with severe RLS, a prolonged release oxycodone/naloxone combination from Mundipharma International produced moderate to excellent reductions in RLS symptoms without evidence of augmentation.[31]

Tasimelteon from Vanda Pharmaceuticals is a melatonin agonist that has been tested in blind subjects who cannot entrain to the usual 24-hour daily cycle. In a phase III trial of 84 adults, tasimelteon improved the timing of sleep, increased sleep at night, and reduced naps during the day.[32] As further evidence that it helps normalize circadian rhythms, it also entrained the circadian rhythms of melatonin and cortisol.[33]

H3 receptor antagonists show promise as a new class of wake-promoting drugs. The H3 receptor is an inhibitory autoreceptor on histaminergic neurons, and it also dampens activity in other monoamine neurons. Thus, an antagonist would be expected to increase activity in histaminergic and other monoaminergic neurons, resulting in increased arousal. Tiprolisant (also known as pitolisant) is an H3 inverse agonist/antagonist being developed by Bioprojet Pharma that is currently in phase III clinical trials for excessive daytime sleepiness and cataplexy in narcolepsy.[34–36]

Possible New Directions for Research

Overall, the currently available medications for many sleep disorders are good, but there is much room for improvement, and for some disorders, treatment options are of limited efficacy. Chronic insomnia affects about 10% of the general population, yet many patients find the current therapies inadequate. With neurological causes of sleepiness such as narcolepsy, it is often difficult to achieve full alertness across the day even with "optimal" medications. In the treatment of RLS, augmentation occurs in a minority of patients but can be very difficult to manage. Hopefully, these unmet clinical needs will spur development of new, rationally designed medications.

About half of all patients with RLS have a family history of restless legs, and several studies have identified clear genetic linkages. Genome-wide association studies have identified variants in *MEIS1*, *BTBD9*, *MAP2K5*, *PTPRD*, and *TOX3*.[37–40] Some of these genes may influence the development or function of motor and sensory neurons, and thus may contribute to the sensory/motor discomfort of RLS. In many patients, low iron stores are thought to contribute to RLS, but the linkage of these and other genes to iron metabolism remains unclear.[38,41] A better understanding of these genes and the underlying pathophysiology should provide many new therapeutic opportunities.

Several large and small pharmaceutical companies are now developing the next generation of orexin antagonists. Some of these are designed to selectively target just the OX1R or OX2R, as animal research suggests these should have different effects. Blockade of the OX2R should promote sleep, and there is a possibility that it may do so with less disinhibition of REM sleep than seen with blockade of both receptors. Orexin signaling has also been implicated in reward mechanisms and substance abuse,[42] and expression of the OX1R is high in the mesolimbic pathway. Thus, it is possible that an OX1R antagonist could be useful in the management of drug addiction but without producing much sedation. Additional orexin antagonists with short half-lives are being developed, as many patients mainly have difficulty initiating sleep.

Beyond orexin antagonists, we are not aware of any genuinely novel medications under development for patients with sleep disorders. This may reflect the many challenges of bringing new neuroscience medications to the clinic, and it could also be due to a lack of economic motivation for pharmaceutical companies, as there are

many inexpensive generic medications for promoting sleep and wakefulness.

Clinically, there is a large need for better wake- and sleep-promoting medications. For example, sodium oxybate is effective at promoting daytime wakefulness in narcolepsy, but it has a short half-life, requiring a second dose in the middle of the night. New compounds working through the same mechanism but with easier dosing and fewer side effects would be a very helpful advance. Novel sleep-promoting drugs could build on the recent discovery of sleep-promoting neurons in the parafacial region of the medulla if one could selectively target this pathway. As narcolepsy is caused by a loss of orexin signaling, restoring orexin signaling should produce great benefit to patients with narcolepsy. The challenge is that orexins are small peptides that do not easily cross the blood–brain barrier, and it has been difficult to identify small-molecule orexin agonists or allosteric modulators that could cross the blood–brain barrier.

Even better would be to target the pathophysiological process that causes narcolepsy. Growing evidence suggests that the loss of orexin-producing neurons in narcolepsy is due to an autoimmune process, and if the specific mechanism can be identified, it may be possible to block this with immunomodulators early in the development of narcolepsy. Another alternative would be an orexin agonist, but it has proven to be difficult to produce a small-molecule orexin agonist that crosses the blood–brain barrier.

Future therapeutics in sleep medicine, as in much of neurology, may depend upon emerging methods for gene therapy or cell replacement. Although these techniques are in their infancy, it is now possible to use viral vectors to target expression of an artificial receptor to a specific population of wake- or sleep-promoting neurons. Until now, we have used drugs that affect endogenous receptors, which are often expressed widely in the nervous system. In contrast, one could use a drug that activates a novel receptor not normally found in the nervous system. Anatomic and cellular specificity could be achieved by injecting a key brain region with a viral vector in which a cell-type–specific promoter drives expression of the receptor. For example, an inhibitory receptor–drug combination could be used to reduce activity in wake-promoting neurons at night, thus producing an ideal drug for insomnia. Alternatively, one could use a similar strategy to reduce activity in sleep-producing neurons during the day, thus combatting excessive daytime sleepiness. We recently targeted the ivermectin receptor, an inhibitory chloride channel, to neurons in the medial prefrontal cortex of mice with genetic narcolepsy. Inhibiting the medial prefrontal neurons with the otherwise innocuous antibiotic ivermectin caused a dramatic reduction in cataplexy in these animals.[43] Although such receptor–drug combinations are currently being used only in animal models, use of viral vectors to deliver new genes to the brains of human subjects has been found to be both feasible and relatively safe[44] and in principle could be applied to human sleep disorders and a wide range of other neurological diseases.

Potential Conflicts of Interest

C.B.S.: consultancy, Allen Institute for Brain Science; grants/grants pending, NIH, Mathers Foundation, Dana Foundation; royalties, McGraw-Hill, Oxford University Press. T.E.S.: consultancy, Merck, Ferrer Pharma, Concert Pharma, Purdue Pharma, Cereve; expert testimony, Ryan Ryan DeLuca; speaking fees, Vox Media; royalties, UpToDate; paid educational presentation, Division of Sleep Medicine.

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