Understanding the Sleep-Wake Cycle: Sleep, Insomnia, and the Orexin System

Andrew D. Krystal, MD, MS; Ruth M. Benca, MD, PhD; and Thomas S. Kilduff, PhD

Insomnia is a common, chronic, and pervasive sleep disorder in which people regularly have difficulty falling asleep and/or staying asleep despite an adequate opportunity to sleep. According to the *International Classification of Sleep Disorders*,[1] *insomnia* is defined as not getting enough sleep or not feeling rested after sleep and is associated with daytime impairments such as diminished quality of life, fatigue, restlessness, irritability, anxiety, or tiredness. People who have insomnia often experience physical and emotional problems, an increased occurrence of accidents and comorbid psychiatric disorders, a loss of work productivity due to absenteeism, and difficulty performing work duties.[2]

Although insomnia is a prevalent and serious problem, it is underdiagnosed and undertreated.[3] Recent research into the sleep-wake cycle and how disruptions to that cycle can cause sleep disorders may provide some promise for new insomnia treatments. Andrew D. Krystal, MD, MS, gathered a panel of experts in the area of the sleep-wake cycle and insomnia to review recent research and advances in understanding, current treatments for insomnia, and how those new advances might be translated into new, more effective treatments.

THE SLEEP-WAKE CYCLE AND THE ROLES OF GABA AND OREXIN IN SLEEP AND INSOMNIA

Dr Krystal began by defining sleep as a state of decreased responsivity to environmental stimuli that occurs on a regular basis. He explained that different animals assume different postures during sleep and that different species have specific characteristic electroencephalographic (EEG) features during sleep as well. Sleep is a reversible state, and, unlike hibernation and torpor, it is not dependent on the availability of food, water, or environmental temperature. Dr Krystal then went on to explore the biological mechanisms that regulate the sleep-wake cycle, both the homeostatic and circadian processes and the neurobiological systems involved.

The Homeostatic and Circadian Processes

The sleep-wake cycle, according to Dr Krystal, is a highly regulated system that has long been believed to be driven by 2 underlying processes: the homeostatic (which regulates the amount of sleep) and the circadian (which regulates the timing of sleep).[4] The interplay between the 2 processes determines when people sleep and when they are awake.

Dr Krystal summed up the sleep-wake homeostatic process, which is sometimes referred to as "Process S," simply—the longer one is awake, the stronger the drive is for sleep. Often measured by analyzing slow-wave activity during sleep via EEG, homeostatic drive builds across waking episodes and dissipates with sleep.[4] In other words, as one goes through a normal day, Process S increases in intensity, and any time that sleep occurs, it is reduced. A daytime nap, for example, causes an exponential decline in Process S to the degree that it may interfere with sleep initiation at the usual bedtime. If one is sleep-deprived, however, the homeostatic sleep drive increases to the point where it becomes overwhelming.

- The sleep-wake cycle is regulated by homeostatic and circadian processes and competing neurobiological structures that tip the balance from sleep to wake.

- Possible mechanisms of insomnia are diminished GABA and elevated orexin levels; more research is needed to clarify these relationships.

The circadian process, Dr Krystal explained, is different. This process is an entrained and synchronized cycle of physiologic systems. He mentioned that the longer that the circadian process, or Process C, has been researched, the clearer it has become that circadian variation occurs in essentially all of the body's systems. This process influences the timing of sleepiness based on the endogenous circadian clock, the suprachiasmatic nucleus (SCN) of the hypothalamus, primarily by activation and deactivation of systems that promote waking. Process C facilitates the rhythmic cycle of sleep at the same approximate nighttime hours each day, reinforced by the light input to the retina during the day and the release of melatonin from the pineal gland during the dark hours of night.[5] In fact, Dr Krystal pointed out that light is the strongest driver of the circadian process as it is currently understood. He also emphasized that it is important to appreciate that the circadian process is not just a driver of sleep-wake processes—it also drives hormone release, body temperature changes, and essentially all regulated physiologic systems. The circadian process has been observed in nearly all species.

These 2 systems—the homeostatic and the circadian—compete against each other, according to Dr Krystal, with the "winner" determining whether one is awake or asleep. During the day, the circadian process opposes the homeostatic drive. The homeostatic drive activates sleep-promoting systems and inhibits wake-promoting systems to a greater degree the longer one is awake and pushes one toward sleep, and the circadian process drives the tendency to stay awake at particular times of the day. The relationship and give-and-take between these 2 processes is also what consolidates sleep and wakefulness into discrete episodes.[4]

Neurologic Systems, Neuroanatomy, and the Sleep-Wake Cycle

Dr Krystal then stated that these 2 processes are mediated by key neurologic systems that regulate sleep-wake function. The set of sleep-promoting neurologic systems includes adenosine, γ-aminobutyric acid (GABA), galanin, and perhaps melatonin, and the set of wake-promoting systems includes orexin (also called hypocretin), norepinephrine, histamine, serotonin, and acetylcholine. Whether one is awake or asleep is not always an all-or-nothing phenomenon. However, Dr Krystal portrayed these sets of systems as being on 2 ends of a seesaw—if one set is more active than the other, then everything tilts toward that side, but if the balance shifts, it tilts toward the other.[5] The wake-promoting systems inhibit the sleep-promoting systems, and the sleep-promoting systems inhibit the wake-promoting systems. That is, if there is greater activity in the wake-promoting systems, then the sleep-promoting systems are inhibited and one is awake. Conversely, if there is greater activity in the sleep-promoting systems, then the wake-promoting systems are inhibited and one is asleep. The orexin system has a special role in this relationship, because it appears to regulate other wake-promoting systems and prevent sudden, unwanted changeover into sleep such as occurs in narcolepsy.[5]
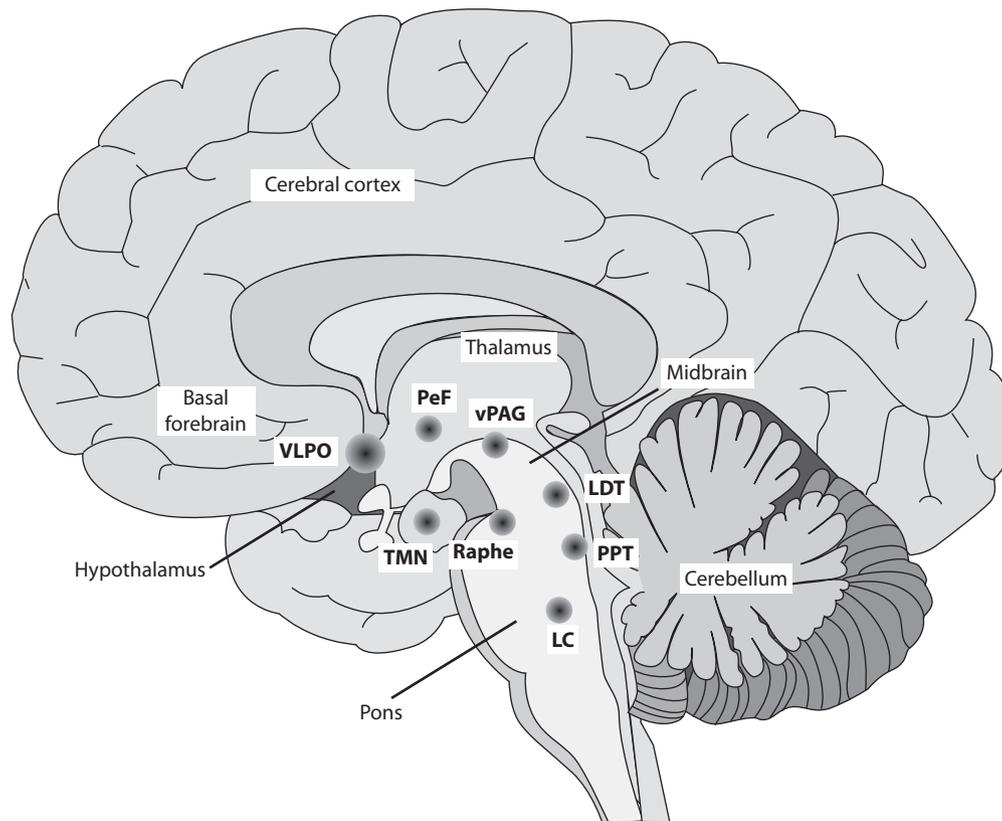
He then went into more detail about the neurobiology of both the GABA and orexin systems (Figure 1). He explained that GABA is the primary inhibitory neurotransmitter in the human brain. In most areas of the brain, GABA is involved in local inhibitory circuits. The ventrolateral preoptic nucleus (VLPO), a hypothalamic nucleus involved in the promotion of sleep, uses GABA as its main neurotransmitter and projects to several sleep active targets. Thus, increased activity of the VLPO during sleep will inhibit the wake-promoting histamines in the tuberomammillary nucleus (TMN), the orexinergic perifornical area (PeF), the serotoninergic neurons in the raphe nuclei, the cholinergic laterodorsal tegmentum/pedunculopontine tegmentum (LDT/PPT), dopaminergic cells in the ventral periaqueductal gray (vPAG), and the noradrenergic locus ceruleus (LC), which in turn will tilt the seesaw toward sleep.[5,6] Conversely, the VLPO itself can be inhibited by these wake-promoting systems, tilting the seesaw toward wakefulness instead of sleep.

Orexin, as recent research indicates, is implicated in the stimulation of the wake-promoting systems and the stabilization of the sleep-wake cycle. Dr Krystal explained that orexin is a peptide produced by neurons in the lateral hypothalamus and that it projects widely to both cortical and subcortical targets, including the same targets that GABA inhibits and additional targets in the cortex.[7] Its activation also leads to diminished activity in sleep-promoting areas, thereby tilting the balance toward wakefulness, and is theorized to be involved in consolidation of wakefulness and associated functions into a sustained episode.[6] The role of orexin in regulating the sleep-wake cycle was first discovered in relationship to narcolepsy. In fact, most people with narcolepsy (90%) are orexin-deficient.[8] Their sleep-wake cycle is destabilized such that, although they sleep the same amount of time as others, sleep happens in short bouts throughout the day and wakefulness occurs more than usual during the night.

Important differences exist between these 2 neurologic sleep-promoting and wake-promoting systems, GABA and orexin. As Dr Krystal mentioned, GABA is the most prevalent inhibitory neurotransmitter in the brain, and, in terms of sleep-wake functions, GABA is primarily driven by the homeostatic side of the sleep process, whereas orexin seems to be primarily driven by the circadian process via the SCN.

Dr Krystal reviewed results of animal studies that show how levels of orexin vary over a 24-hour cycle.[9,10] First, he presented results from a primate study that measured orexin

Figure 1. Neurotransmitters and Areas of the Brain Involved in Sleep-Promoting and Wake-Promoting Processes

Abbreviations (neurotransmitters): LC = locus coeruleus (norepinephrine), LDT/PPT = laterodorsal tegmentum/pedunculopontine tegmentum (acetylcholine), PeF = perifornical area (orexin), raphe = Raphe nuclei (serotonin), TMN = tuberomammillary nucleus (histamines), VLPO = ventrolateral preoptic nucleus (GABA), vPAG = ventral periaqueductal gray (dopamine).
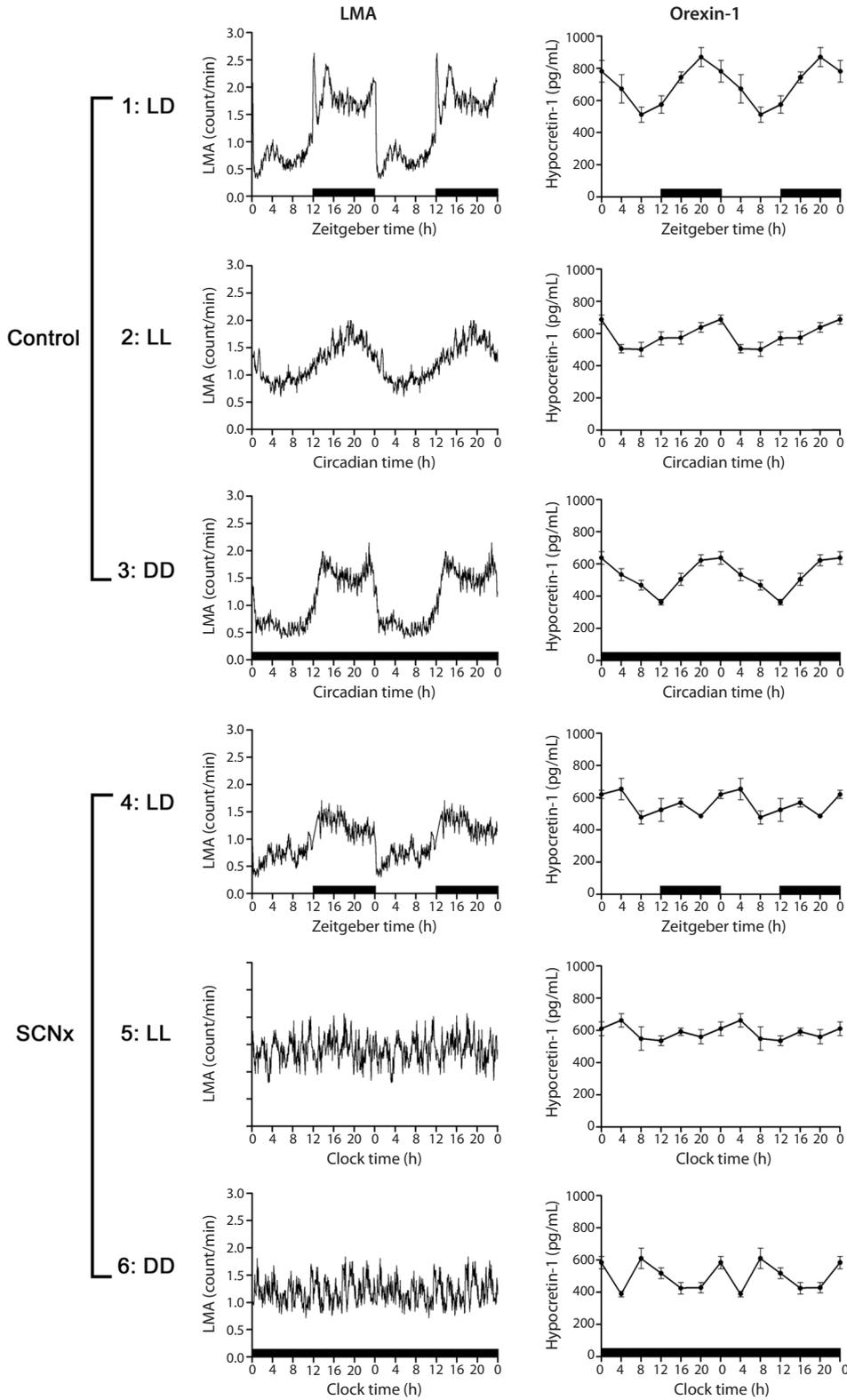
levels in cerebrospinal fluid (CSF) over 24 hours.[9] The study used squirrel monkeys, animals that have a sleep pattern similar to that of humans, ie, they are diurnal. The monkeys were studied on 2 days at least 2 weeks apart. The studied colony was kept in an area that was lit from 7 AM to 7 PM. Investigators went into the cages during the mornings to ensure that the monkeys were awake and stimulated activity. The researchers found that orexin levels were low upon awakening and gradually increased over the course of the day, coinciding with greater levels of activity and reaching the highest levels during the last third of the day (with a peak at 6:11 PM); levels then dropped during the night hours when the animals were asleep. A significant ($P < .0001$) relationship was found between time of day and CSF orexin levels.

In the second phase of the study,[9] the researchers increased the animals' wake periods by about 4 hours by extending the amount of time that the area was lit by 5 hours (to 12 AM) and by having investigators in the room with the animals during the extension to stimulate activity. They reported a corresponding increase in orexin levels during that extended period of wakefulness over the amount the animals had had when asleep at that time. The authors theorized that the extended period of light during this phase of the study could have changed the phase of the SCN, thereby altering

the circadian phase as well. They also suggested that the relationship between orexin and wakefulness might flow both ways, such that being awake and being asleep might directly affect orexin levels. Dr Krystal concluded that orexin was increasingly released during the day to counteract the homeostatic sleep drive, which would also increase during the day the longer the animal was awake, but the orexin dropped at the time the animal usually went to sleep, creating a sleep-wake pattern that coincided with night and day.

Dr Krystal went on to present results from a study in rats,[10] which are nocturnal animals. This study illustrated how much the orexin system is dependent on the SCN "clock" (Figure 2). The study rats were divided into 2 groups: those with an intact SCN and those that underwent lesion of the SCN. The animals were studied in 3 conditions: alternating light and dark (12 hours of each to simulate day and night), constant light, and constant dark. The levels of orexin (as well as activity and body temperature) in the normal rats in the alternating light and dark condition fluctuated in a pattern inverse to that seen in the monkey study; orexin levels increased when the rat was awake and active, ie, at night. Orexin levels in normal rats that were kept in constant light or constant dark were subject to similar fluctuations, although they were not as steep.

Figure 2. Relationships Among Orexin, Locomotor Activity (LMA), and Light Conditions in Nocturnal Rats[a]

[a]Adapted with permission from Zhang et al.[10] Black bars indicate dark conditions.
Abbreviations: DD = all dark conditions, LD = alternating light and dark conditions, LL = all light conditions, SCNx = lesioned suprachiasmatic nucleus.

Table 1. Sleep-Wake and GABA Measures in Primary Insomnia Group vs Control Group[a]

Variable	Primary Insomnia, Mean (SD)	Control Group, Mean, (SD)	P Value
SOL based on sleep diary, min	40.5 (24.0)	8.9 (4.0)	<.0001*
WASO based on sleep diary, min	52.6 (34.3)	6.4 (5.4)	<.0001*
TST based on sleep diary, hr	6.36 (1.0)	7.95 (0.6)	<.0001*
SOL based on actigraphy, min	23.4 (13.9)	13.4 (9.2)	.01*
WASO based on actigraphy, min	49.2 (17.6)	40.2 (12.4)	.07
TST based on actigraphy, hr	6.65 (1.1)	7.33 (0.6)	.02*
GABA level in OC (GABA/Cr)	0.18 (0.06)	0.27 (0.07)	.0005*
GABA level in ACC (GABA/Cr)	0.15 (0.05)	0.19 (0.05)	.03*

[a]Data from Plante et al.[12]
*Statistically significant.
Abbreviations: ACC = anterior cingulate cortex,
GABA/Cr = γ-aminobutyric acid/creatine ratio, OC = occipital cortex,
SOL = sleep onset latency, TST = total sleep time, WASO = wake after
sleep onset.

In rats with lesioned SCNs who were exposed to alternating light and dark, a pattern of elevated orexin during wakefulness (ie, dark) appeared but in a very weak manner. However, when these animals were exposed to constant light or constant dark conditions, they lost the pattern entirely. The authors concluded that orexin is controlled by the SCN. Dr Krystal suggested that, in the lesioned rats, the light and dark exposure drove orexin release instead of the animal's internal clock. He stated that these 2 studies illustrate that orexin activation is occurring in a cyclic manner, driven by the SCN—the clock part of the brain—and that it does so to maintain wakefulness during the "day" (or whenever animals are typically awake) and allowing sleep at night (or the appropriate time for the species).

Role of GABA and Orexin in Insomnia

After establishing the importance of GABA and orexin in the sleep-wake cycle, Dr Krystal then examined their roles in sleep disorders such as insomnia. He theorized that GABA release might be diminished and orexin activation increased at night in insomnia patients, but he explained that more research needs be done. The bottom line, according to Dr Krystal, is that the role these 2 neurotransmitters play in insomnia is still largely unknown.

Some evidence does suggest that GABA levels in the brain are lower in patients with insomnia than in those without insomnia. For example, Dr Krystal cited a recent study[11] in which patients with insomnia and a control group underwent proton magnetic resonance spectroscopy (MRS), which can measure levels of brain chemicals in a living person, to have brain GABA levels measured during their regular times in bed. GABA levels (GABA levels in vivo are expressed as a GABA/creatine ratio) in the occipital cortex were then compared with sleep diary and polysomnography results. In this case, the researchers found that GABA levels during the night were inversely correlated with the degree of sleep disturbance in all subjects—the more sleep disturbance there was, the lower the GABA levels were—suggesting that diminished GABA was linked to poor sleep.

Another recent study,[12] Dr Krystal reported, also investigated whether GABA in the occipital cortex, anterior cingulate cortex, and thalamus was decreased in patients with primary insomnia compared with control participants. Participants kept a sleep diary and wore an actigraph unit on their wrist for 2 weeks, and then, as in the previous study,[11] they underwent an MRS study. Patients with primary insomnia recorded longer sleep onset and time awake after sleep onset durations as well as shorter total sleep times than controls, according to both sleep diary entries and actigraphy results; they also had lower GABA levels in the occipital and anterior cingulate cortices by 33% and 21%, respectively (Table 1).

According to Dr Krystal, these studies provide a way to understand how and why medications that increase GABA might be therapeutic in patients with insomnia, but it is uncertain whether the effect on GABA is a primary or secondary effect in insomnia patients. Decreased GABA may be a secondary effect of elevated wake-promoting systems inhibiting the sleep-promoting system.

Orexin receptors are compromised in narcolepsy and are therefore a logical target for the development of narcolepsy treatments, but they may also provide targets for insomnia treatments. In a pharmacologic study,[13] blockade of orexin receptors was shown to promote sleep in rats, dogs, and humans. An agent that blocked both orexin receptors was administered orally during the normal wake time of the study subjects. In rats, electrophysiological signs of both rapid-eye movement (REM) and non–rapid-eye movement (NREM) sleep increased after the agent was administered, and in dogs, sleepiness and other markers of REM sleep increased. In humans, the orexin antagonist caused signs of sleep both subjectively and according to electrophysiological measures.

More work is needed to understand the pharmacology of insomnia, but research on GABA and orexin in the sleep-wake cycle provides the first step and, hopefully, gives a sense of the way in which the neurotransmitter systems differ and how they might have differential effects on patients with insomnia.

Discussion

Dr Krystal: I have suggested that GABA is primarily driven by homeostatic processes and orexin by circadian processes. Is it that simple? How clear are the data on this point?

Dr Kilduff: The first point I question is the strength of the association between activity of the circadian system and orexin release. The intervening variable is the activity level of the person or animal, and it is very difficult to disassociate activity from the circadian system. One study[14] has shown that periods of exercise in dogs will cause an acute release of orexin. In that study, 24 hours of sleep deprivation produced a 70% increase in orexin levels, and 2 hours of exercise saw a 57% increase. I would not make the argument that the circadian system is the only factor driving orexin release, because it could be a secondary consequence of activity.

Dr Krystal: How would you explain the results of the Zhang and colleagues study[10] I discussed in which they lesioned the SCN of rats? Lesions led to loss of the variation in the CSF orexin levels in rats kept in constant light or constant dark, but in animals with an intact SCN, the pattern and rhythmicity were still seen.

Dr Kilduff: In the case of the SCN lesion group in that study, the pattern of locomotor activity was also lost along with the rhythm of orexin release in constant light or dark. In fact, the authors found a relationship between locomotor activity and orexin release separate from the circadian process in that group. Overall, in these studies, it is difficult to dissociate the activity component from the circadian component. Physical activity is the potential intervening variable that needs to be considered.

Dr Krystal: What about the role of GABA and orexin interactions?

Dr Kilduff: Hypocretin/orexin neurons have both GABA$_A$ and GABA$_B$ receptors, so a potential feedback loop or control mechanism exists between the GABAergic and the orexin systems. I do not know if anyone has studied the effect of local injection of GABAergic antagonists on orexin release, but that probably is an experiment worth doing.

Dr Krystal: How much activity is there in the orexin system at night? What do we know about that in normal sleepers?

Dr Kilduff: A bit of a dissociation exists between orexin levels measured by either microdialysis or withdrawal of CSF and the measurement of the activity of the orexin neurons themselves. In large part, the orexin neurons are silent across wakefulness, slow-wave sleep, and REM sleep, except when animals are engaged in behavior involving locomotor activity, in particular, when they are engaged in motivated behavior.[15] Motivated or goal-directed behavior that has emotional salience seems to cause the highest firing of orexin neurons, and that firing tends to be phasic in nature. So, that plays to some extent into the comment I was making about the relationship between orexin release and locomotor activity. When you measure CSF orexin levels, you are looking at a cumulative amount of orexin peptide that was released over an indeterminate period of time. Although the Zhang et al study,[10] for example, used 4-hour samples, by the time you measure something in CSF, it is unclear how those results relate to what is being released locally in the brain on a moment-to-moment basis. An analogy is what an EEG measures as opposed to measuring activity at the level of a single cell.

Dr Krystal: That is a very important point, that the CSF data provide an integration of a prior period of release. Can we guess that orexin activity in humans might be pretty strong at night if one were engaged in a goal-directed activity, even if it is not a very physical activity, like searching for something on the Internet, playing a video game, or things that people (especially teenagers and young adults) often do that excite them and keep them up late at night?

Dr Kilduff: That could very well be the case. Primate models would probably be better than rodent models to test whether the emotional aspect itself, in the absence of physical activity, is enough to cause activation of orexin. Jerry Siegel's laboratory has just published a very interesting paper on hypocretin/orexin release in the human brain across a range of daily activities indicating that peptide levels are greatest during periods of positive emotion and social interaction.[16]

Dr Benca: Isn't there a drop in orexin at the end of the night due to circadian factors?

Dr Kilduff: There certainly seems to be a plummet in orexin CSF levels, in rodents in particular, as soon as the light goes on, which is the beginning of the major sleep period for nocturnal animals.

INSOMNIA TREATMENTS: CURRENT OPTIONS AND ONGOING UNMET NEEDS

Because insomnia has both biological and behavioral causes, Ruth M. Benca, MD, PhD, stated that the recommended treatments for insomnia should target these components and should be specific to the type of insomnia the patient is experiencing, ie, chronic primary insomnia versus insomnia related to comorbid conditions.[17] The goals of insomnia treatment should focus on improving sleep quality, increasing sleep quantity, and reducing daytime impairment and dysfunction.[17] Before initiating treatment, clinicians should consider patients' primary complaints and most distressing symptoms, and then discuss treatment goals to tailor interventions to each individual patient.[17] Clinicians should always try to promote good sleep habits as well as address any co-occurring conditions or underlying causes, such as comorbid psychiatric disorders, pain, apnea, or other medical or sleep disorders.

Dr Benca explained that current treatments for insomnia include psychological and behavioral therapies (possibly in conjunction with pharmacotherapy), and pharmacotherapy, which may include over-the-counter medications, prescription agents approved by the Food and Drug Administration (FDA), and agents not approved by the FDA but that may still be effective in treating some aspects of insomnia.

Psychological and Behavioral Interventions for Insomnia

According to the American Academy of Sleep Medicine,[18] psychological and behavioral interventions, such as cognitive-behavioral therapy (CBT), are effective and recommended first-line treatments for chronic insomnia.[19]

During the course of an insomnia disorder, patients may develop behaviors that can contribute to their sleep problems. For example, lying in bed while awake for long periods of time can reinforce an association between the bed and the inability to sleep, as well as lead to negative attitudes and beliefs about sleeping and sleep disorders, increased frustration, and anxiety about sleeping. Trying to extend time in bed to make up for "missed sleep," either by sleeping in later or napping during the day can disrupt

both the homeostatic and circadian regulation of sleep.[17] CBT targets these behaviors with interventions aimed at improving patients' overall sleep hygiene, addressing their attitudes about insomnia and its treatment and helping them learn behavioral approaches to decrease their arousal levels and improve their homeostatic and circadian drives to sleep. Although delivery of CBT has not been widely available, Dr Benca stated that there is increasing evidence for the use of various delivery models for CBT; clinicians might more efficiently provide services and tailor resources to individual patients' needs using an evidence-based stepped-care model of CBT administration (Figure 3).[19]

Some of the specific behavioral treatment components of CBT for insomnia include stimulus control therapy (re-association of the bed and bedroom with sleep), sleep restriction (mild sleep deprivation to induce better quality sleep), relaxation training (tension release and cognitive arousal reduction), and patient education about sleep hygiene (awareness of sleep-promoting health and environmental factors).[17,18]

The overall objectives of psychological and behavioral therapies are to identify the negative thoughts and behaviors of patients that perpetuate the insomnia, alert the patient to these actions, use specific tailored interventions to restructure the patient's behaviors and promote good sleep hygiene, establish a regular sleep pattern, and reduce arousal and anxiety about sleep.[17]

A randomized, double-blind, placebo-controlled trial[20] of primary insomnia (N = 75) examined the efficacy of CBT plus stimulus control therapy, sleep education, and time-in-bed restrictions. Results showed that CBT produced greater improvements on most outcome measures than did relaxation therapy or placebo, including reducing wake after sleep onset (WASO), normalizing sleep and subjective symptoms, and increasing sleep efficiency. Another controlled trial[21] reported that CBT was superior in reducing sleep latency and nighttime wakefulness in comparison to the self-monitoring control. Patients in the self-monitoring group who then went on to participate in CBT had a significant increase in sleep as well.

A meta-analysis[22] of studies conducted between 1998 and 2004 that examined psychological and behavioral treatment of insomnia confirmed that these therapies reliably improved several sleep parameters in individuals with primary and secondary insomnia. However, evidence of meaningful changes in areas such as quality of life and improved daytime functioning has not been established. Studies are also needed to validate these therapies in primary care settings.

While psychological and behavioral therapies are effective in helping to manage insomnia and enabling patients to develop favorable sleeping habits, use of medication is sometimes necessary, either as a primary intervention or in conjunction with behavioral treatment.

Over-The-Counter Medications for Insomnia

Over-the-counter (OTC) agents for insomnia include antihistamines, melatonin, and valerian. According to

Dr Benca, the consensus[17] is that OTC sleep aids are not recommended due to their lack of available efficacy and safety data.
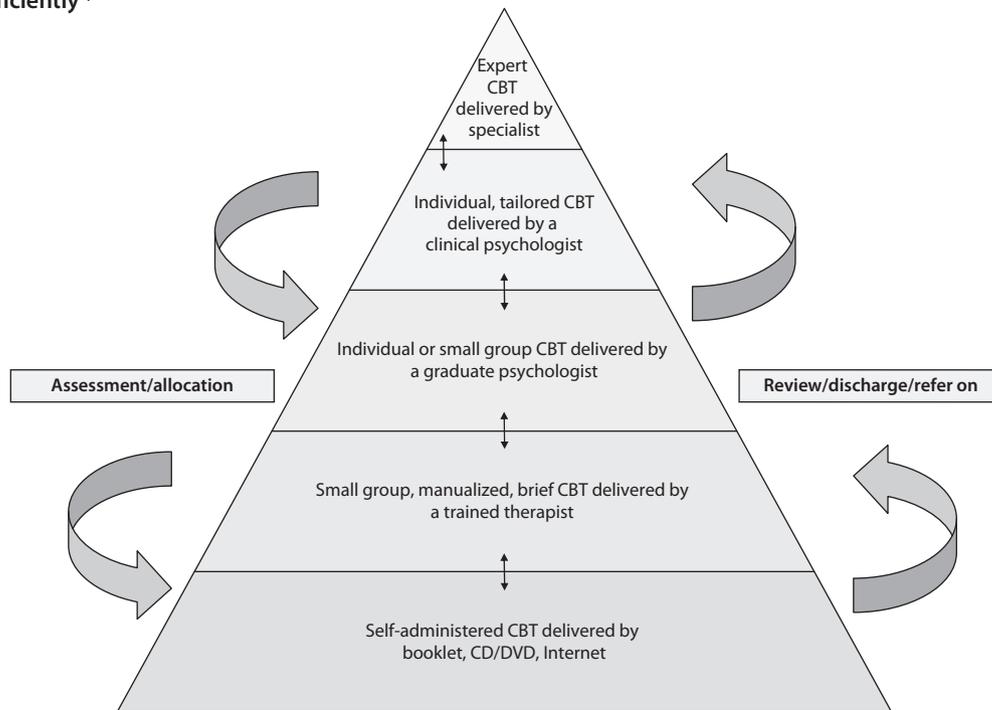
Antihistamines. Antihistamines are a common and convenient OTC modality for people with sleep problems. The active ingredient in antihistamine products is usually either diphenhydramine or doxylamine, both of which are FDA-approved as OTC nighttime sleep aids to relieve occasional sleeplessness or to reduce difficulty falling asleep, respectively.

Antihistamines primarily block histamine H_1 receptors; however, their sedative effects appear to be compounded by nonselective binding to other neurotransmitter sites. For example, diphenhydramine is also a potent muscarinic M_1 receptor antagonist, which causes anticholinergic effects of dry mouth, blurred vision, memory problems, and constipation.[23,24] H_1 and M_1 receptors are thought to mediate sedation (in addition to dopamine D_2 and α_1-adrenergic receptors), so antagonism at both sites theoretically causes an agent to have hypnotic and sedative effects.[23]

Although these OTC medications are widely available, few rigorous studies have been conducted on the efficacy of first-generation antihistamines such as diphenhydramine and doxylamine in the treatment of insomnia. Data[24] suggest that sleep maintenance may be more greatly affected by antihistamines than is sleep onset, and tolerance to these agents is likely to develop rapidly. Because older antihistamines are nonselective in their affinity, their efficacy as primary histaminergic antagonists remains uncertain; however, newer second-generation antihistamines may display a greater selectivity for H_1 receptors, resulting in fewer side effects.[25]

Melatonin. Melatonin is a hormone secreted by the pineal gland that helps to regulate circadian rhythms and the sleep-wake cycle. Typically, melatonin levels in the body increase in the evening, maintain a high level throughout the night, and then decrease in the morning. In patients with insomnia, nocturnal melatonin secretion may be blunted,

Figure 3. An Evidence-Based Stepped-Care Model for Delivering Cognitive-Behavioral Therapy (CBT) Efficiently[a,b]

[a]Reprinted with permission from Espie.[19]
[b]Pyramid illustrates how patients could be allocated to resources in relation to assessed need to achieve optimal service provision. Arrows represent self-correcting referral movements.

which negatively affects normal sleep patterns.[26] As an OTC dietary supplement, melatonin targets MT_1 and MT_2 melatonin receptors in the brain; acting at MT_1 receptors may decrease circadian pacemaker wake-promoting actions, thereby promoting sleep, and MT_2 receptors may induce phase shifts in the circadian clock to induce sleep at a desired time.[23]

A recent meta-analysis[27] of primary sleep disorders (insomnia, delayed sleep phase syndrome, and REM sleep behavior disorder) found that melatonin was effective in decreasing sleep onset latency, increasing sleep duration, and improving sleep quality, although the sizes of the effects were smaller than those reported for benzodiazepine and nonbenzodiazepine hypnotics. Additionally, the prolonged-release melatonin formulation has been reported to increase sleep quality, decrease sleep latency, and improve quality of life, without causing withdrawal or hangover effects, morning sedation, or safety concerns in patients 55 years and older.[28] Rigorous clinical studies are needed to replicate these findings.

Valerian. *Valeriana officinalis* (valerian) is an herb that may be used as a dietary supplement to aid in sleep onset and sleep quality. It is thought to act on the GABA neurotransmitter system, the primary system at which benzodiazepines act, which may explain its potential sedative properties. Data[29,30] on the efficacy of valerian as a sleep-promoting agent have been inconsistent and inconclusive, resulting in weak and unsupportive evidence. However, evidence suggests that valerian may be a relatively safe dietary supplement.[31]

FDA-Approved Prescription Medications for Insomnia

A number of prescription agents are approved by the FDA for the treatment of insomnia, said Dr Benca. These agents include benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam), benzodiazepine receptor agonists (BZRAs; eszopiclone, zaleplon, and zolpidem), a melatonin receptor agonist (ramelteon), and a tricyclic antidepressant (doxepin) (Table 2).[32–43] When administering pharmacotherapy for primary insomnia, clinicians should choose agents based on individual patients' symptom patterns, treatment goals, past treatment response, medication preferences, and current medications (regarding contraindications and interactions), as well as the chosen agent's cost, availability, and side effect profile.[17]

Benzodiazepines. Benzodiazepines have been a staple of pharmacotherapy for the treatment of insomnia since the early 1960s. The sedative effects of benzodiazepines result from their binding with GABA receptors to increase the flow of chloride in the brain, thereby hyperpolarizing neurons and making them less excitable. Dr Benca noted that the effects of benzodiazepines on GABAergic transmission are dependent on plasma drug levels at the time of desired sleep. (For more information on the GABA neurotransmitter system, see the next section by Dr Kilduff.)

Most benzodiazepines used as hypnotics have a rapid onset of action, making them useful treatments for difficulty falling asleep; those with longer half-lives are more helpful for frequent nighttime awakenings, or problems awakening too early (see Table 2).[32] Additionally, they have been shown

Table 2. FDA-Approved Prescription Agents for the Treatment of Insomnia[a]

Medication	Mechanism of Action	Peak Concentration, hr	Half-life, hr	Recommended Dose	Timing of Dose	Indication
Benzodiazepines						
Estazolam[b,c]	Benzodiazepine receptor agonist; binds to GABA receptor complexes	0.5–6	10–24	Adults: 1–2 mg Elderly: 0.5–1 mg	Bedtime	Insomnia: • Difficulty falling asleep • Frequent nocturnal awakenings • Early morning awakenings
Flurazepam[b,c]	Binds to $GABA_A$ receptors	0.5–1	47–100	Adults: 15–30 mg Elderly: 15 mg	Bedtime	Insomnia: • Difficulty falling asleep • Frequent nocturnal awakenings • Early morning awakenings
Quazepam[b]	$GABA_A$ agonist	2	39–73	Adults: 7.5–15 mg		Insomnia: • Difficulty falling asleep • Frequent nocturnal awakenings • Early morning awakenings
Temazepam[b,c]	Binds to $GABA_A$ receptors	1.2–1.6	8–10	Adults: 7.5–30 mg Elderly: 7.5 mg	Before bedtime	Insomnia
Triazolam[b,c]	Binds to $GABA_A$ receptors	2	1.5–5.5	Adults: 0.25–0.5 mg Elderly: 0.125–0.25 mg	Before bedtime	Insomnia
Benzodiazepine Receptor Agonists (BZRAs)						
Eszopiclone[b]	Acts at benzodiazepine receptors via GABA-receptor complexes interaction	1	6	Adults: 2–3 mg Elderly: • For difficulty falling asleep, 1 mg • For difficulty staying asleep, 2 mg	Immediately before bedtime	Insomnia: • Difficulties with sleep latency • Difficulties with sleep maintenance
Zaleplon[c]	Interacts with the $GABA_{BZ}$ receptor complex	1	1	Adults: 10 mg Elderly: 5 mg	Immediately before bedtime or after difficulty falling asleep	Insomnia: • Difficulty with sleep onset
Zolpidem[c]	$GABA_A$ agonist; interacts with the $GABA_{BZ}$ receptor complex; binds in vitro to BZ_1 receptor with a preferential affinity for α_1/α_5 subunits	1.6	2.5	Adults: • Women, 5 mg • Men, 5–10 mg Elderly: 5 mg	Immediately before bedtime with at least 7–8 hours before planned awakening	Insomnia: • Difficulty with sleep initiation
Zolpidem ER[c]	Same as zolpidem	1.5	~2.5	Adults: • Women, 6.25 mg • Men, 6.25–12.5 mg Elderly: 6.25 mg	Immediately before bedtime	Insomnia: • Difficulties with sleep onset • Difficulties with sleep maintenance
Zolpidem SL[c]	Same as zolpidem	0.5–1.25	1.4–3.6	Adults: • Women, 1.5 mg • Men, 3.5 mg Elderly: 1.75 mg	In bed after a nocturnal awakening with at least 4 hours of sleep time remaining	Insomnia: • Difficulties with nocturnal awakenings and trouble returning to sleep
Melatonin Receptor Agonist						
Ramelteon	Binds to M_1 and M_2 receptors	0.5–1.5	1–5	Adults: 8 mg	30 min before bedtime	Insomnia: • Difficulty with sleep onset
Tricyclic Antidepressant						
Doxepin	H_1 receptor antagonist	3.5	15	Adults: 6 mg Elderly: 3 mg	30 min before bedtime	Insomnia: • Difficulties with sleep maintenance

[a]Based on information contained in product package inserts.[32–43]
[b]Tolerance may develop.
[c]For short-term use only.
Abbreviations: BZ = benzodiazepine, ER = extended release, FDA = Food and Drug Administration, GABA = γ-aminobutyric acid, H = histamine, M = muscarinic, SL = sublingual.

to increase the amount of time in stage N2 sleep and decrease N3 or slow-wave sleep.[44]

Because some of the benzodiazepines are longer-acting, they carry the risk of next-day hangover, including problems with memory and psychomotor performance, thereby impairing patients' daytime function.[23,44] Other adverse events include complex sleep-related behaviors, including sleep walking, eating, or driving, and aggressive behavior.[44] When taken chronically, patients may experience drug accumulation, loss of efficacy over time, drug dependence with selected agents, and withdrawal effects such as rebound insomnia.[23] In elderly patients, benzodiazepines may

increase the risk of falls.[23] These agents should generally be administered at the lowest effective dosage and long-term use should be avoided due to their risk for accumulation (for those with long half-lives) and dependence.

Although benzodiazepines are effective and approved for the short-term treatment of insomnia, clinicians must consider the risk-benefit ratio when using these agents over the long-term.

Benzodiazepine receptor agonists. A newer medication class, the BZRAs, was introduced as an alternative to benzodiazepines. Although BZRAs have similar properties as benzodiazepines, their mechanism of action is similar in that they interact with the GABA-benzodiazepine receptor complexes, although they tend to have greater affinity for specific subtypes of the GABA receptor as well as shorter half-lives than the benzodiazepines, resulting in somewhat better safety and tolerability profiles. Dr Kilduff reviews this mechanism of action in more detail in the next section.

BZRAs have been shown to decrease sleep latency,[44] and those agents with longer durations of action may decrease WASO (see Table 2). For example, a meta-analysis[45] of 5 large, double-blind, placebo-controlled trials found that eszopiclone (3 mg) significantly increased total sleep time ($P < .0001$) and reduced sleep latency ($P < .0001$) and WASO ($P < .001$) for patients with primary insomnia; these measures were also significantly improved for patients with insomnia secondary to generalized anxiety disorder, major depression, menopause, and rheumatoid arthritis.[45] However, effect sizes for improvements in daytime functioning, including alertness, ability to concentrate and to function, and physical well-being, were modest for all groups, although highest in groups with primary insomnia and lowest in those with comorbid psychiatric conditions.

Roth et al[46] examined sublingual low-dose zolpidem (3.5 mg) for patients with primary insomnia and difficulty returning to sleep after nighttime awakenings (N = 295). Results showed that, compared with placebo, this formulation significantly decreased sleep latency ($P < .0001$) and favored zolpidem in ratings of morning sleepiness/alertness ($P = .004$). Dr Benca noted that the short half-life of zolpidem enables its use to get back to sleep after nocturnal awakenings with low risk of next-day impairment. Both groups experienced the same rate of mild adverse events (19%), and no serious adverse events occurred.

As with benzodiazepines, complex sleep-related behaviors (eg, sleepwalking, sleep-driving) may occur with BZRAs, but BZRAs are associated with fewer residual side effects and less rebound insomnia and dependence than benzodiazepines.[44] General side effects include fatigue, drowsiness, dizziness, headache, unpleasant taste, and diarrhea.

Melatonin receptor agonist. The melatonin receptor agonist ramelteon is indicated only to reduce sleep latency (see Table 2). The mechanism of action of ramelteon is based on a high affinity for MT_1 and MT_2 receptors,[47] which regulate neuronal firing and circadian sleep rhythms. Ramelteon can reduce time to fall asleep and increase total time spent asleep.[47,48] For example, ramelteon significantly decreased latency to persistent sleep ($P = .001$) and lengthened total sleep time ($P = .001$) versus placebo in a randomized, double-blind study[47] of 405 adults with chronic insomnia. WASO and number of awakenings were not significantly different between ramelteon and placebo.

Side effects reported with ramelteon are minimal and include headache, somnolence, and sore throat.[47] Ramelteon yielded no significant next-morning residual symptoms and no evidence of rebound insomnia or withdrawal.[47,48] Additionally, ramelteon is not a controlled substance, in contrast to benzodiazepines and BZRAs.

Studies comparing ramelteon with other hypnotic agents are lacking,[44] and the optimal dose has yet to be determined.

Tricyclic antidepressant. Dr Benca stated that doxepin, a potent H_1 antagonist, is probably the first agent that was aimed at blocking wakefulness rather than promoting sleep. Histamine levels increase at the end of the night, which likely explains why doxepin and other H_1 antagonists have properties of helping promote sleep maintenance. Some of their effects are more prominent after blood levels peak, unlike the benzodiazepines and BZRAs that seem to work when blood levels are high.

A randomized, placebo-controlled trial[49] showed that doxepin significantly reduced wake time during sleep and WASO with the 3-mg and 6-mg doses ($P < .0001$) and increased total sleep time and sleep efficiency with the 1-mg, 3-mg, and 6-mg doses ($P < .0005$) compared with placebo. Another randomized, placebo-controlled, crossover study[49] of elderly adults with insomnia also found that doxepin significantly reduced wake time during sleep and related WASO ($P < .0001$) and increased total sleep time and sleep efficiency ($P < .001$) with all doses of doxepin (1, 3, and 6 mg) compared with placebo.

Side effects for doxepin are comparable to those with placebo, with no significant anticholinergic effects, memory impairment, or next-day residual effects noted.[49,50] The lower doses of doxepin recommended for treating insomnia (3–6 mg) are not known to be associated with suicide risk, which is a concern with other antidepressants and higher doses of doxepin (25–150 mg).[51]

Off-Label Prescription Medications for Insomnia

Other medications with sedative effects are often prescribed as treatment for patients with insomnia despite having no FDA-approved indication to treat insomnia. Antidepressants, antipsychotics, and anticonvulsants may be particularly useful for specific subsets of patients with comorbid insomnia, but evidence is lacking that supports their efficacy and tolerability in patients with primary insomnia. Therefore, these classes of agents are not recommended as first-line treatment.

Antidepressants. Antidepressants with sedating properties are sometimes prescribed for primary and comorbid insomnia. Many of these antidepressants act at histaminergic, cholinergic, and serotonergic receptor sites. For example, trazodone, when given at lower doses, acts as an H_1 and $5\text{-}HT_2$ antagonist, which may give it sedating properties and help to induce sleep.[23]

Although trazodone is widely prescribed for insomnia, a review[52] of studies of trazodone for insomnia revealed a lack of objective efficacy measures, poor study design, and small study populations; additionally, most studies were conducted in only depressed patients. Trazodone can cause adverse effects such as dizziness and psychomotor impairment, which are especially concerning in elderly patients.[52]

In addition to trazodone, other 5-HT and H_1 antagonist antidepressants such as amitriptyline and mirtazapine are sometimes used for treating insomnia, but large, randomized, controlled trials are lacking to measure their efficacy and tolerability.[53] Sedating antidepressants may be considered for patients who do not respond to first-line insomnia treatment, but long-term use is not recommended.[53] Patients with insomnia secondary to depression or anxiety, or those who should not be prescribed controlled substances, may be the best candidates for antidepressant treatment of insomnia.

Antipsychotics. Antipsychotics have also been used to treat insomnia, but agents differ in their sedative effects based on the dose and the drug's affinity for H_1 receptors as well as the amount of medication reaching the central nervous system.[54] Generally, the high-dose, low-potency antipsychotics (eg, chlorpromazine, mesoridazine) create more sedation than low-dose, high-potency antipsychotics (eg, haloperidol, fluphenazine). This principle also applies to the atypical antipsychotics. Quetiapine and clozapine, which are low-potency, high-dose agents, are more sedating than risperidone, a high-potency, low-dose agent. Dose, however, does not always dictate level of sedation, as is the case with olanzapine, a low-dose atypical antipsychotic whose hypnotic effect may be related to its affinity for the H_1 receptor.[54]

Studies of antipsychotics have generally been conducted for insomnia secondary to psychosis, anxiety, or depression.[55] The efficacy of antipsychotics for primary insomnia not associated with psychiatric disorders has not been established in controlled trials.[56]

Side effects vary for antipsychotics, but they are associated with significant metabolic problems, weight gain, movement disorders, anticholinergic effects, cardiac risks, and sexual dysfunction.[57] As a result, their use for primary insomnia is strongly discouraged, and even when used in psychiatric patients, clinicians must monitor side effects closely.

Anticonvulsants. Anticonvulsants, such as gabapentin, pregabalin, and tiagabine, may promote sleep and enhance slow-wave sleep through various mechanisms. Gabapentin and pregabalin act on voltage-gated calcium channels and both increase GABA concentration in synapses and decrease stimulus-evoked glutamate release.[58] Tiagabine increases GABA activity in synapses by preventing GABA reuptake. Pain disorders, like fibromyalgia, with secondary insomnia have generally been the focus of studies analyzing anticonvulsants as treatment for insomnia, for which they have been effective.[55] However, controlled clinical trials of anticonvulsants are needed in primary insomnia to establish their efficacy. Side effects of anticonvulsants include dizziness, somnolence, tremors, confusion, and nausea or vomiting.

Unmet Needs in the Treatment of Insomnia

Unfortunately, there are many unmet needs related to the treatment of insomnia. For example, evidence showing efficacy of hypnotics for specific populations is lacking. Currently, there are no placebo-controlled trials of hypnotic agents for use in children, despite the frequent prescribing of pharmacotherapy for pediatric insomnia in clinical practice. Additionally, very few efficacy trials exist for hypnotic use in older adults. Comorbid insomnia is rarely studied, and no clinical trials have been conducted of medications that are frequently prescribed off-label (eg, antidepressants, antipsychotics, anticonvulsants).

Other unmet needs include the evaluation of long-term treatment in terms of the development of tolerance and addiction with currently approved medications. Daytime side effects, like cognitive impairment, should be studied with benzodiazepines and BZRAs, especially in susceptible populations like the elderly.

A better understanding of the underlying neural mechanisms of insomnia would aid the development of more effective treatment, as both homeostatic and circadian factors may contribute to sleep disorders. New treatment targets, based on the underlying neural mechanisms involved in the sleep-wake cycle, are needed for development of new pharmacotherapy approaches. Most importantly, long-term studies are needed to demonstrate that treatment of insomnia reduces associated medical and psychiatric comorbidities and improves quality of life.

Conclusion

Insomnia is a widespread problem with effects that hinder patients' daily functioning and quality of life. Treatments are needed to target sleep latency, sleep maintenance, and quality of sleep. An effective but often underused treatment is CBT for insomnia, which can help patients overcome negative sleep attitudes and implement sleep interventions. Over-the-counter medications including antihistamines and melatonin can help reduce difficulty falling asleep, but their efficacy is not confirmed in controlled trials. While valerian is a safe dietary supplement, its effects on sleep are inconsistent and unconfirmed.

Among the FDA-approved prescribed medications for insomnia, several treatment classes exist. Benzodiazepines are effective for insomnia and approved for short-term use, but their risk for developing tolerance, withdrawal, and abuse make them less appropriate for some patients, especially any who have had a substance use disorder. The improved side effect profile of BZRAs, based on their shorter half-lives and more specific mechanism of action at $GABA_A$ receptors, offers several options for effective insomnia relief, but these are also controlled substances. The melatonin receptor agonist ramelteon and the tricyclic antidepressant doxepin have been shown to improve sleep onset and sleep maintenance, respectively.

Off-label use of medications for insomnia can include antidepressants, antipsychotics, and anticonvulsants with sedative effects. While some may be suitable for patients

who do not respond to recommended first-line treatments for insomnia, the dose and side effects must be carefully monitored. Future studies into specific populations and the long-term tolerability and effectiveness of both approved and off-label medications will help clinicians choose appropriate insomnia treatments for patients of all ages. As the complex mechanisms involved in insomnia come to light, new treatment targets should be developed.

Discussion

Dr Krystal: I gather that there is going to be something different about enhancing GABAergic inhibition than blocking the activity in a wake-promoting system, be it hypocretin/orexin or histamine. My assumption is that GABA inhibition is broad and dominant and that the effects of the drugs are pretty global. We know that many different functions can be inhibited as doses are affected. However, with the wake-promoting system blockers, we have relatively little experience. And we know that with antihistamines, unlike agents that enhance GABAergic inhibition, pharmacodynamic effects are relatively unlinked from pharmacokinetics. A manifestation of this is that there are selective antihistamines that have relatively long half-lives compared with other insomnia agents, but do not seem to be sedating people. My hypothesis is that, because there are several parallel wake-promoting systems, if you block one, you still have others that can turn on and keep you awake and prevent you from being sleepy and impaired. Is that a viable model, based on what we know about the anatomy and physiology?

Dr Kilduff: Yes. Among the monoaminergic systems, in particular, there seems to be a good bit of redundancy—they all seem to be wake-promoting. Historically, serotonin was originally thought to be a sleep-promoting system, but in large part, it is actually wake-promoting. I think in the case of the hypocretin system, as you pointed out, it is upstream from all of these monoaminergic and cholinergic systems and it provides excitatory input to all of them. The hypocretins are uniformly excitatory (although they can also modulate GABA release locally). So, the prospect is that an antagonist for that system is going to work fundamentally differently than a GABAergic antagonist or inhibition of the GABAergic system because, rather than having an overall inhibition of activity, you are selectively blocking an excitatory system, thereby disfacilitating this particular system. But, in theory, other wake-promoting systems could still be recruited, with benefits for those having to awaken in the middle of the night to respond to an emergency situation.

Dr Krystal: Additionally, based on my clinical practice, I see several unmet needs. First, I have some patients who do not respond to available treatments, so we need new options for them; second, I have some patients who have side effects they cannot tolerate with available treatments; and third, as far as I know, we do not have any medications that help both sleep onset and sleep at the end of the night without a pretty high risk of daytime sedation.

Dr Benca: I agree. Also, regarding the issue of improving both sleep onset and sleep maintenance, data have suggested that some of the longer acting medications or the delayed-release formulations do increase sleep later in the night. But, again, I think it gets to whether these increases are sufficient to really correct some of the clinical problems that we deal with in our insomnia patients. Additionally, we often find that hangover the next day is problematic for many people, yet they do not always get that much better sleep later in the night, at least according to their clinical reports.

MECHANISM OF ACTION OF INSOMNIA TREATMENTS: GABA AGONISTS VERSUS OREXIN ANTAGONISTS

Next, Thomas S. Kilduff, PhD, outlined 2 systems involved in brain circuitry that regulate sleep and wakefulness: the GABAergic system and the more recently discovered orexin/hypocretin system. Understanding the mechanism of action of the medications that target these systems will help clinicians select treatments for their patients with insomnia.
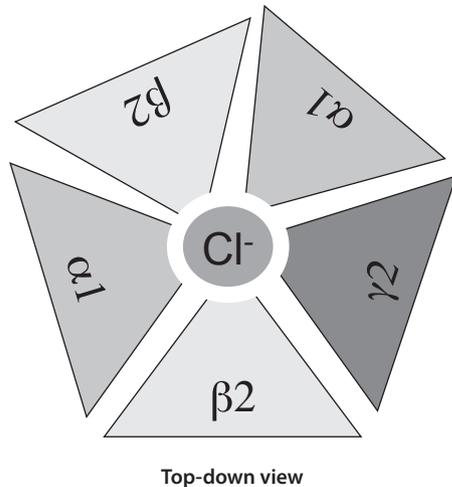
GABAergic System

Dr Kilduff described how GABA, as the principal inhibitory neurotransmitter in the central nervous system, plays a role in the regulatory mechanisms of the hypothalamus. About one-third of all brain synapses are estimated to use GABA as the transmitter.[59] GABA is converted from glutamic acid by the action of glutamic acid decarboxylase and then broken down by GABA transaminase to form succinic semialdehyde. Succinic semialdehyde is converted either to succinic acid or into γ-hydroxybutyric acid.[60] Succinic semialdehyde is involved in the tricarboxylic acid or Krebs cycle, which creates cellular energy. Several compounds affect the sleep-wake cycle by acting on GABA receptors.

GABA receptors. Dr Kilduff explained that $GABA_A$ receptors are linked to ion channels, whereas $GABA_B$ receptors are not.[61]

<u>$GABA_A$.</u> The $GABA_A$ receptor is a ligand-gated ion channel receptor that opens channels for chloride ions to flow through the cell membrane. The exchange of negatively-charged chloride ions causes neurons to become more hyperpolarized and less likely to discharge an action potential. $GABA_A$ receptors have different subunits containing sites that differentially bind GABA, benzodiazepines, barbiturates, convulsant agents, anesthetics, and steroids. Although $GABA_A$ receptors regulate the passage of chloride ions, benzodiazepine site ligands modulate the capacity of GABA to open the channel rather than directly opening the channel themselves.[62]

The composition and location of $GABA_A$ receptor subunits determine the effects of various drugs, making them useful study targets. For example, different $GABA_A$ α subtypes were shown to mediate different effects of benzodiazepines.[63] The most prevalent $GABA_A$-benzodiazepine receptor is a pentamer composed of 5 protein subunits including $α_1$, $β_2$, and $γ_2$, arranged around a central core (Figure 4).[62] Drugs

Figure 4. GABA$_A$/Benzodiazepine Receptor Complex^a

Top-down view

^{a}Based on Nutt and Malizia.[62] The GABA$_A$/benzodiazepine receptor complex has 5 subunits that form a central chloride channel. The composition of the subunits determines the pharmacology of the receptor, with different subtypes conferring differential sensitivities to benzodiazepine receptor ligands.
Abbreviation: GABA = γ-aminobutyric acid.

■ The GABAergic system has been the focus of hypnotics until the orexin system became a treatment target.

■ Benzodiazepines and BZRAs both act on the GABA$_A$ receptor, although their shorter half-lives and the specificity of BZRAs for subunits on the GABA$_A$ receptor provide better tolerability profiles than the benzodiazepines.

■ The orexin system has provided a new mechanism of action for hypnotics; at certain doses, antagonists may improve sleep without some of the adverse effects associated with benzodiazepines and BZRAs.

Clinical Points

with a greater selectivity for specific subunits may yield selective clinical effects.[63]

GABA$_B$. As a G protein-coupled receptor, the GABA$_B$ receptor activates a G protein in the postsynaptic cell. The G protein opens or closes ion channels located elsewhere on the cell membrane through a series of intracellular reactions. GABA$_B$ receptors can be divided into presynaptic and postsynaptic receptors, which are linked to either Ca^{2+} or K$^+$ channels, respectively.[64] GABA$_B$ receptors play a major role in regulating release of GABA from presynaptic terminals, as well as release of glutamate. Dr Kilduff noted that GABA$_B$ receptors seem to be important for presynaptic modulation of neuronal activity, whereas GABA$_A$ receptors are primarily postsynaptic. Agonists and antagonists have been created to target these receptors, causing different effects on the sleep cycle.

GABA-directed hypnotics. Three generations of hypnotic agents have been directed toward the GABA$_A$ receptor.[65] Barbiturates and benzodiazepines, the first and second generations, decrease waking and increase slow-wave sleep (SWS). The third generation of hypnotics, the benzodiazepine receptor agonists (BZRAs; also called nonbenzodiazepines because of their different chemical structures), are improved over previous generations because they decrease waking and improve SWS without increasing the intermediate sleep stage.[65] The nonbenzodiazepine BZRAs act as positive allosteric modulators of GABA at the GABA$_A$ receptor, specifically, the α and γ subunits.[61] When a BZRA is present, more chloride ions are able to enter the cell.

The current FDA-approved medications for insomnia include 5 benzodiazepines, 4 BZRAs, and the selective melatonin receptor agonist ramelteon (see Table 2). Ramelteon acts at MT$_1$ and MT$_2$ receptors, which are involved in the circadian cycle, whereas the benzodiazepines and BZRAs act at GABA$_A$ receptors and display different pharmacologic and clinical characteristics from ramelteon.[61]
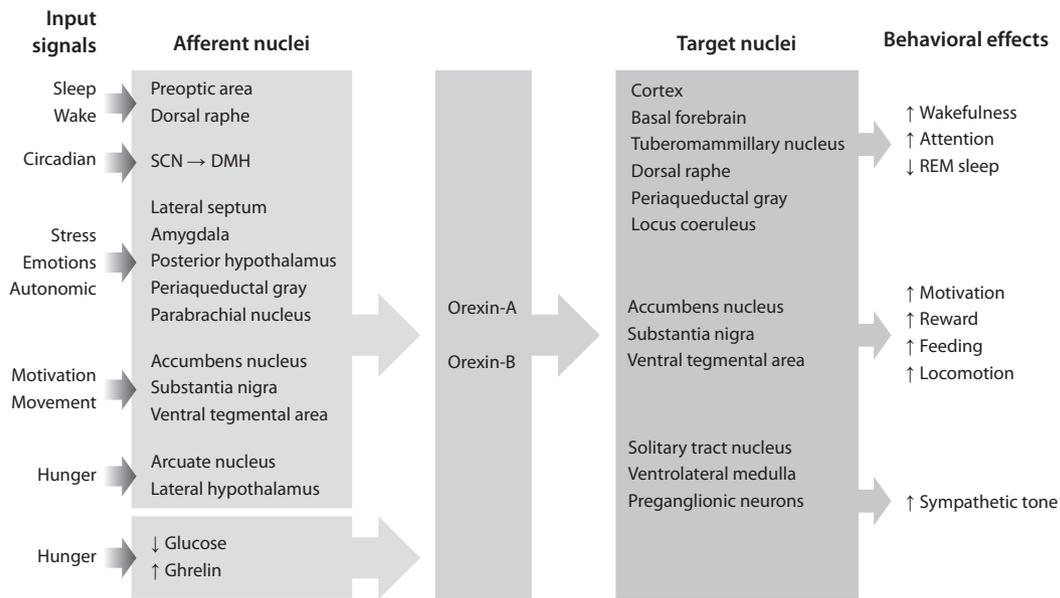
Flurazepam was the first benzodiazepine medication promoted for insomnia treatment, but other approved benzodiazepines now include temazepam, triazolam, estazolam, and quazepam.[61] A meta-analysis[66] found that benzodiazepines decreased sleep latency by only 4.2 minutes but increased sleep duration by about 60 minutes compared with placebo. Patients taking benzodiazepines reported more drowsiness, dizziness, and cognitive impairment, but these side effects did not cause higher discontinuation rates than with placebo. Dependence is another risk of benzodiazepines, with rebound insomnia as a result of withdrawal.

Next, Dr Kilduff reviewed the BZRAs, which include zaleplon, eszopiclone, and zolpidem. Zolpidem is available in immediate- and extended-release formulations. These nonbenzodiazepines, sometimes called Z drugs, are commonly prescribed worldwide.[67] A meta-analysis[67] of FDA data on the approved Z drugs showed that they produce slight improvements in subjective and polysomnographic sleep latency compared with placebo, but they carry the risk of side effects including cognitive impairment, psychomotor effects, daytime fatigue, tolerance, and addiction.

Unlike traditional benzodiazepine hypnotics that do not differentiate GABA$_A$ subunits, BZRAs have selectivity for specific α subunits, which may contribute to their slightly improved side effect profiles.[61] While traditional benzodiazepines have a half-life ranging from a few hours to a few days, the newer hypnotics have shorter half-lives ranging from 1 hour (zaleplon) to 7 hours (eszopiclone). The benefit of a shorter half-life means that patients experience less residual sedation in the morning, but a shorter half-life does not improve sleep maintenance.[61] One solution to this problem is controlled-release formulations, which maintain steady medication concentrations throughout the night. Because zolpidem extended-release improves sleep onset and maintenance and limits morning sleepiness,[68] more controlled-release formulations are likely to be developed.[61]

While long-term data are lacking for most of the BZRAs, a 6-month randomized, double-blind, placebo-controlled

Figure 5. Orexin System Pathways Related to Arousal[a]

[a]Reprinted with permission from Scammell and Winrow.[86]

This figure summarizes putative pathways through which signals related to sleep, stress, motivation, and hunger activate the orexin neurons to drive various aspects of arousal.

Abbreviations: DMH = dorsomedial nucleus of the hypothalamus, REM = rapid eye movement, SCN = suprachiasmatic nucleus.

study[69] was conducted for eszopiclone in 593 adults with chronic insomnia. Eszopiclone improved all the *DSM-IV* aspects of insomnia as well as daytime function. The minimal side effects, mostly unpleasant taste and headache, and considerable efficacy showed promising results for long-term use.[69] As the development of BZRAs continues, the focus will be on short half-life medications, α subunit selectivity, long-term efficacy and tolerability, sleep maintenance, and controlled-release formulations.[61]

In addition to their hypnotic effects, BZRAs may function as sedatives, muscle relaxants, anxiolytics, and anticonvulsants.[61]

Dr Kilduff mentioned that other GABAergic compounds have been shown to affect sleep. Sodium oxybate (also called γ-hydroxybutyrate or GHB), a GABA$_B$ agonist, increases SWS and EEG delta power and limits nighttime awakenings.[70,71] The use of GHB is limited by its abuse potential and association with dependence and seizures.[72]

Baclofen, a GABA$_B$ agonist used as a muscle relaxant and antispasmodic agent, has a sedative effect, increasing both REM and NREM sleep and reducing time awake after sleep onset.[73] It also improved total sleep time and sleep efficiency in patients with gastroesophageal reflux and sleep problems.[74]

Another medication that has proven effective for sleep problems is tiagabine, a GABA reuptake inhibitor that is used as an anticonvulsant. Tiagabine inhibits GABA transporter 1, which is 1 of 4 transporter proteins that promote the reuptake of GABA.[75] By increasing the duration of SWS, tiagabine improves sleep quality because SWS seems to be the most productive period for neurophysiologic restoration.[75]

For example, tiagabine improved sleep quality in 10 elderly patients with little SWS and high intermittent wakefulness by increasing both SWS and low-frequency activity in the EEG within NREM sleep.[76] Because elderly individuals spend less time in SWS, medications that increase this sleep phase should yield beneficial restorative effects.

Orexin System

In addition to outlining the sleep-promoting effects of GABAergic insomnia medications, Dr Kilduff discussed a new approach to treating insomnia that instead focuses on counteracting wakefulness. He recounted how 2 research groups working independently and using different approaches both discovered a new system of peptides and their receptors in 1998. The group at the Scripps Research Institute named the new peptides hypocretin 1 and 2 because they partially resembled the incretin peptides and were found in the hypothalamus.[77] The University of Texas Southwestern Medical Center group named the same peptides orexin A and B.[78] Thus, the names *hypocretin* and *orexin* are used interchangeably to refer to the same system of peptides and their receptors. Although the initial thought was that the orexin system influenced feeding and appetite, a connection was made between the loss of orexin-producing neurons and the development of narcolepsy.[79,80]

Narcolepsy is a chronic, disabling disorder associated with the brain's inability to control sleep-wake cycles. Narcolepsy causes sudden sleep episodes during normal times of wakefulness, ranging from seconds to minutes. Major symptoms include excessive daytime sleepiness, disturbed nighttime sleep, hallucinations, sleep paralysis,

and cataplexy.[81] Cataplexy is the sudden loss of muscle tone, and cataplexy attacks can vary from a drooping eyelid to a total physical collapse that leaves the individual inert but conscious.[81]
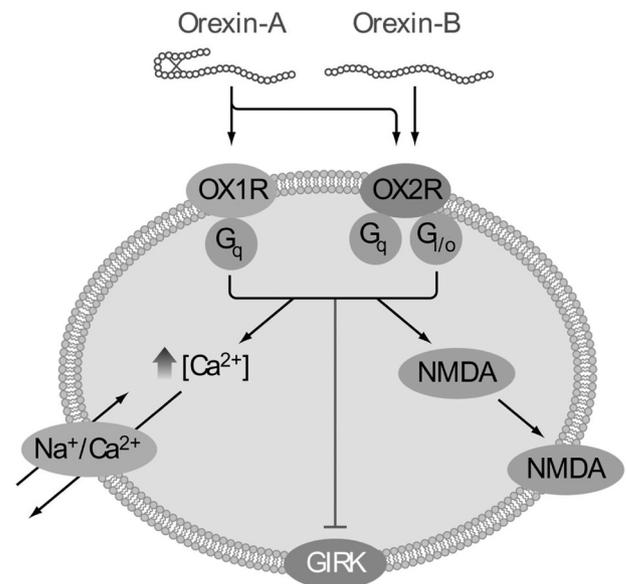
Orexin's connection with narcolepsy was first discovered in animal studies. In 1999, a year after the orexin system was first described, Lin and colleagues[82] found that canine narcolepsy was caused by a defect in the orexin receptor 2 gene. In parallel, orexin knockout mice were found to exhibit a similar phenotype to that of the canine and human narcolepsy.[83] Then in 2000, 2 groups discovered a massive loss in orexin neurons in the postmortem brains of humans with narcolepsy.[79,80] These studies confirmed that defects in the production and release of orexin, either postsynaptic (eg, dog) or presynaptic (eg, mouse, human), result in narcolepsy. After a study[84] showed that orexin A deficiency in cerebrospinal fluid (CSF) was present in over 90% of narcoleptic patients with cataplexy, a low CSF level of orexin A became a diagnostic criterion for narcolepsy-cataplexy according to the *International Classification of Sleep Disorders*, second edition.[85] This link between narcolepsy and orexin deficiency created interest in the orexin system's ability to regulate the sleep-wake cycle.

Neurobiology of the orexin system. Dr Kilduff described how orexin peptides are made by a cluster of neurons located in the posterior lateral hypothalamus (see Figure 1).[7,86] Between 50,000 and 80,000 orexin-producing neurons are in the human brain, and they follow ascending and descending pathways to brain regions associated with arousal (Figure 5).[7,86]

Orexin receptors. The orexin peptides A and B bind selectively to the orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R), which are both G protein-coupled receptors with 7 transmembrane domains.[86] OX1R binds orexin A with high affinity and orexin B with lower affinity. OX2R is less selective than OX1R and binds both orexin A and B with equal affinity (Figure 6).[78,86] OX2R shares 64% amino acid similarity with OX1R, and both receptors have some structural homology with other neuropeptide receptors.[78,86] Acting through orexin receptors, the hypocretin/orexin peptides excite neurons related to GABA, glutamate, and *N*-methyl-D-aspartate (NMDA) in various parts of the brain.[86]

Orexin antagonists. Dr Kilduff explained that because orexin peptides are excitatory and promote wakefulness, antagonists that block orexin receptors inhibit excitatory input to other arousal systems and create conditions for sleep to occur, rather than imposing sedation like GABAergic drugs. Upon recognition of this mechanism, companies began developing orexin antagonists to inhibit wakefulness and promote sleep. Hopes are high for this novel type of insomnia treatment for a number of reasons. First, orexin antagonists have the potential to selectively promote sleep without certain side effects such as the balance problems associated with sedating drugs like benzodiazepines, although clinical trials will need to monitor adverse effects such as morning sleepiness. Second, orexin antagonists

Figure 6. Orexin Signaling Mechanisms[a]

[a]Reprinted with permission from Scammell and Winrow.[86]
Orexin-A signals through both OX1R and OX2R, whereas orexin-B signals mainly through OX2R. Intracellular cascades mediated by G proteins (G) increase intracellular calcium and activate the sodium/calcium exchanger, which depolarizes target neurons. These cascades also inactivate G protein–regulated inward rectifier (GIRK) channels. Increased expression of *N*-methyl-D-aspartate (NMDA) receptors on the cell surface produces long-lasting increases in neuronal excitability.

are not associated with the dependence, abuse, or overdose issues of the benzodiazepines. Third, the new mechanism of action of orexin antagonists may improve insomnia in treatment-resistant patients.[86] Some orexin antagonists are in development and some have been discontinued, but the field is progressing.

Almorexant. The dual orexin receptor antagonist (DORA) almorexant showed efficacy in inducing sleep in rats, dogs, and humans without producing signs of cataplexy.[13] In a Phase II trial of 147 patients with insomnia, almorexant improved sleep efficiency by 10%,[86] but Phase III trials were stopped in 2011.[87]

Suvorexant. Another DORA agent is suvorexant (MK-4305). Suvorexant reduced wakefulness and increased REM and NREM sleep in telemetry-implanted rats.[88] A 2-period, 8-week crossover trial[89] of suvorexant in nonelderly adult patients with insomnia showed significant improvements ($P = .01$) over placebo in sleep efficiency and was well tolerated. A 4-period crossover study[90] of suvorexant in healthy men used polysomnography to measure sleep parameters. The sleep-promoting effects of suvorexant were apparent with all doses (10, 50, and 100 mg) compared with placebo, but some residual morning effects were experienced at the 2 higher doses. Since suvorexant has demonstrated efficacy and tolerability in Phase II and III trials, the FDA is reviewing its approval for the treatment of insomnia.[91]

SB-649868. SB-649868 is another DORA medication under investigation for insomnia treatment. Phase I studies[92] showed that this agent improved latency to sleep, total sleep

time, and wake after sleep onset in 103 male participants. The drug was well tolerated with no evidence of residual cognitive effects the following morning. In Phase II trials,[93] SB-649868 improved sleep induction and maintenance in 52 male patients with insomnia. The most common side effects were headache, dry mouth, and nasopharyngitis. Next-day cognitive tests produced mixed results.

<u>JNJ-10397049.</u> Unlike the DORA agents, JNJ-10397049 acts on the OX2R alone. JNJ-10397049 decreased the time to persistent sleep and increased REM and NREM sleep time in rat studies.[94] Initial results suggest that blocking the OX2R is sufficient to cause and maintain sleep, although uncertainty exists whether an OX2R-selective approach is more effective than that exemplified by the DORAs.[95]

Conclusion

Dr Kilduff concluded that insomnia treatments can now target 2 different systems that control sleep-wake cycles. The GABAergic system has been the focus of treatment since the advent of the benzodiazepines, which act as agonists at GABA$_A$ receptors. Nonbenzodiazepine hypnotics have a shorter half-life than benzodiazepines and target specific subunits of GABA$_A$ receptors, giving them improved side effect profiles. Controlled-release formulations offer a solution to the problem of sleep maintenance, which most insomnia medications do not address.

The discovery of the orexin system's role in narcolepsy has led to research into how it affects the sleep-wake cycle. Because a deficiency of orexin was found in people with narcolepsy who fall asleep during typical waking hours, the orexin system was found to be central to the maintenance of wakefulness. Therefore, orexin receptor antagonists promote sleep in people with insomnia by reducing waking "drive." Orexin antagonists offer the potential to treat insomnia without morning sedation, balance problems, dependence, or the risk for abuse that are associated with many GABA agonists. Their unique mechanism of action has the potential to provide effective and tolerable treatment for insomnia.

Discussion

Dr Krystal: Since the wake-promoting and sleep-promoting systems are mutually inhibitory, if orexin is blocked, does that increase GABAergic activity?

Dr Kilduff: That is an interesting point that has not been addressed directly.

Dr Benca: Because orexin levels are increased at the beginning of the night and decrease throughout the night during sleep, would an orexin antagonist have much effect on sleep during the latter part of the night?

Dr Kilduff: Probably not, although it depends on what the high and low CSF levels of orexin actually mean. As we discussed earlier, although CSF measurements of orexin reflect prior neural activity, the temporal relationship between these 2 processes is incompletely understood. If levels of orexin in CSF are reflecting what is happening in local areas of the brain, excitation would still be occurring in the early part of the night even when CSF levels are low, meaning that

an antagonist at that time should be more effective than later in the night/early in the morning when lower levels occur.

Dr Krystal: What is the role of the activity of other systems? In the early morning, most wake-promoting systems, except histamine, are relatively less active.

Dr Kilduff: The hypothalamic-pituitary-adrenal axis is an important component in terms of arousal and plays a role in wake promotion. Cortisol levels are typically highest shortly after awakening.

Dr Krystal: How might the effects differ between antagonism of OX1R and OX2R?

Dr Kilduff: There are different views about the utility of a receptor-specific antagonist versus the synergism between the 2 orexin receptors. Almorexant, which has clear sleep-inducing activity, is a dual receptor compound. Not a lot of work has been done with receptor 2 antagonists because they are not readily available, although some believe that the most effective sleep-producing activity is through OX2R. However, the literature and experience to date suggest that sleep is effectively produced by dual receptor antagonism.

Dr Benca: Do orexin antagonists have the potential to produce narcoleptic-like symptoms in people with and without a tendency toward narcolepsy?

Dr Kilduff: Yes, which may be one reason why the dual receptor approach is less risky than receptor-2 specific antagonists. In mouse models, narcolepsy is not receptor-2 specific as it seems to be in dogs.[96] To generalize from the dog model to humans, receptor-2 specific antagonists would be more likely to cause narcoleptic symptoms than the dual-receptor approach. To this point, clinical studies with DORAs have not provoked cataplexy in humans, although we have documented some very rare cataplexy episodes induced by almorexant in wild type mice.[97]

Dr Krystal: Based on what we know about the science of the orexin system, what might be other adverse effects, besides narcoleptic effects, of the orexin antagonist drugs?

Dr Kilduff: Because the orexin system plays a role in metabolism, weight gain is a possible side effect with chronic use. People with narcolepsy who lack orexin peptides tend to have a higher body mass index than the general population, but they also tend to be less active.[98]

Dr Krystal: What about the common side effects with benzodiazepines, like cognitive impairment, balance disturbance, and myo-relaxation?

Dr Kilduff: I am unaware of any specific concerns that orexin antagonists would affect those particular functions, although there are certainly orexin receptors in the cerebral cortex. In theory, awakening from an orexin-receptor antagonist-induced sleep should not produce the same adverse effects as benzodiazepine-receptor agonist-induced sleep. Studies are needed to confirm this, though.

Dr Krystal: Is there any reason to believe that medications which block orexin might eventually lose hypnotic effect over time?

Dr Kilduff: Studies of chronic use are necessary to answer that question, and those data are not yet available. Long-term tolerability and efficacy are critical areas to be studied.

Drug names: baclofen (Gablofen, Lioresal, and others), clozapine (Clozaril, FazaClo, and others), doxepin (Zonalon, Silenor, and others), eszopiclone (Lunesta), gabapentin (Neurontin, Gralise, and others), haloperidol (Haldol and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), pregabalin (Lyrica), quazepam (Doral), quetiapine (Seroquel and others), ramelteon (Rozerem), risperidone (Risperdal and others), sodium oxybate (Xyrem), temazepam (Restoril and others), tiagabine (Gabitril), trazodone (Oleptro and others), triazolam (Halcion and others), trimipramine (Surmontil and others), zaleplon (Sonata and others), zolpidem (Ambien, Zolpimist, and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, almorexant, amitriptyline, chlorpromazine, clozapine, diphenhydramine, doxylamine, fluphenazine, gabapentin, haloperidol, mesoridazine, mirtazapine, olanzapine, pregabalin, quetiapine, risperidone, sodium oxybate, tiagabine, trazodone, trimipramine, and suvorexant are not approved by the US Food and Drug Administration for the treatment of insomnia.

REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual*. Chicago, IL: American Academy of Sleep Medicine; 2001. http://www.esst.org/adds/ICSD.pdf. Accessed June 4, 2013.
2. Ishak WW, Bagot K, Thomas S, et al. Quality of life in patients suffering from insomnia. *Innov Clin Neurosci*. 2012;9(10):13–26.
3. Roth T. Prevalence, associated risks, and treatment patterns of insomnia. *J Clin Psychiatry*. 2005;66(suppl 9):10–13.
4. Borbély AA. A two process model of sleep regulation. *Hum Neurobiol*. 1982;1(3):195–204.
5. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437(7063):1257–1263.
6. Saper CB, Cano G, Scammell TE. Homeostatic, circadian, and emotional regulation of sleep. *J Comp Neurol*. 2005;493(1):92–98.
7. Peyron C, Tighe DK, van den Pol AN, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci*. 1998;18(23):9996–10015.
8. Zeitzer JM, Nishino S, Mignot E. The neurobiology of hypocretins (orexins), narcolepsy and related therapeutic interventions. *Trends Pharmacol Sci*. 2006;27(7):368–374.
9. Zeitzer JM, Buckmaster CL, Parker KJ, et al. Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. *J Neurosci*. 2003;23(8):3555–3560.
10. Zhang S, Zeitzer JM, Yoshida Y, et al. Lesions of the suprachiasmatic nucleus eliminate the daily rhythm of hypocretin-1 release. *Sleep*. 2004;27(4):619–627.
11. Morgan PT, Pace-Schott EF, Mason GF, et al. Cortical GABA levels in primary insomnia. *Sleep*. 2012;35(6):807–814.
12. Plante DT, Jensen JE, Schoerning L, et al. Reduced γ-aminobutyric acid in occipital and anterior cingulate cortices in primary insomnia: a link to major depressive disorder? *Neuropsychopharmacology*. 2012;37(6):1548–1557.
13. Brisbare-Roch C, Dingemanse J, Koberstein R, et al. Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nat Med*. 2007;13(2):150–155.
14. Wu MF, John J, Maidment N, et al. Hypocretin release in normal and narcoleptic dogs after food and sleep deprivation, eating, and movement. *Am J Physiol Regul Integr Comp Physiol*. 2002;283(5):R1079–R1086.
15. Mileykovskiy BY, Kiyashchenko LI, Siegel JM. Behavioral correlates of activity in identified hypocretin/orexin neurons. *Neuron*. 2005;46(5):787–798.
16. Blouin AM, Fried I, Wilson CL, et al. Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. *Nat Commun*. 2013;4:1547.
17. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487–504.
18. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. *Sleep*. 2006;29(11):1415–1419.
19. Espie CA. "Stepped care": a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep*. 2009;32(12):1549–1558.
20. Edinger JD, Wohlgemuth WK, Radtke RA, et al. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA*. 2001;285(14):1856–1864.
21. Espie CA, Inglis SJ, Tessier S, et al. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: implementation and evaluation of a sleep clinic in general medical practice. *Behav Res Ther*. 2001;39(1):45–60.
22. Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep*. 2006;29(11):1398–1414.
23. Stahl MS. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 3rd ed. New York, NY: Cambridge University Press; 2008.
24. Krystal AD, Richelson E, Roth T. Review of the histamine system and the clinical effects of H1 antagonists: basis for a new model for understanding the effects of insomnia medications. *Sleep Med Rev*. 2013;17(4):263–272.
25. Kalpaklioglu F, Baccioglu A. Efficacy and safety of H1-antihistamines: an update. *Antiinflamm Antiallergy Agents Med Chem*. 2012;11(3):230–237.
26. Hajak G, Rodenbeck A, Staedt J, et al. Nocturnal plasma melatonin levels in patients suffering from chronic primary insomnia. *J Pineal Res*. 1995;19(3):116–122.
27. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS ONE*. 2013;8(5):e63773.
28. Lemoine P, Zisapel N. Prolonged-release formulation of melatonin (Circadin) for the treatment of insomnia. *Expert Opin Pharmacother*. 2012;13(6):895–905.
29. Sarris J, Byrne GJ. A systematic review of insomnia and complementary medicine. *Sleep Med Rev*. 2011;15(2):99–106.
30. Gooneratne NS. Complementary and alternative medicine for sleep disturbances in older adults. *Clin Geriatr Med*. 2008;24(1):121–138, viii.
31. Taibi DM, Landis CA, Petry H, et al. A systematic review of valerian as a sleep aid: safe but not effective. *Sleep Med Rev*. 2007;11(3):209–230.
32. Silenor (doxepin) [package insert]. San Diego, CA: Somaxon Pharmaceuticals, Inc; 2010.
33. Estazolam [package insert]. Sellersville, PA: Teva Pharmaceuticals USA; 2008.
34. Lunesta (eszopiclone) [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc; 2012.
35. Flurazepam [package insert]. Libertyville, IL: A-S Medical Solutions; 2010.
36. Doral (quazepam) [package insert]. Hayward, CA: Questor Pharmaceuticals, Inc; 2013.
37. Rozerem (ramelteon) [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2010.
38. Restoril (temazepam) [package insert]. Hazelwood, MO: Mallinckrodt Inc; 2011.
39. Halcion (triazolam) [package insert]. New York, NY: Pharmacia & Upjohn Inc; 2013.
40. Sonata (zaleplon) [package insert]. Bristol, TN: King Pharmaceuticals, Inc; 2011.
41. Ambien (zolpidem) [package insert]. Bridgewater, NJ: sanofi-aventis US LLC; 2013.
42. Zolpidem extended release [package insert]. Irvine, CA: Anchn Pharmaceuticals, Inc; 2011.
43. Intermezzo (zolpidem sublingual) [package insert]. Stamford, CT: Purdue Pharma LP; 2014.
44. Drugs for insomnia. *Treat Guidel Med Lett*. 2009;7(79):23–26.
45. Krystal AD, McCall WV, Fava M, et al. Eszopiclone treatment for insomnia: effect size comparisons in patients with primary insomnia and insomnia with medical and psychiatric comorbidity. *Prim Care Companion CNS Disord*. 2012;14(4):doi:10.4088/pcc.11m01296.
46. Roth T, Krystal A, Steinberg FJ, et al. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. *Sleep*. 2013;36(2):189–196.
47. Zammit G, Erman M, Wang-Weigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med*. 2007;3(5):495–504.
48. Erman M, Seiden D, Zammit G, et al. An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Med*. 2006;7(1):17–24.
49. Roth T, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep*. 2007;30(11):1555–1561.
50. Scharf M, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry*. 2008;69(10):1557–1564.
51. Patel D, Goldman-Levine JD. STEPS New Drug Reviews: Doxepin (Silenor) for Insomnia. http://www.aafp.org/afp/2011/0815/p453.html. August 15, 2011. Accessed June 11, 2013.
52. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry*. 2005;66(4):469–476.
53. Vande Griend JP, Anderson SL. Histamine-1 receptor antagonism for treatment of insomnia. *J Am Pharm Assoc (2003)*. 2012;52(6):e210–e219.
54. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. *Prim Care Companion J Clin Psychiatry*. 2004;6(suppl 2):3–7.
55. McCall C, McCall WV. What is the role of sedating antidepressants, antipsychotics, and anticonvulsants in the management of insomnia? *Curr Psychiatry Rep*. 2012;14(5):494–502.
56. Wilson S, Nutt D. Management of insomnia: treatments and mechanisms. *Br J Psychiatry*. 2007;191(3):195–197.
57. Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician*. 2010;81(5):617–622.
58. Quintero JE, Dooley DJ, Pomerleau F, et al. Amperometric measurement of glutamate release modulation by gabapentin and pregabalin in rat neocortical slices: role of voltage-sensitive Ca2+ α2δ-1 subunit. *J Pharmacol Exp Ther*. 2011;338(1):240–245.

59. Purves D, Augustine GJ, Fitzpatrick D, et al. *Neuroscience*. 2nd ed. Sunderland, MA: Sinauer Associates; 2001.
60. Wong CG, Bottiglieri T, Snead OC 3rd. GABA, gamma-hydroxybutyric acid, and neurological disease. *Ann Neurol*. 2003;54(suppl 6):S3–S12.
61. Neubauer DN. The evolution and development of insomnia pharmacotherapies. *J Clin Sleep Med*. 2007;3(suppl):S11–S15.
62. Nutt DJ, Malizia AL. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. *Br J Psychiatry*. 2001;179(5):390–396.
63. Sieghart W, Sperk G. Subunit composition, distribution and function of GABA(A) receptor subtypes. *Curr Top Med Chem*. 2002;2(8):795–816.
64. Ong J, Kerr DI. Recent advances in GABAB receptors: from pharmacology to molecular biology. *Acta Pharmacol Sin*. 2000;21(2):111–123.
65. Gottesmann C. GABA mechanisms and sleep. *Neuroscience*. 2002;111(2):231–239.
66. Holbrook AM, Crowther R, Lotter A, et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ*. 2000;162(2):225–233.
67. Huedo-Medina TB, Kirsch I, Middlemass J, et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ*. 2012;345(6):e8343.
68. Krystal AD, Erman M, Zammit GK, et al, for the ZOLONG Study Group. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep*. 2008;31(1):79–90.
69. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003;26(7):793–799.
70. Vienne J, Lecciso G, Constantinescu I, et al. Differential effects of sodium oxybate and baclofen on EEG, sleep, neurobehavioral performance, and memory. *Sleep*. 2012;35(8):1071–1083.
71. Pardi D, Black J. gamma-Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs*. 2006;20(12):993–1018.
72. O'Connell T, Kaye L, Plosay JJ 3rd. Gamma-hydroxybutyrate (GHB): a newer drug of abuse. *Am Fam Physician*. 2000;62(11):2478–2483.
73. Finnimore AJ, Roebuck M, Sajkov D, et al. The effects of the GABA agonist, baclofen, on sleep and breathing. *Eur Respir J*. 1995;8(2):230–234.
74. Orr WC, Goodrich S, Wright S, et al. The effect of baclofen on nocturnal gastroesophageal reflux and measures of sleep quality: a randomized, cross-over trial. *Neurogastroenterol Motil*. 2012;24(6):553–559, e253.
75. Walsh JK. Enhancement of slow wave sleep: implications for insomnia. *J Clin Sleep Med*. 2009;5(suppl):S27–S32.
76. Mathias S, Wetter TC, Steiger A, et al. The GABA uptake inhibitor tiagabine promotes slow wave sleep in normal elderly subjects. *Neurobiol Aging*. 2001;22(2):247–253.
77. de Lecea L, Kilduff TS, Peyron C, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci U S A*. 1998;95(1):322–327.
78. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*. 1998;92(4):573–585.
79. Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;27(3):469–474.
80. Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med*. 2000;6(9):991–997.
81. National Institute of Neurological Disorders and Stroke. Narcolepsy Fact Sheet. http://www.ninds.nih.gov/disorders/narcolepsy/detail_narcolepsy.htm. Updated December 28, 2011. Accessed June 4, 2013.
82. Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell*. 1999;98(3):365–376.
83. Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*. 1999;98(4):437–451.
84. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol*. 2002;59(10):1553–1562.
85. Tsujino N, Sakurai T. Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. *Pharmacol Rev*. 2009;61(2):162–176.
86. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol*. 2011;51(1):243–266.
87. Actelion. Actelion and GSK discontinue clinical development of almorexant. http://www1.actelion.com/en/our-company/news-and-events/index.page?newsId=1483135. Published January 28, 2011. Accessed June 5, 2013.
88. Whitman DB, Cox CD, Breslin MJ, et al. Discovery of a potent, CNS-penetrant orexin receptor antagonist based on an n,n-disubstituted-1,4-diazepane scaffold that promotes sleep in rats. *ChemMedChem*. 2009;4(7):1069–1074.
89. Herring WJ, Snyder E, Budd K, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*. 2012;79(23):2265–2274.
90. Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. 2013;36(2):259–267.
91. Winrow CJ, Renger JJ. Discovery and development of orexin receptor antagonists as therapeutics for insomnia [published online ahead of print June 3, 2013]. *Br J Pharmacol*. doi:10.1111/bph.12261.
92. Bettica P, Nucci G, Pyke C, et al. Phase I studies on the safety, tolerability, pharmacokinetics and pharmacodynamics of SB-649868, a novel dual orexin receptor antagonist. *J Psychopharmacol*. 2012;26(8):1058–1070.
93. Bettica P, Squassante L, Zamuner S, et al. The orexin antagonist SB-649868 promotes and maintains sleep in men with primary insomnia. *Sleep*. 2012;35(8):1097–1104.
94. Dugovic C, Shelton JE, Aluisio LE, et al. Blockade of orexin-1 receptors attenuates orexin-2 receptor antagonism-induced sleep promotion in the rat. *J Pharmacol Exp Ther*. 2009;330(1):142–151.
95. Morairty SR, Revel FG, Malherbe P, et al. Dual hypocretin receptor antagonism is more effective for sleep promotion than antagonism of either receptor alone. *PLoS ONE*. 2012;7(7):e39131.
96. Willie JT, Chemelli RM, Sinton CM, et al. Distinct narcolepsy syndromes in orexin receptor-2 and orexin null mice: molecular genetic dissection of Non-REM and REM sleep regulatory processes. *Neuron*. 2003;38(5):715–730.
97. Black SW, Morairty SR, Fisher SP, et al. Almorexant promotes sleep and exacerbates cataplexy in a murine model of narcolepsy. *Sleep*. 2013;36(3):325–336.
98. Poli F, Plazzi G, Di Dalmazi G, et al. Body mass index-independent metabolic alterations in narcolepsy with cataplexy. *Sleep*. 2009;32(11):1491–1497.