



Targeting Neurotransmitters in the Management of Insomnia

LEARNING OBJECTIVE

Evaluate how research findings for emerging agents will likely affect routine clinical practice in the care of patients with insomnia.

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PART 2 OF THIS TWO-SUPPLEMENT SERIES

This supplement provides the second of two articles that will explore new insights into the sleep-wake system, advances in the understanding that insomnia may be a result of hyperarousal, and how sleep and wake are regulated by classical neurotransmitters and the neuropeptides orexin-A and -B. This supplement will focus on current treatments for insomnia encompassing cognitive behavioral therapy, over-the-counter and prescription medications, including a newly approved agent, an orexin antagonist. This supplement will also highlight how insomnia impacts patients with insomnia ("Voice of the Patient") through case vignettes.

For a thorough discussion of the neurobiology and pathophysiology of sleep and wakefulness in the first part of this series, refer to: Krystal, A. D., et al. (2014). New insights in to the sleep-wake system: the neurobiology and pathophysiology of insomnia. *Psychiatric News*, 49 (10) (Suppl). (May 16, 2014).

ACTIVITY GOAL

Psychiatrists will stay abreast of emerging research findings and describe the treatments for insomnia

TARGET AUDIENCE

Psychiatrists and other health care professionals interested in sleep-wake medicine.

COMMERCIAL SUPPORT STATEMENT

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STATEMENT OF NEED

Insomnia can affect many aspects of an individual's life: impairing concentration and memory, increasing the risk of incident depression or recurrence of a depressive episode, diminishing a patient's ability to enjoy family and social relationships, and increasing the risks of falls and motor vehicle accidents.

This neuroscienceCME *Clinical Navigator* is the second supplement in a two-part series derived from an Expert Roundtable. Following up on the May 2014 *Psychiatric News* supplement titled, "New Insights Into Sleep-Wake System Neurobiology and Pathophysiology of Insomnia¹," it will describe the treatments used in insomnia, so that clinicians understand more about the roles of neurotransmitters and therapeutic agents, including orexin antagonists. It is important for clinicians to be aware of emerging agents in order to tailor treatments to individual needs as new therapeutic options for insomnia become available.

1. Krystal AD, et al. New Insights Into the Sleep-Wake System: The Neurobiology and Pathophysiology of Insomnia. *Psychiatric News*. May 16, 2014; 49 (10) [Suppl].

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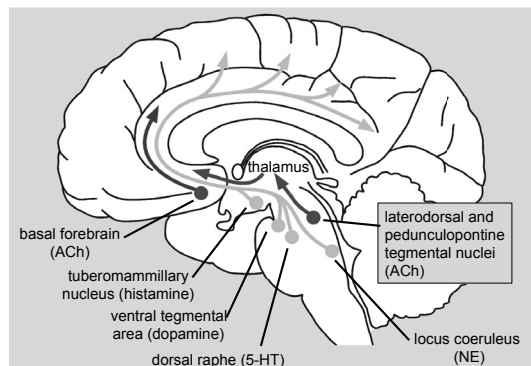
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NEUROBIOLOGY OF SLEEP AND WAKEFULNESS

Insomnia is a common yet often challenging clinical problem, and clinicians can manage insomnia more thoughtfully when equipped with a deeper understanding of the neural pathways that regulate sleep and wakefulness. Wake-promoting signals arise from neurons in the brainstem, hypothalamus, and basal forebrain that activate the cerebral cortex and other parts of the forebrain (Figure 1) (Saper, Scammell, & Lu, 2005). These neurons use acetylcholine and monoaminergic neurotransmitters such as norepinephrine, dopamine, serotonin, and histamine to promote arousal, and the clinical importance of these pathways is clear as sedation is common with many monoamine antagonists and anticholinergics (e.g. haloperidol, doxepin, and diphenhydramine) (Scammell & Winrow, 2011).

FIGURE 1:
WAKE-PROMOTING PATHWAYS

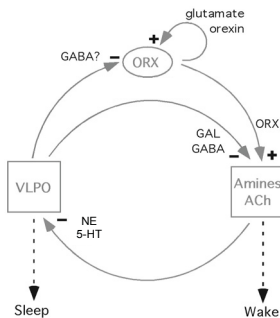


Neurons producing orexins are another key element of the wake-promoting system (Sakurai, 2007; Scammell & Winrow, 2011; Alexandre, et al., 2013). Orexin-A and orexin-B are peptide neurotransmitters produced only by a small cluster of neurons in the lateral hypothalamus. The orexins are released during wakefulness, and they act through the OX1 and OX2 receptors to increase activity in target neurons that promote wakefulness, including monoaminergic and cholinergic neurons. The orexins produce long-lasting activation of these target neurons, and consequently produce long, sustained periods of wakefulness, and suppression of REM sleep (Scammell & Winrow, 2011). In addition, orexins enhance activity in brain regions that regulate motivation and reward.

On the other hand, one of the key factors promoting sleep is GABA. During sleep, GABAergic neurons in the rostral part of the hypothalamus inhibit all the key wake-promoting brain regions, and this inhibition helps ensure that all arousal systems are inhibited in a coordinated fashion (Saper, et al., 2005). Conversely, during wakefulness, the sleep-promoting GABAergic neurons are inhibited by acetylcholine, monoamines, and the orexins, ensuring long stable periods of alertness across the day (Figure 2, next page).

Pharmacologically, one can promote sleep by enhancing GABAergic signaling or by inhibiting wake-promoting signals (Scammell & Winrow, 2011). Drugs that enhance GABAergic signaling such as benzodiazepine receptor agonists including zolpidem, zaleplon, and eszopiclone are often effective for insomnia, but as GABA-A receptors are found throughout the nervous system, these agents have broad effects on brain function which can include producing side effects such as confusion and unsteady gait. In contrast, orexins primarily excite neurons that promote wakefulness, so orexin antagonists are relatively specific in their effects such that they mainly promote sleep, although they have their own side effects.

FIGURE 2:
OREXINS STABILIZE WAKEFULNESS



5-HT = 5-hydroxytryptamine (serotonin); ACh = acetylcholine; GABA = gamma-aminobutyric acid; GAL = galanin; NE = norepinephrine; ORX = orexin; VLPO = ventrolateral preoptic nucleus.
The neural systems that promote sleep and wakefulness are mutually inhibitory. During wakefulness, monoamine neurotransmitters and acetylcholine inhibit VLPO area neurons that produce sleep. This reduction in VLPO activity allows the wake-promoting brain regions to be fully active, ensuring a high level of arousal. The opposite occurs during sleep. The orexin neurons excite the other wake-promoting brain regions, and their activity is enhanced by an autoexcitatory feedback loop which may help drive sustained activity in the orexin neurons and other wake-promoting systems.

For a thorough discussion of the neurobiology of sleep and wakefulness, refer to Krystal AD et al. *New Insights Into the Sleep-Wake System: The Neurobiology and Pathophysiology of Insomnia*. *Psychiatric News*, May 16, 2014; 49 (10) (Suppl).

HYPERAROUSAL AS A MAJOR ASPECT OF INSOMNIA

Substantial clinical research has shown that insomnia is strongly associated with relatively increased activity in various arousal systems and relatively decreased activity in sleep promoting systems. Compared with healthy control subjects, subjects with insomnia show signs of hyperarousal such as elevations in core body temperature, heart rate, catecholamine levels, reactivity to stress, and other physiologic changes (Box 1). (Bonnet & Arand, 1995, 2001; Drake et al, 2006; Lushington et al, 2000; McClure et al, 2003; Perlis et al., 2001; Roehrs et al, 2012;). These physiological measures support the conceptualization of insomnia as a disorder of hyperarousal.

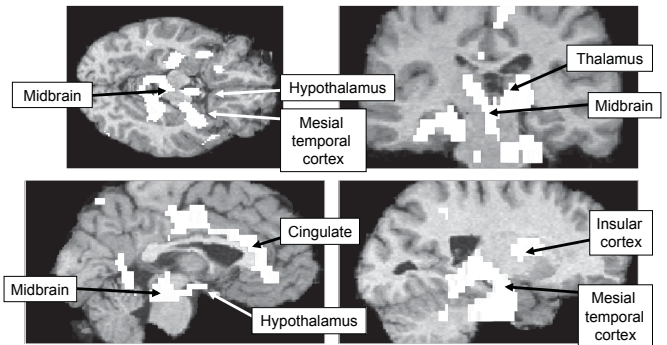
BOX 1: PHYSIOLOGICAL MEASURES OF HYPERAROUSAL IN INSOMNIA

- Heart rate (Stepanski, et al., 1994)
- Metabolic rate (Bonnet & Arand, 1995)
- Body temperature (Lushington, et al., 2000)
- EEG high-frequency/low-frequency ratio (Bonnet & Arand, 2001)
- High-frequency EEG activity (Perlis, et al., 2001)
- Catecholamine levels (McClure, et al., 2003)
- Daytime alertness (T. Roehrs & Roth, 2008)
- Reactivity to stress (C Drake, et al., 2013)

Hyperarousal in people with insomnia is not limited to the sleep period but is present during the day as well. The level of daytime arousal can be measured by the Multiple Sleep Latency Test (MSLT) in which short sleep latencies on this test indicate daytime sleepiness and longer latencies indicate higher levels of arousal. Roehrs and colleagues found that, among patients with insomnia, those who are most alert (i.e., have the longest MSLT sleep latency), have the worst nighttime sleep (Roehrs et al, 2011). Thus, while reduced sleep is typically associated with decreased alertness, lower sleep times in patients with insomnia is associated with increased alertness (Roehrs, et al., 2011).

Further, hyperarousal in people with insomnia has also been documented in neuroimaging studies showing greater brain metabolism in some regions. In comparing subjects with and without insomnia, positive emission tomography imaging demonstrates greater overall cerebral glucose metabolism in patients with insomnia when asleep as well as when awake and a smaller decline in relative metabolism from waking to sleep in wake-promoting brain regions (Figure 3).

FIGURE 3:
AROUSAL SYSTEMS IN INSOMNIA SUBJECTS THAT DO NOT DEACTIVATE FROM WAKING TO SLEEP



Adapted from: Nofzinger, E. A., Buysse, D. J., Germain, A., Price, J. C., Miewald, J. M., & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry*, 161(11), 2126-2128. doi: 10.1176/appi.ajp.161.11.2126.

Clues to this hyperarousal include patient reports of cognitive intrusion during presleep ruminations and mentation expressed as statements like "I can't shut my mind off." Pre-sleep arousal scales may be clinically useful in diagnosing hyperarousal in patients. For example, the Pre-Sleep Arousal Scale-13 (PSAS-13) and the two subscales show discriminant validity between three sleep groups (normal sleep, poor sleep, and insomnia disorder) ($R(2) = .24-.34$). The PSAS-13 and the subscales demonstrated convergent validity with measures on sleep-related worry, sleep-related beliefs, anxiety, and depression. The PSAS-13 and the two subscales were significantly correlated with sleep parameters and daytime impairment (Janssen-Fröjmark & Norelle-Clark, 2012; the pre-arousal scale is available at <http://uofthenet.org/alliant/Garrison-Sleep/8-PSAS.pdf>).

For a thorough discussion of the neurobiology of sleep and wakefulness, refer to Krystal AD et al. *New Insights Into the Sleep-Wake System: The Neurobiology and Pathophysiology of Insomnia*. *Psychiatric News*, May 16, 2014; 49 (10) (Suppl).

CURRENT TREATMENTS AND TREATMENT GAPS

Considerations for Treatment Selection

Treatment selection for insomnia needs to be tailored to individual patients, with emphasis on the age and sex of the patient, need for rapid onset of action, sleep patterns, comorbidities, concomitant medications, respiratory status, and other factors (Box 2 & Figure 4, next page). These considerations are relevant from the standpoints of both efficacy and side effects. Nevertheless, the selection of the optimal medication for an individual patient can still be challenging. The risk benefit of many agents commonly used to treat insomnia has not yet been established and the effects of many agents used to treat insomnia on common comorbid conditions remains unknown (Krystal et al., 2014b).

BOX 2:

CONSIDERATIONS FOR INSOMNIA TREATMENT SELECTION

- Need for rapid onset of action
- Need for intermittent administration
- Sleep pattern (Figure 4)
- Sex (women may be vulnerable to dosages in some agents)
- Age of patient: pediatric (not indicated), elderly
- Abuse potential of patient
- Circadian rhythm disorder presence
- Comorbidities: hepatic impairment, respiratory compromise, major depression, generalized anxiety disorder, posttraumatic stress disorder (Krystal et al., 2014b)

FIGURE 4:

SLEEP PATTERNS AND MORE RECENTLY INTRODUCED HYPNOTIC AGENTS

Sleep Pattern Disturbance	Selected Recommended Treatments
Initial insomnia-prolonged sleep latency	Psychological and behavioral strategies AND one of the following: <ul style="list-style-type: none">• Eszopiclone• Ramelteon• Suvorexant• Zaleplon• Zolpidem• Zolpidem ER
Middle or Terminal Insomnia	Psychological and behavioral strategies AND one of the following: <ul style="list-style-type: none">• Doxepin-low dose• Eszopiclone• Suvorexant• Zolpidem-sublingual, middle-of-the-night• Zolpidem ER
Initial, middle, and terminal insomnia	Psychological and behavioral strategies AND one of the following: <ul style="list-style-type: none">• Eszopiclone• Suvorexant• Zolpidem ER

Krystal et al., 2014b; product package inserts.

FIGURE 5:

PSYCHOLOGICAL AND BEHAVIORAL TREATMENTS FOR INSOMNIA

Techniques	Method
Stimulus control therapy*	If unable to fall asleep within 20 minutes, get OOB and repeat as necessary
Relaxation therapies*	Biofeedback, progressive muscle relaxation
Restriction of time in bed (sleep restriction)	Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves
Cognitive therapy	Talk therapy to dispel unrealistic and exaggerated notions about sleep
Paradoxical intention	Try to stay awake
Sleep hygiene education	Promote habits that help sleep; eliminate habits that interfere with sleep
Cognitive-Behavioral Therapy*	Combines sleep restriction, stimulus control and sleep hygiene education with cognitive therapy

*Standard Treatment according to American Academy of Sleep Medicine
Morgenthaler T et al. *Sleep*. 2006;29:1415.
Bootzin RR, Perlis ML (1992). *J Clin Psychiatry* (53 Suppl):37-41.

biofeedback, and paradoxical intention. There was insufficient evidence to recommend sleep hygiene education, imagery training, or cognitive therapies as single treatments or added to other approaches (Morgenthaler et al, 2006).

Sleep experts recommend instituting psychological and behavioral techniques alone or in combination with pharmacological agents to diminish insomnia behavioral perpetuating factors and improve long-term effects (Morin, 2006; Morgenthaler et al, 2006, Krystal et al, 2014b).

Non-prescription Agents and Over-the-Counter Agents Sedating Antihistamines

The first-generation sedating antihistamines (active ingredients are typically diphenhydramine or doxylamine) have undergone little systemic study, and the effects on sleep and next morning function are not well characterized. These agents can produce adverse effects such as daytime sedation, cognitive impairment, dizziness or incoordination, epigastric distress, thickening of bronchial secretions, and paradoxical excitation. These medications are anticholinergic, and therefore care must be taken for total anticholinergic load especially for elderly patients. Clinicians should be aware of possible pharmacokinetic interactions due to CYP2D6 inhibition (NHLBI Working Group, 1998; Borbely et al., 1998; Schweitzer et al., 1994; Morin et al., 2005; Agostini et al., 2001).

Herbals and Supplements

The efficacy and safety of most herbals and dietary supplements for insomnia have not been rigorously investigated. Examples of these products include: valerian, kava-kava (piper methysticum), melatonin, chamomilla, passiflora, avena sativa, and humulus lupulus. These products are often thought of as without risks, yet there are some safety concerns associated with such interventions. Factors contributing to safety uncertainty are that the constituents vary greatly, there is variation in the purity of the active ingredients and additives since they are not regulated or inspected by the FDA, optimal dosages are not well established, efficacy and side effects are not well investigated, and questions about interactions with other medications are not well investigated. Moreover, their use may delay medical attention for insomnia (Ringdahl et al., 2004 & Morin, et al., 2005).

A comprehensive evaluation of individual patients is essential before treatment selection. In general, the lowest, effective dose should be used. Special care should be taken to select the least effective dose in all patients. Hypnotic agents should be taken at bedtime or middle-of-the-night for some agents and patients should expect to be in bed for 7-8 hours (or 4 hours for low sublingual dosages of some agents where FDA indicated). The efficacy of some hypnotics may be improved when taken on an empty stomach. Further, clinicians need to ensure appropriate follow-up with patients who are prescribed hypnotics and, depending on the dose, discontinuation of these agents should be gradual (Krystal et al., 2014b). There is an array of psychological and pharmaceutical treatment options for the treatment of insomnia. These strategies and classes of pharmaceutical agents are discussed below.

Psychological and Behavioral Treatments for Insomnia

Psychological and behavioral treatments for insomnia (Figure 5) produce effective and long-term success in chronic insomnia. Importantly, researchers have demonstrated that improvements in sleep utilizing these methods were maintained for up to two years following their initiation (Morin, 2006; Krystal et al, 2014b).

Treatment guidelines from the American Academy of Sleep Medicine recognize the following behavioral treatments as effective for chronic insomnia: sleep restriction therapy,

Prescription Agents for Insomnia

Agents That Are Not FDA-Approved for Insomnia

There are three main classes of agents that are routinely used for insomnia but are not FDA-approved: sedating antidepressants, antipsychotics, and anticonvulsants. The sedating antidepressants have sedating side effects and at appropriate dosages, may be effective for insomnia. There is a low risk of abuse and a large dose range which can be advantageous. However, the efficacy for insomnia is not well established. In addition, most of these agents have long half-lives and produce daytime sedation, anticholinergic effects, weight gain, and may have drug-drug interactions (Kupfer & Reynolds, 1997; Sharpley et al., 2000; Karam-Hage & Brower, 2003; National Institutes of Health State of the Science Conference Statement, 2005). One of the most commonly used sedating antidepressant is trazodone, whose properties include substantial inter-individual variation in metabolism. Safe and effective dosages of trazodone have not been formally established for insomnia (Krystal et al., 2014b).

Atypical antipsychotics, at appropriate dosages, are effective for psychotic disorders, offer low abuse potential, and produce sedation. Other potential disadvantages include: daytime sedation, anticholinergic and extrapyramidal effects, weight gain, and lipid and glucose abnormalities (Kupfer & Reynolds, 1997; Sharpley et al., 2000; Karam-Hage & Brower, 2003; National Institutes of Health State of the Science Conference Statement, 2005).

FDA-Approved Hypnotic Agents

The FDA has approved the following classes of agents for insomnia: benzodiazepine receptor agonists (benzodiazepines and non-benzodiazepines), melatonin-receptor agonists, H-1 receptor antagonists, and a recently-approved orexin antagonist.

Benzodiazepine Receptor Agonists

All of these agents decrease sleep latency and are well-suited for those who report difficulty falling asleep (Figure 6 & Figure 7). Zolpidem extended-release (ER) and eszopiclone are also indicated for patients with difficulty remaining asleep, as opposed to just initiating sleep. Recent variations include low dose buffered zolpidem sublingual, or regular sublingual zolpidem, and zolpidem oral spray (Figure 8). The buffered low-dose sublingual (SL) product is given in the middle-of-the-night for patients have intermittent difficulty returning to sleep after awakenings and can be taken as needed for those who may prefer not taking a medication every night. The data indicate that the oral spray and SL preparations of zolpidem have a faster onset of action and a faster time to maximum concentration (T_{max}). Adverse effects of these agents include daytime residual sedation, psychomotor and cognitive impairment (dependent on dosage and half-life and time of ingestion), and abuse potential (Krystal et al., 2014b; Mitler, 2000; Holbrook et al., 2000; Micromedex, 2014; zolpidem package insert, 2013; eszopiclone package insert, 2010; Charney et al., 2001.).

Melatonin Receptor Agonists

Ramelteon, a melatonin-1 receptor agonist (selectively binding to melatonin-1 and melatonin-2 receptors), has a half-life of only 1-2.6 hours and is FDA-approved for treating patients with sleep onset difficulty (Figure 9). The adverse effects of ramelteon include: headache, somnolence, fatigue, and dizziness and is not recommended for use with fluvoxamine due to CYP1A2 drug interaction. This agent is not scheduled so it may be useful in patients with abuse potential with only sleep onset difficulties (Krystal et al., 2014b; ramelteon package insert, 2005).

FIGURE 6:
BENZODIAZEPINE RECEPTOR AGONISTS: BENZODIAZEPINES

Medication	Brand Name	Dosage Range [†] (mg)	Onset of Action	Half-life (h)	Short-term Limitation?
Estazolam	Prosom®	0.5 – 2	Rapid	10 - 24	Yes
Flurazepam	Dalmane®	15 – 30	Rapid	47 - 100	Yes
Quazepam	Doral®	7.5 – 15	Rapid	39 - 100	Yes
Temazepam	Restoril®	7.5 – 15	Slow-Intermediate	9.5 - 12.4	Yes
Triazolam	Halcion®	0.25 – 0.50	Rapid	1.5 - 5.5	Yes

[†]Normal adult dose. Dosage may require individualization

MICROMEDEX. <http://www.micromedex.com>
PDR. www.PDR.net

FIGURE 7:
SELECTIVE BENZODIAZEPINE RECEPTOR AGONISTS

	Zaleplon ¹	Zolpidem ²	Zolpidem ER ³	Eszopiclone ⁴
Dose – mg [elderly]	5,10,20 [5]	5,10 [5]	6.25,12.5 [6.25]	1,2,3 [1]
T _{max} (hours)	1	1.6	1.5	1
Half-life [elderly] (hrs.)	1	2.5 [2.9]	2.8 [2.9]	6 [9]
Sleep latency	↓	↓	↓	↓
Wake After Sleep Onset	--	--	↓	↓
Total sleep time	↑ (20 mg)	↑	↑	↑
Schedule	IV	IV	IV	IV

¹Sonata® [package insert] King Pharmaceuticals. Feb 2000

²http://www.kingpharm.com/products/product_document.cfm?brand_name=Sonata&product_specific_name=CIV&document_type_code=PI. Accessed Aug 4, 2011;
³Ambien® [package insert] sanofi-aventis US LLC; Aug 2010. <http://products.sanofi.us/ambien/ambien.pdf>. Accessed Aug 4, 2011;
⁴Ambien CR® [package insert] sanofi-aventis US LLC; Oct 2010. http://products.sanofi.us/ambien_cr/ambienCR.html. Accessed Aug 4, 2011;
⁵Lunesta® [package insert] Sunovion Pharmaceuticals Inc. Nov 2010. <http://www.lunesta.com/PostedApprovedLabelingText.pdf>. Accessed Aug 4, 2011.

FIGURE 8:
ZOLPIDEM VARIANTS FOR INSOMNIA

	Zolpidem	ZolpidemSL ¹	Zolpidem SL ²	Zolpidem Oral Spray ³
Dose – mg [elderly]	5,10 [5]	5,10 [5]	Men: 3.5 Women: 1.75 [1.75] MOTN, 4 hrs remaining until AM awakening	5,10 [5]
T _{max} (hours)	1.6	1.4	1.3	0.9
Half-life [elderly] (hrs)	2.5 [2.9]	2.9	2.5	2.7

¹ Edluar™ [package insert] Meda Pharmaceuticals Inc; Oct 2010.

² <http://www.edluar.com/EDLUAR-PI.pdf>. Accessed May 7, 2012;

³ Intermezzo [package insert] Transcept Pharmaceuticals Inc (November, 2011) and Purdue Pharma LLP (December, 2011). <http://pdr.purduepharma.com/intermezzo/intermezzo.asp?cid=1>. Accessed May 7, 2012;

⁴ Zolpimist Oral Spray [package insert] ECR Pharmaceuticals; 2010. <http://www.ecrpharma.com/images/Zolpimist%20Product%20Insert.pdf>. Accessed May 7, 2012

H-1 Receptor Antagonists

Doxepin has a half-life of 15 hours and is indicated for issues with sleep maintenance and is the only selective H1 antagonist approved by the FDA for treatment of insomnia (Figure 9). Doxepin is unique among available agents by having its greatest effect in the last third of the night. Possible adverse effects include sedation and anticholinergic side effects. Doxepin and other H-1 receptor antagonists are contraindicated in patients with severe urinary retention, narrow-angle glaucoma, and those taking monoamine oxidase inhibitors (MAOIs) within the previous two weeks. It does not have significant abuse potential, so it may be useful in patients prone to drug abuse (Krystal et al., 2014b; doxepin package insert, 2010).

FIGURE 9:
NEWER HYPNOTICS

	Ramelteon ¹	Doxepin ²	Suvorexant ³
Dose – mg [elderly]	8	3,6 [3]	5-20
T _{max} (hours)	0.75	3.5	2
Half-life [elderly] (hrs.)	1-2.6	15.3	12
Sleep latency	↓	--	↓
Wake After Sleep Onset	--	↓	↓
Total sleep time	--	--	↑
Schedule	None	None	IV

¹Rozereon® [package insert]. Takeda Pharmaceuticals America Inc. No 2010. <http://www.rozereon.com/en/?>. Accessed Aug 4, 2011; ²Silenor® [package insert]. San Diego, CA: Somaxon; 2010. Accessed Aug 4, 2011. ³Belsomra package insert, accessed 8/13/14.

Orexin Receptor Antagonists

Suvorexant is an orexin antagonist recently approved by the FDA to “treat difficulty in falling and staying asleep” (suvorexant package insert, 2014) (Figure 8.5). Suvorexant is thought to improve insomnia by blocking the wake-promoting signal mediated by orexin receptors. In clinical trials, suvorexant reduced time to sleep onset and increased total sleep time. The most common adverse effect was somnolence in 13% of patients receiving suvorexant, and in 3% receiving placebo. As the orexin system mainly promotes arousal, blocking orexin receptors selectively with this new agent may improve insomnia without incurring some of the side effects encountered with other medications (Box 3) (Scammell & Winrow, 2011; suvorexant package insert, 2014). Suvorexant is a DEA Schedule-IV

BOX 3:
EXPECTED OREXIN ANTAGONIST THERAPEUTIC EFFECTS

- Insomnia for those having difficulty falling and staying asleep
- Insomnia due to hyperarousal
- Stress-or anxiety-related arousal
- Arousal in setting of loss of rewarding stimuli, including substances of abuse
- Early awakening (Krystal et al., 2014b)

controlled substance (Michelson, et al., 2014; suvorexant package insert, 2014). Suvorexant was approved in four different strengths – 5, 10, 15, and 20 milligrams and should be administered within 30 minutes of going to bed with at least seven hours remaining before the planned time of waking (suvorexant package insert, 2014).

PHARMACOLOGY OF SLEEP-WAKE FUNCTION

Medications that modulate specific sleep-promoting and wake-promoting systems differ in their clinical effects. This provides the potential for specific, targeted types of interventions, although this is an area whose clinical relevance at this point in time is unclear. (Box 4 & Figure 10). Enhancing activity of sleep-promoting systems inhibits brain functions broadly which includes inhibiting arousal systems and shifting the sleep/wake balance towards sleep. Examples of agents that enhance sleep promoting systems include those that enhance GABAergic inhibition such as benzodiazepines and non-benzodiazepines.

BOX 4:
SLEEP PROMOTING AND WAKE PROMOTING NEUROTRANSMITTERS

Neurotransmitters That Increase the Activity of Sleep-Promoting Systems:

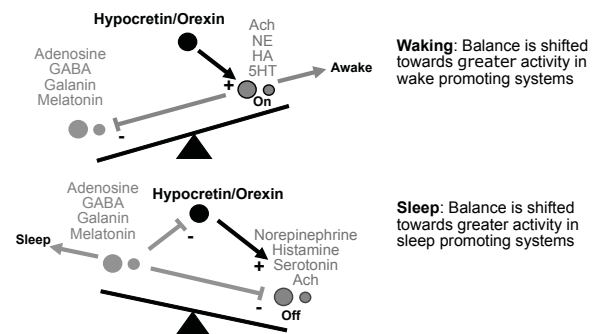
- Adenosine
- Gamma-aminobutyric acid (GABA)-A
- Galanin
- Melatonin

Neurotransmitters That Block the Activity of Wake-Promoting Systems:

- Norepinephrine
- Serotonin
- Acetylcholine
- Histamine
- Orexin/hypocretin

(Saper et al., 2005)

FIGURE 10:
FRAMEWORK: SLEEP-WAKE REFLECTS BALANCE BETWEEN OPPOSING PHARMACOLOGIC SYSTEMS



Modified from Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

Enhancing the Sleep-Promoting System

GABAergic Inhibition

The GABA-A receptor complex is comprised of five subunits that form a channel which controls the flow of chloride ions in and out of the neuron. Generally, chloride concentration is greater outside neurons than inside neurons. GABA binding opens the channel and the resulting inward flux of chloride hyperpolarizes the membrane resulting in neuronal inhibition. Benzodiazepines (e.g., temazepam, flurazepam, triazolam, etc.) bind to a site on an alpha subunit of the GABA receptor complex and enhance GABA-mediated inhibition. The non-benzodiazepines (e.g., zolpidem, zaleplon, and eszopiclone) have the same mechanism of action as the benzodiazepines though they possess more specificity in binding to some alpha subunits. Properties of GABA-A enhancement include: broadly inhibiting brain function because of the broad distribution of GABA-A receptors; significant sedation effects could occur because these medications inhibit wake-promoting systems, and sleep enhancing effects are largely proportional to blood level (Krystal, et al., 2013).

The effects of benzodiazepines and non-benzodiazepines reflect global inhibition due to an increase in GABA-A activity in multiple brain regions. Possible therapeutic actions encompass sleep-enhancement, myorelaxant, anxiolytic, and antiseizure effects. Potential adverse effects involve cognitive and psychomotor impairment and the potential for abuse (Roehrs et al, 1996, 2001, 2002; Oswald et al, 1999; Hajak, 1999; Soyka et al, 2000).

Melatoninergic Enhancement

Medications such as melatonin and ramelteon promote sleep onset by binding to the MT1 receptors, though how this ultimately promotes sleep is poorly understood. Notable attributes of these agents are (1) there is no dose dependence; and (2) there are no effects on sleep stages, or abuse potential (Johnson et al., Arch Gen Psych. 2006; Roth et al. Sleep Med 2006; Erman et al., Sleep Med. 2006).

CASE VIGNETTES

Case Vignette #1: Sleep Maintenance Insomnia

Presenting Complaint: John Knowles is a 41-year-old, married attorney who complains to his psychiatrist, Dr. Jones, that he is having difficulty sleeping and is feeling increasingly despondent and tired during the day.

History of Present Illness: John has been seeing Dr. Jones on a regular basis, usually once every 3 months, for three years for medication management of the first episode of a major depressive disorder. He also sees a therapist twice a week for insight-oriented psychotherapy. John has been on a stable dose of escitalopram 20 mg for the past 8 months with effective resolution of most depression-related symptoms including hopelessness, anhedonia, poor appetite, insomnia, and weight loss. However, John notes that his recent sleep difficulties began around 3 months ago, without any clear precipitant, characterized by an inability to stay asleep; although initially episodic and occasional, the problem has gradually progressed to become a nightly phenomenon. He goes to bed at 11 pm after working on his computer for 2 hours, falls asleep fairly rapidly, but wakes up around 3:30 am and either can't fall asleep, or falls asleep an hour or two later, sleeping fitfully thereafter. He emerges from bed at 6 am on weekdays, and tries to sleep in on

weekends until 9 am, and tries to take a nap or two to make up for lost sleep. While awake in bed, he works on his PDA and watches television.

The psychiatrist asks John about his emotional and cognitive experiences during bedtime. John replies that during the initial phases of the problem, he would lie in bed, awake, with little distress, simply ruminating. Over the past few weeks, however, his mind has begun to "race" while he lies in bed, and he has become increasingly tense in bed, worrying regarding the possibility of not obtaining sufficient sleep to function properly during the ensuing day. Working with his PDA has been helpful in distracting his thoughts from sleep-related concerns, yet levels of tension have been increasing.

Social History: John denies use of substances and alcohol, yet drinks 6 cups of coffee during the course of the day, the last one being consumed at dinnertime; when asked about the possibility that caffeine may be affecting his sleep, John notes that he does not believe so, since he falls asleep quickly even on nights when he has coffee just prior to bedtime. He notes that he is experiencing significant turmoil at work, due to downsizing and re-organization within his firm. His wife, who also works on a full time basis, has urged him to leave the firm, yet John feels that this would represent a defeat. One of his 2 children, a 10-year-old boy, suffers from Down syndrome.

Past Medical and Psychiatric History:

John has GERD. He had no major difficulties until college, when he began to feel depressed after a relationship breach, for which he saw a therapist for a few weeks, following which symptoms resolved. Recent visit to internist, which included a physical exam and routine bloodwork, revealed normal vital signs and no abnormalities on testing.

Medications: Omeprazole 20 mg daily

Family history: Mother suffered from chronic insomnia and had numerous depressive episodes. Father is being treated for prostate cancer; John is very concerned about his health

Review of systems: Denies mood decrement, anhedonia, weight or appetite loss. Other systems also negative. He does not snore, and denies symptoms compatible with restless legs syndrome.

Mental status examination: Well groomed, dressed in business attire. Thoughts are goal-oriented, no perceptual aberrations; you note that his mood is "fine," he appears mildly anxious; evidence of mild psychomotor activation.

Formulation:

1. History of major depressive disorder, currently in remission
2. Comorbid insomnia
3. Stressors include concerns regarding occupational issues and family illnesses

Treatment Options and Rationale:

Non-pharmacological interventions include:

1. Dr. Jones encourages him to continue in insight-oriented therapy, as he navigates through difficult career-related considerations and anxiety related to illnesses on the part of his son and father
2. Dr. Jones points out to John that he is engaging in behavior that may be intensifying his insomnia, such as exposure to sources of light during nighttime hours, delayed morning awakening times on weekends, napping, and excessive reliance on caffeine. He discussed proper sleep hygiene behavior with him, including the recommendation that he not

lie in bed for more than 30 minutes if unable to get back to sleep, but go into a different room, read in a dimly lit environment, and return to bed after feeling sleepy. He also suggests that John use dark sunglasses during nocturnal awakenings to mitigate the effects of nighttime light exposure on circadian rhythms. He suggests that John limit caffeine intake to 2-3 cups of coffee per day, consumed prior to lunchtime, and that he keep a regular morning wake time of 6-7 am, and avoid napping.

3. Cognitive behavioral therapy for insomnia. John's preoccupation with sleeplessness seems to be fomenting insomnia during nocturnal awakenings. Dr. Jones suggests that he confer with John's therapist regarding the possibility of incorporating insomnia-specific CBT (CBT-I) facets into the therapeutic process. John agrees.

John returns to Dr. Jones's office at his regularly scheduled 3 month visit time. He and his therapist have been working together in CBT-I. He now keeps regular bedtimes, does not nap, and limits caffeine consumption to 2 beverages with breakfast. He avoids lengthy times in bed while awake, and avoids electronic devices while in bed and just prior to bedtime. His mental "spinning" has diminished substantially, and he has developed strategies to deal with negative and self-defeating thoughts while in bed. However, he continues to wake up multiple times after falling asleep, and feels increasingly fatigued during the day. His concentration and memory have been deteriorating. In addition, he now has, on occasion, difficulty falling asleep, spending up to an hour trying to fall asleep at the beginning of the night. Dr. Jones suggests that they consider pharmacological options for the insomnia.

Pharmacological options include:

1. Dr. Jones recommends a hypnotic medication that can be taken just prior to bedtime, but which enhances sleep maintenance, i.e., diminishes awakenings following sleep onset. Choices include the traditional benzodiazepine receptor agonists (benzodiazepines), some of the selective benzodiazepine receptor agonists (zolpidem ER and eszopiclone), and suvorexant. Although low-dose doxepin would address mid-nocturnal awakenings, it is not indicated for initiation insomnia and would not address John's occasional difficulty with falling asleep at bedtime. Alternatively, low dose sublingual zolpidem can be taken following mid-nocturnal awakenings on an as-needed basis; however, since John's insomnia is a nightly occurrence, Dr. Jones suggests that the latter option may be less preferred, in favor of a nightly hypnotic that is taken just prior to bedtime.
2. John is concerned about the long term effects of these medications. Dr. Jones explains that the long-term safety for zolpidem ER, eszopiclone, and suvorexant has been established in 1-year studies of continuous administration.
3. John asks regarding the abuse potential of these agents. Dr. Jones explains that they all have a low, but definite, abuse potential, but, given John's lack of a history of substance use or misuse, he does not anticipate that this will be an issue, as long as John's treatment is carefully monitored. He also notes that some sedating antidepressants such as low dose trazodone, used on an off-label basis to treat insomnia, have less abuse potential than these agents, yet the primary drawbacks are the potential for morning drowsiness, and the effective hypnotic dose of these agents has yet to be determined. He also notes that the combination of multiple antidepressants raises the potential for unwanted drug-drug interactions. Low doses of atypical antipsychotics are occasionally used by psychiatrists for comorbid insomnia, yet they are not indicated for insomnia and raise the risk of other

complications such as metabolic abnormalities; in addition, their effective dosages for insomnia have not been determined.

4. Dr. Jones notes that, following institution of treatment with a hypnotic, John should take the hypnotic just prior to bedtime, should avoid alcohol, and should contact him in the event of daytime sedation or any other side effects. He schedules a follow-up visit in 2 weeks.

Case Vignette#2: Substance Abuse and Insomnia

Presenting Complaint: Lucy Walker is a 32-year-old woman presenting to a psychiatrist. Lucy describes difficulty falling asleep at night; lies awake for at least one hour before falling asleep.

Psychiatric Interview: The psychiatrist asks Lucy about her thoughts and mood while she is trying to go sleep. Lucy replies that it is as though like her "mind can't shut down." Her psychiatrist asks her how often she wakes up at night, after falling asleep. Lucy reports that she wakes up several times during the night and is quite fatigued the next day; she feels like she hasn't had restful sleep most nights (Karam-hage, 2004).

Her psychiatrist asks Lucy what does she do to try to go to sleep? She states that she drinks 2 glasses of wine late in the evening so she can relax and go to sleep (Karam-hage, 2004). Her psychiatrist asks if she drinks alcohol besides the glasses of wine. She reports that she has 2-3 glasses of wine when she gets home from work to unwind and with dinner during the week and in addition, 2 glasses of wine in the afternoon on the weekends.

Past Medical and Social History: Sleeping difficulties have been present since childhood but have gotten worse in last year since her divorce. She is employed as an executive assistant and needs to be sharp and focused when she gets to work and throughout the day. Many of her friendships are work-related. She works 40-45 hours per week. Her finances are stable. Patient reports she is in good health otherwise.

Family History: Patient's father died at age 51 from a heart attack. Patient reports father had history of alcohol abuse and chronic insomnia. Mother and siblings are in good health.

Treatment Options and Rationale:

Non-pharmacological intervention:

1. Lucy should be referred for alcohol counseling and join a support group for alcohol abuse.

Pharmacological options:

1. For Lucy's insomnia, a pharmaceutical agent is advised in addition to her alcohol counseling. The ideal pharmacotherapy for this group of patients would need to be sedating, have a short half-life, possess little or no interaction with other prescriptions, have minimal or no liver metabolism, and should not induce reward to minimize abuse potential (Karam-hage, 2004).
2. Pharmacological agent options include:
 - a. Benzodiazepines are not recommended for a patient with substance issues. Their use has been controversial in the substance user, specifically the alcoholic patient (Karam-hage, 2004). In part, this is due to benzodiazepine's nonselective action at two central gamma-aminobutyric acid (GABA)-A receptor sites: alpha (1) and alpha (2). The sedative action of benzodiazepines is related to alpha (1) site, whereas alpha (2) sites are thought to affect memory and cognitive functioning. Since alcohol is a GABA-ergic drug, these medications have a high liability for misuse, abuse and dependence by patients who are alcoholics (Karam-hage, 2004).

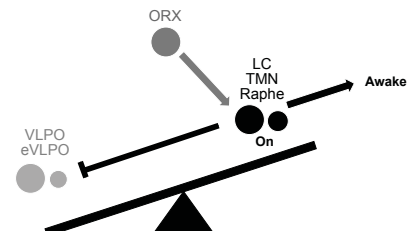
- b. A group of benzodiazepine-like medications have been FDA approved for insomnia due to their selective action on the alpha (1) subunit of the GABA (A) receptor. These include zolpidem, zaleplon, and zopiclone. Unfortunately, several case reports and case series have referred to abuse of the alpha (1) subunit drugs. Especially at high doses, these drugs can become undistinguishable from benzodiazepines (Karam-hage, 2004). Other agents such as trazodone (not FDA approved for the treatment of insomnia), have less abuse potential than triazolam and may be a viable alternative to benzodiazepine hypnotics in individuals with histories of alcohol or drug abuse. The main reported drawback of trazodone (not FDA approved for the treatment of insomnia) is that it causes morning drowsiness (Karam-hage, 2004).
- c. Gabapentin has been commonly prescribed as pharmacotherapy for insomnia in individuals with alcohol or substance abuse as it appears to have little potential for abuse (Karam-Hage and Brower, 2000). Gabapentin is not FDA approved for the treatment of insomnia.
- d. Antidepressant drugs with 5-HT₂ blocking properties, such as mirtazapine (not FDA approved for the treatment of insomnia) or nefazodone (not FDA approved for the treatment of insomnia), are believed to alleviate insomnia and improve sleep patterns. In patients with depression, mirtazapine produces a significant shortening of sleep-onset latency, increases total sleep time, which can lead to an improvement in sleep efficiency (Karam-hage, 2004).
- e. Sedating atypical antipsychotics (olanzapine and quetiapine; not FDA approved for the treatment of insomnia) have been suggested as alternative sleep aids for the substance user, they may be useful due to their sedative effect and impact on reducing background anxiety.
- f. An orexin antagonist, suvorexant, may be an appropriate option for this patient. In addition to promoting sleep, animal research suggests that an orexin antagonist might also be useful in the treatment of substance abuse including alcohol abuse although this is not an FDA approved indication (Anderson, et al, 2014; Mahler, et al, 2012). Clinical research on this topic is limited but orexin antagonists may produce somewhat less "drug liking" than zolpidem (Cruz, et al, 2014).
- g. Melatonin receptor agonists are indicated for insomnia characterized by difficulty with sleep onset (ramelteon package insert, 2010).
- h. Selective histamine-1 receptor antagonists are indicated for insomnia characterized by difficulty with sleep maintenance (doxepin package insert, 2010)

MECHANISMS OF BLOCKING THE WAKE-PROMOTING SYSTEM

In contrast to the sleep-promoting system, the activity of blocking the wake-promoting system shifts the balance toward sleep and decreases arousal (Figure 11) (Saper et al, 2005). Potential mechanisms that may account for blocking of the wake-promoting system are antagonism of: acetylcholine, dopamine, norepinephrine, serotonin (5-HT), histamine, and hypocretin/orexin. Specifically, acetylcholine antagonists decrease arousal

FIGURE 11:
BLOCKING THE WAKE-PROMOTING SYSTEM

- Blocking wake-promoting systems shifts balance towards sleep and decreases arousal



Saper, et al. 2005.

and REM sleep; serotonin antagonists tend to decrease the number of awakenings but do not enhance sleep onset, decrease wake time during sleep, or cause daytime sedation. Further, selective antihistamines have the greatest effects in last half of the night with relatively minimal effects shortly after waking. Blocking orexin receptors reduces arousal and increases sleep (Krystal et al, 2014b).

Agents That Block the Wake-Promoting System

Antidepressants*

**These agents are not FDA-approved for the treatment of insomnia*

Antidepressants may block serotonin, norepinephrine, acetylcholine, or histamine receptors involved in sleep. The agents most commonly used to treat insomnia are doxepin, amitriptyline, and trimipramine. Other agents include: trazodone and mirtazapine. Possible adverse effects include anticholinergic side-effects, orthostatic hypotension, daytime sedation, and increased appetite (Figure 12, next page) (Winokur, et al, 2001; Krystal, et al., 2007).

Antipsychotics*

**These agents are not FDA-approved for the treatment of insomnia*

These agents may block serotonin, norepinephrine, acetylcholine, dopamine, or histamine receptors. The most common agents used to treat insomnia are quetiapine and olanzapine. Potential adverse effects are Extrapyramidal side-effects, tardive dyskinesia, and akathisia as well as weight gain, and daytime sedation (Winokur, et al., 2001; Krystal, et al., 2007).

Non-Selective Antihistamines

Antihistamines block the wake-promoting effects of histamine at the H₁ receptor. Most commonly used agents to treat insomnia are diphenhydramine and doxylamine. As noted, antihistamines are the primary constituents of the over-the-counter sleep aids and may be used in the treatment of allergies. These agents are not only antihistaminergic but also block cholinergic receptors. As a result, possible adverse effects may include anticholinergic effects as well as daytime sedation increased appetite (Winokur, et al, 2001; Krystal, et al., 2007).

FIGURE 12:
EFFECTS OF BLOCKING WAKE-PROMOTING SYSTEM RECEPTORS

	Agents with Significant Effects	Possible Adjunctive Therapeutic Effects	Potential Adverse Effects
Histamine H1	Antidepressants, Antipsychotics, Anti-histamines	Allergy	Increased Appetite
Dopamine	Antipsychotics	Psychosis, Mania	Extrapyramidal side-effects (EPS): Tardive Dyskinesia, Akathisia, Parkinsonism
Acetylcholine	Doxepin, Amitriptyline, Trimipramine, Quetiapine, Olanzapine, Diphenhydramine, Doxylamine	Motion Sickness; Nasal Congestion	Dry Mouth, Blurred Vision, Constipation, Urinary Retention, Narrow-Angle Glaucoma Risk
Serotonin 5-HT ₂	Trazodone, Mirtazapine, Quetiapine, Olanzapine	Antidepressant, Anxiolytic	Increased Appetite
Norepinephrine α ₁	Doxepin, Amitriptyline, Trimipramine, Trazodone, Quetiapine, Olanzapine	Anxiolytic	Orthostatic Hypotension

Winokur et al. *Depress Anxiety*, 2001; Krystal et al. *Current Psychiatry Reviews*, 2007.

KNOWLEDGE GAP WITH WAKE-PROMOTING SYSTEM AGENTS

Overall, there is very little systematic research on the sleep effects of wake-promoting agents. Most of these agents have significant receptor effects other than the antagonism of one or more of the wake-promoting systems that cloud the understanding of their sleep effects. This is because of the relative specificity of antagonism is dose-dependent for some agents. Also, there are sleep/wake effects that add to or detract from the sleep-enhancing effects of wake-promoting system antagonism. Further, these agents may cause adverse effects that are not related to blocking the wake-promoting system. It is important to note that these effects are dose-dependent (Krystal et al, 2014b).

How Does Blocking the Wake-Promoting System Differ From Enhancing the Sleep-Promoting System?

There are significant differences in the agents that block wake-promoting system when compared with the sleep-promoting system. First, sleep effects are dependent on the degree of activity in the wake promoting system being blocked, such as the time of day, the context (stressful versus non-stressful), motor activity (moving versus stationery), and level of activity. Also, there are parallel systems which can mediate arousal (orexin, norepinephrine, dopamine, serotonin, acetylcholine, and histamine). The antagonism of one target does not prevent the wake-promoting effects of the other systems (Krystal et al, 2014b).

As a result, unlike agents which enhance GABAergic inhibition and sleep-promotion, wake-promoting agents may have clinical effects that are not proportional to blood level of the agent. For example, selective histamine antagonists demonstrate peak blood level in 3-4 hours, but have peak sleep effect 7 or 8 hours after dosing with minimal effects 9 hours after dosing. Another illustration is a serotonin inverse agonist which had sedative effect at peak blood level with daytime dosing but had significant effects on awakenings and wake after sleep onset (WASO) when dosed at bedtime (Rosenberg, et al, 2008; Krystal et al., 2010, 2011, 2013).

Targeted Wake-Promoting System Agents

Orexin Antagonists

Orexin antagonists are a new class of agents for the treatment of insomnia with a focused pharmacologic effect. Orexin antagonists specifically block the receptors targeted by the relative small number (10,000-20,000) of orexin-producing neurons in the brain. Effects of orexin antagonists would be expected to depend upon the time of day, as there is a daily circadian rhythm to orexin activity, and dependent on the activity in other parallel wake-promoting systems. Based on the neural inputs to orexin neurons, one would expect orexin antagonism to have therapeutic effects sleep problems occurring due to circadian rhythm disorders and on stress and anxiety-related arousal and arousal in the setting of loss of rewarding stimuli including substances of abuse (Scammell & Winrow, 2011; Krystal et al, 2014b).

CONCLUSION

Armed with a better understanding of the difference between sleep-promoting and wake-promoting neural systems, clinicians should be better able to meet patient needs. The differences between agents impact patient outcomes, thus it is important to tailor the agent to the patient. Without understanding that there are two systems involved in sleep (sleep-promotion and wake-promotion), clinicians that may be in the habit of giving the same agent to everyone and not personalizing insomnia treatment to the patient fail to capitalize on the rich set of options that are available for optimizing treatment for the many patients with insomnia.

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