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Educational Objectives and Agenda

Educational Objectives

The educational objectives for the proposed activity are based on the identified gaps and needs, and will allow us to measure improvements in the participants' knowledge and competence.

After participating in the activity, the learners are expected to be better able to:

1. Recognize the individual disorders that are considered to be sleep-wake disorders.
1. Identify current barriers to the optimal management of insomnia and other sleep-wake disorders.
2. Cite current data on approved and emerging dual orexin receptor antagonists for the management of sleep-wake disorders.
3. Develop strategies to incorporate dual orexin receptor antagonists into treatment protocols for individuals with insomnia and other sleep-wake disorders.

Agenda

The Live Webcast and onDemand Activity will be held over the course of 1.0 credit hour; this program will feature insight from a leading expert in the management of sleep-wake disorders. This activity will be the basis of the material developed for the live, local interventions, updated as appropriate in order to capture new evidence or therapeutic advances.

10 min - Welcome, Introduction, Pre-Polling
After welcoming participants, the faculty expert will briefly review the topics that will be covered during the activity. The audience will also be polled on their knowledge and competence in the diagnosis and management of sleep-wake disorders in an era of development of therapeutics specifically targeting hypothalamic pathways controlling sleep-wake cycles.
20 min - Diagnosing Sleep-Wake Disorders and the Limitations of FDA-approved Treatment Options

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In the first segment the faculty expert will begin with a review of the prevalence and impact of untreated sleep-wake disorders on chronic disease risk and quality of life. Faculty will then describe the various sleep wake disorders and current issues associated with the use of benzodiazepines, hypnotics, and antidepressants for their treatment. A critical review of the most common side effects and withdrawal syndromes associated with each categorical treatment approach for the FDA-approved will be presented. This will be followed by coverage of the proper recognition and diagnosis distinct sleep-wake disorders. The most common pitfalls associated with current clinical recognition will be covered.
20 min - Safety and the Treatment of Sleep-Wake Disorders with Dural Orexin Receptors Agonists (DORAs)
The second segment will focus on DORAs for the treatment of sleep-wake disorders.This will include coverage of the clinical data on approved and emerging dual orexin receptor antagonists for the management of sleep-wake disorders. The faculty expert will describe cases and strategies for incorporating dual orexin receptor antagonists into treatment protocols for individuals with insomnia and other sleep-wake disorders. This section will conclude with a discussion of the potential implications for these emerging therapies on the future management of insomnia.
10 min -Take-Home Strategies, Ask an Expert Q&A, Conclusions
In the final segment, the faculty expert will summarize the key objectives and take-home points discussed during the activity. Before closing the event, the presenter will address questions submitted from the online audience (live webcast). The audience will also be polled on changes in knowledge and competence.

Faculty Considerations

The faculty will be selected based on expertise, research, and published data. Faculty selection will also take into account the ability of particular experts to stimulate interactivity in the learning experience through their presentation style. All final decisions regarding activity faculty will be made by Medical Learning Institute.

Potential Chair and Faculty Members include, but are not limited to:

Christian Guilleminault, MD, Professor of Psychiatry and Behavioral Sciences, Stanford University Sleep Medicine Division, Redwood City, CA

Snigdha Pusalavidyasagar, MD, Assistant Professor of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Minnesota, Minneapolis, Mn

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Daniel Hoyer, PhD, Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA

Joyce K Lee-Iannotti, MD, Sleep Neurologist, Banner University Medical Center, Phoenix, Az

Sarah L. Anderson, PharmD, Associate Professor, Department of Clinical Pharmacy, University of Colorado, Aurora, Co

Rajesh Tampi, MBBS, DFAPA, MS, Professor of Psychiatry at Case Western Reserve University School of Medicine, Cleveland Clinic, Cleveland, Oh

James M. Parish, MD, Sleep Medicine Specialist, Pulmonary Medicine, Mayo Clinic, Phoenix, Az

Kannan Ramar, MD, Sleep Medicine, Mayo Clinic, Rochester, Mn

Allison Wilkerson, Ph.D, Assistant Professor, Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC

James K. Walsh, PhD, Clinical Professor, Department of Psychiatry, St. Louis University, St. Louis, Mo

Meir Kryger, MD, Professor of Medicine (Pulmonary) and Clinical Professor of Nursing, Pulmonary, Critical Care, and Sleep Medicine, Yale School of Medicine, New Haven, Ct

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APPENDIX

Summary of Gaps and Needs with Related Educational Objectives for the Proposed Intervention

The different elements of this needs assessment demonstrate that significant gaps and unmet needs exist and further education is needed for optimal early recognition and management of patients with insomnia or related sleep-wake disorders, which are summarized in the following sections.

A. Summary of Sleep-Wake Disorders Landscapey

Sleeping well is essential for good health. Poor sleep is associated with a wide range of health consequences, including an increased risk of heart disease, accidental injury, diabetes, obesity, depression, stroke, and dementia, as well as adverse effects on mood and behavior.[1,2] Stroke and asthma attacks tend to occur more frequently during the night and early morning, likely due to changes in hormones, heart rate, and other characteristics associated with sleep.[3]

Sleep-wake disorders exert dramatic impacts on both health and cost burden. The National Commission on Sleep Disorders Research estimates that sleep apnea is probably responsible for causing 38,000 cardiovascular deaths per year and studies indicate that obstructive sleep apnea increases the risk of heart failure by 140%, the risk of stroke by 60%, and the risk of coronary heart disease by 30%.[4,5] While indirect costs of sleep-disorder associated accidents, property destruction, litigation, hospitalization, and death are much higher, costing an additional $50 to $100 billion.

The most common sleep disorders are insomnia followed by sleep apnea, restless legs syndrome, and narcolepsy. Insomnia affects approximately 10-20% of the population, half of insomniacs suffer from chronic insomnia.[4] Laboratory tests performed to assess and treat sleep-wake disorders include the polysomnogram, multiple sleep latency test, maintenance of wakefulness test, and actigraphy. Appropriate treatments must be tailored to the individual characteristics of the patient based on medical history and laboratory tests.

The majority of FDA-approved treatments for treating insomnia are fraught with many side effects and in some cases withdrawal syndromes.[6] Moreover, these are considered only useful as short-term therapy for a few days or weeks during periods when attacks are more common. These include insomnia medications targeting GABA (benzodiazepine and nonbenzodiazepine), histamines receptors (anti-histamine), serotonin/catecholamine reuptake (tricyclic anti-depressants), or melatonin. With the exception of the pathway melatonin, all of these medications do not specifically target pathways with primary dedicated physiologic roles in modulating the sleep-wake cycle.

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Orexin receptor antagonists represent a relatively new therapeutic drug class for treating insomnia.[7] Dual orexin receptor antagonists (DORAs) have a novel mechanism of action and may represent an alternative for patients who cannot tolerate or do not receive benefit from common sleep agents. Suvorexant was the first dual orexin receptor antagonist (DORA) to be FDA-approved in 2014. Suvorexant demonstrated efficacy in both decreasing time to sleep onset and also increasing total sleep time compared to placebo. Other DORAs currently under investigation in clinical trials included filorexant and lemborexant.[8] Recently completed phase 3 clinical trials involving 900 insomnia disorder patients treated with either lemborexant or placebo demonstrated that lemborexant confers statistically significant improvements in sleep maintenance, daily functioning, and subjective wakefulness without causing significant adverse events compared to placebo.

It is imperative that clinicians prescribing these therapies be fully versed in the relevant risks, drug monitoring recommendations, and available alternatives. Educational support in a team-based approach is needed to more efficiently manage treatment decisions. General practitioners and psychiatrists should be able to recognize and initiate treatment of patients with insomnia to more effectively reduce associated risks for cardiovascular disease, obesity, diabetes, depression, and dementia.

B. Optimal/Desired State of Practice

General practitioners and psychiatrists should possess the necessary knowledge and competence to recognize, differentially diagnose, and treat patients with sleep-wake disorders based on the latest clinical data. This should include awareness of the impact of poor sleep quality along with the safety, adverse events, and efficacy of both the traditional FDA-approved medications and the newly approved treatment options targeting orexin receptors. Physicians should possess the ability to effectively assess and monitor sleep-wake cycles in patients with insomnia.

C. Gaps Based on Current Practice

Needs assessment research indicates that there are significant gaps awareness of the significant impact of sleep-wake disorders on cardiovascular disease, the limitations of FDA-approved traditional therapies, and the clinical practice guidelines. Significant advances have been made in our understanding of how we may successfully pharmacologically target the orexin receptor system to control sleep-wake cycles. Recent updates continue to highlight the need to increase awareness of the mechanisms controlling a healthy sleep-wake cycle, the latest clinical trial data on DORAs, the recent first FDA-approval for suvorexant, and additional set of DORAs in the clinical development pipeline.

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D. Underlying Unmet Needs

Psychiatrists and general practitioners need to improve knowledge and awareness of:

- The impact of sleep-wake disorders on cardiovascular and mental health disease risk
- The clinical presentation of sleep-wake disorders
- The importance, benefits, and significance of *early* initiation of therapies for promoting rejuvenating sleep
- The risks versus therapeutic benefits of traditional FDA-approved and newly emerging therapies

General practitioners and psychiatrists managing patients with sleep-wake disorders need to improve competence in:

- Methods of differentially diagnosing specific sleep-wake disorders
- Identify current barriers to the optimal management of insomnia
- The potential impact of traditional therapies or newly emerging therapies for treating insomnia or related sleep-wake disorders

E. Educational Gaps Grid

To address the gaps and unmet needs related to the recognition and management of pediatric-onset multiple sclerosis we are proposing the development of an educational activity (please see the section of the proposal titled “Educational Rationale, Design, and Features” for further details) with the following educational objectives and goals:

Proposed educational objectives (*as a result of participating in this activity, the learners are expected to be better able to)*:	**Relevant outcome level*** (*this learning objective will measure a change in*)**: ABMS, IOM, & National Quality Strategy (NQS)**	**competencies & domains** (*the proposed activity based on these learning objectives will address the following competencies*)**:**
1. Recognize the individual disorders that are considered to be sleep-wake disorders.	Knowledge (Level 3)	**ABMS:** ☒ Patient care ☒ Medical knowledge ☒ Interpersonal & communication skills

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2. Identify current barriers to the optimal management of insomnia and other sleep-wake disorders.	Knowledge (Level 3)	**IOM:** ☒ Provide patient-centered care ☒ Work in interdisciplinary teams ☒ Employ evidence-based practice **NQS:** ☒ Making Care Safer ☒ Patient and Family Engagement ☒ Communication and Care Coordination ☒ Prevention and Treatment Practices
3. Cite current data on approved and emerging dual orexin receptor antagonists for the management of sleep-wake disorders.	Knowledge (Level 3)	
4. Develop strategies to incorporate dual orexin receptor antagonists into treatment protocols for individuals with insomnia and other sleep-wake disorders.	Competence (Level 4)	

F. Details of Underlying Unmet Needs & Proposed Educational Objectives

The following sources were used in this gap analysis and needs assessment:

- Review of published evidence in sleep-wake disorders particularly involving insomnia[4,6,9-12]
- Expert perspectives on the advances and challenges in the clinical diagnosis and management of chronic insomnia and sleep-wake disorders[8,13-16]

Lack of awareness of updates in the classification and treatment of patients with sleep-wake disorders among psychiatrists and family practitioners is one of the limitations to advancing the recognition and management of insomnia. Delays in diagnosis and treatment due to a lack of awareness of clinical presentation and treatment selection, and a poor appreciation of the importance of *early* initiation will lead to greater risks for cardiovascular events, mental health disorders, cognitive decline, and accidents. It is critical that family physicians and psychiatrists are aware of the impact of untreated insomnia and the latest treatment options towards striving for more rested, rejuvenated, and healthy life for patients with sleep-wake disorders.

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Educational Need 1: Ability to recognize insomnia and the competence to diagnose the related sleep-wake disorders.
Learning Objective 1: Recognize the individual disorders that are considered to be sleep-wake disorders.

Evaluation and treatment of sleep disorders are of paramount importance to the prevention of disease, morbidity, and mortality. An accurate and detailed history from the patient, bed partner, or family member combined with a sleep questionnaire is essential to making an accurate sleep disorder diagnosis. The International Classification of Sleep Disorders diagnostic manual categorizes four major sleep disorders: dysomnias, parasomnias, sleep disorders associated with mental or other medical disorders, and proposed sleep disorders.[4] Insomnias, which are a type of dysomnias are the most common. It is essential to attempt to distinguish whether the disorder is *intrinsic* or *extrinsic* in origin as this will affect the design of the treatment decision. *Intrinsic* sleep disorders originate within the body, while *extrinsic* sleep disorders are caused by external factors such as inadequate sleep hygiene, environmental factors, or stimulant/alcohol-dependent sleep disorders.

It can be especially difficult to distinguish between dysomnias and sleep disorders associated with mental or other medical disorders. Sleep disorders are often accompanied by depression, anxiety, and cognitive changes that must be addressed depending on the diagnosis. Particularly growing research indicates a strong link between insomnia and the likelihood for suicide ideation or attempts.[11,12]

In fact, the American Psychiatric Association updated The Diagnostic and Statistical Manual version 5 (DSM-5) to address this issue, now distinguishing insomnia as a condition that must be addressed *separately* from mental health conditions as the two conditions of insomnia and mental health disease are so frequently connected. Significantly, DSM-5 calls for clinicians to specify comorbid conditions, both medical and psychiatric.

Insomnia is a disorder unto itself that needs *independent* clinical attention. Dr. Charles Reynolds III, MD, chair of the DSM-5 Sleep-Wake Disorders Work Group emphasizes, “To achieve optimal treatment outcomes in people with both a psychiatric disorder and insomnia, the clinician needs to target both disorders.” Significantly, DSM-5 incorporates current advancements in our understanding of narcolepsy by incorporating orexin deficiency into its diagnostic criteria.[16] The revised DSM-5 criteria of irrepressible sleepiness occurrence is now at least 3 times per week over the past 3 months (previously specified as daily).

The point is to acknowledge the bidirectional etiology of sleep disorders and coexisting psychiatric illness. For example, in DSM-4, a psychiatrist treating a patient with major depression and prominent insomnia complaints would have specified a sleep disorder related to another mental disorder. However now, with DSM-5, the clinician is asked to consider whether the patient has an insomnia disorder in addition to a mood disorder. By diagnosing both a major depressive disorder and insomnia, the treatment plan can be designed address both issues. This conceptualization reflects a paradigm change that is now widely accepted in the field of sleep medicine and that holds great relevance for psychiatric practice.

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Collectively, the distinct recognition of *intrinsic* dysomnias combined with the potential lifelong impact of non-diagnosis on the greater disease risk highlights the need to increase physician awareness of the symptoms and clinical presentation of sleep-wake disorders. Only knowledgeable physicians will be ready to perform the proper diagnostic testing to effectively design appropriately targeted treatments as soon as possible.

Educational Need 2: Greater awareness of the risks associated with FDA-approved insomnia medications especially concerning side effects, withdrawal symptoms, and more.
Learning Objective 2: Identify current barriers to the optimal management of insomnia and other sleep-wake disorders.

While an accurate diagnosis based on the etiology of sleep-wake disorders is essential to designing the proper treatment, it is equally requisite to understand the strengths, risks, and limitations of the traditional approaches of FDA-approved therapeutics in order to successfully treating insomnia and related sleep-wake disorders. The American College of Physicians recommends that clinicians use a shared decision-making approach that includes a discussion of the benefits, harms, and costs of short-term use of medications.[6]

FDA labeling recommends that pharmacologic treatments for insomnia are intended only for short-term use, and patients should be discouraged from using these drugs for extended periods because few studies have evaluated the use of the medications for more than 4 weeks. The number of prescriptions filled for sedative/hypnotic agents have significantly increased in the past 20 years, with more than 4% of adults having reported prescription sleep aid in the last month according to a 2013 report.[17] Only short-term treatment with hypnotics should be undertaken because of these risks.

The pharmacokinetic profile of any insomnia agent is a critical factor influencing the benefits to risk for potential adverse ratio.[8] An agent with too short a half-life will fail to promote adequate sleep. However, an agent with excessively long half-life poses greater risk for residual sleepiness, withdrawal, and adverse events. However, short half-life hypnotics can be useful for shift workers to help initiate sleep, but chronic hypnotic use by long-term shift workers is not recommended.

The FDA-approved pharmacological treatment options for insomnia include over-the-counter antihistamines, benzodiazepines, nonbenzodiazepine receptor agonists, tricyclic antidepressants, and melatonin agonists. Benzodiazepines and nonbenzodiazepine receptor agonists, enhance the functioning of the brain's primary inhibitory neurotransmitter, which contributes to their risk profile, including impaired motor coordination, lethargy, slurred speech, dizziness, intense mood swings, and fatigue.

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Prolonged use of benzodiazepines leads to adaptations of GABA receptors, resulting in tolerance and withdrawal symptoms. Benzodiazepine withdrawal is a growing problem with increasing with 400,000 emergency visits involving benzodiazepines among the Drug Abuse Warning Network (DAWN) estimates in 2010.[18]

In fact benzodiazepine usage can result in impaired sleep quality, residual sedation, or rebound insomnia. Moreover, the American Geriatric Society recommends against the use of benzodiazepine hypnotics for treatment of insomnia in the elderly population because of an increased risks for medication-associated cognitive impairment, falls, and motor vehicle crashes.

In summary, the pharmacological treatment of insomnia exceptionally challenging. Family physicians and psychiatrists must be made aware of the limitations of traditional FDA-approved insomnia treatment regimens so they can minimize the risk of adverse events, while providing therapeutic benefit in the appropriate patients with sleep-wake disorders.

Educational Need 3: Greater awareness of the benefits and risks associated with approved and investigational dual orexin receptor medications involving somnolence, headache, dizziness, and abnormal dreams.
Learning Objective 3: Cite current data on approved and emerging dual orexin receptor antagonists for the management of sleep-wake disorders.

Most currently FDA-approved therapeutics do not specifically target sleep-specific mechanisms of action. Fortunately, progress has been made in the development of pharmacological approaches uniquely and distinctly targeting the orexin neuropeptide pathway to regulate sleep-wake cycles by antagonizing these specific receptors present in the hypothalamus.

In 1998 two independent research laboratories discovered the that loss of function of the same novel neuropeptide orexin (or “hypocretin”) would cause narcolepsy in mice and dogs.[8] Later experiments determined that patients with narcolepsy can have a 90% reduction in orexin-producing neurons.

These discoveries generated considerable interest for identifying small-molecule orexin receptor antagonists as a novel approach for promoting sleep and treating insomnia.[14] Targeting the orexin receptor system as a treatment of insomnia offered an alternative pharmacological approach to gamma aminobutyric acid agonist sedative hypnotic treatment.

Orexin antagonists now have the potential to improve insomnia in patients who have found other agents ineffective. Suvorexant was the first in-class FDA-approved in (2014) targeted at orexin antagonism.[15] Studies showed both the orexin-1 and -2 receptors signaling is involved in

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shifting between sleep stages to offer a more holistic approach to the treatment of insomnia. Since suvorexant targets and inhibits both orexin receptors it is referred to as a dual orexin receptor antagonist (DORA).

Clinical trials involving suvorexant demonstrated efficacy at decreasing time to sleep onset while also increasing total sleep time. Clinical trials indicate efficacy and safety after 12 months of use with lack of withdrawal effects after discontinuation. Accordingly, suvorexant is a potential alternative for patients with chronic insomnia who cannot tolerate or do not receive benefit from more traditional sleep agents. However, physicians must be aware that precautions exist for certain patient populations especially involving females, obese patients, and patients with respiratory disease. Moreover, suvorexant is a schedule IV medication with potential for addiction that will need to be estimated over time.

In randomized, double-blind clinical trials examining suvorexant for treatment of primary insomnia demonstrated dose-dependent activity after 4-week oral administration periods at increasing doses (10 mg, 20 mg, 40 mg, and 80 mg). Subsequent phase 3 clinical trials proved efficacy at improving sleep onset and maintenance in adult insomnia patients. While data available on the safety profile of suvorexant is limited because small sample sizes from published studies, the medication has thus far been well tolerated by elderly (≥ 65y) and non-elderly (18–64y) men and women with insomnia at doses up to 20 mg, where several studies report somnolence as the most frequent adverse event.

Lemborexant is another DORA currently under investigation both phase 3 trials in patients with general insomnia, along with a phase II study testing lemborexant in patients with irregular sleep-wake rhythm disorder and dementia.[8,9] Phase 2 clinical trials have already demonstrated significantly improvements in mean sleep efficiency and wake after sleep onset in patients with insomnia after treatment with lemborexant. Adverse side effects such as somnolence, headache, and sleep paralysis have been reported. The ongoing SUNRISE 2 long-term phase 3 study involves 900 patients with insomnia disorder.[19] Thus far at the end of the six-month period, lemborexant 5 mg and 10 mg provided statistically significant improvement in subjective sleep onset latency and sleep maintenance relative to placebo.

Filorexant is another DORA currently under active investigation that is showing promise in part due to its favorable short half-life (3 to 6 hours) relative to other DORAs. A double-blind, placebo-controlled, 51-site randomized study, filorexant demonstrably improved sleep efficiency in non-elderly patients with insomnia. Somnolence was the only significant at doses above 10mg thus far.

It is imperative that clinicians prescribing these emerging DORA therapies be fully knowledgeable of the latest clinical data for treating chronic insomnia so they can assess the relevant risks, costs, appropriate patient populations, and pre-treatment assessments.

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Educational Need 4: Greater awareness of emerging therapeutic strategies addressing insomnia and related sleep-wake disorders.
Learning Objective 4: Develop strategies to incorporate dual orexin receptor antagonists into treatment protocols for individuals with insomnia and other sleep-wake disorders.

General practitioners and psychiatrists considering the use of antagonists must fully understand how to effectively communicate and participate in a shared decision process together with the patient in order to establish optimal compliance and administration of these novel agents towards achieving optimal outcomes in patients with sleep-wake disorders.

There are several precautions of special note for which physicians considering prescribing DORAs should be aware. These include concerns for patients regarding additive daytime impairment (e.g. falling asleep while driving), CNS depression when co-administered with other CNS depressants, worsening depression or increases in suicidal ideation, and sleep paralysis.[7] Patients must be made aware of the importance of the timing and setting of administration of DORAs before performing specific activities, such as driving or operating heavy machinery.

Medication-related adverse effects have a dose-dependent relationship. Patients treated above the maximum recommended dose of suvorexant demonstrably experience somnolence twice as frequently as those treated with the recommended dose. Physicians must clearly communicate these risks to patients, that they should not take more than the recommended dose.

Physicians must be made aware of potential drug interactions that may cause adverse events so they can adjust treatment plans accordingly. It is recommended that suvorexant is not used in patients taking strong CYP3A4 inhibitors and to use a reduced dose of 5 mg in patients concurrently receiving moderate CYP3A4 inhibitors since this demonstrably increases the metabolic clearance time of suvorexant.[15] Moreover, monitoring of digoxin is recommended when taken concomitant with suvorexant, due to the narrow therapeutic window of digoxin and previously observed increases digoxin when taken with suvorexant.

The only population specifically contraindicated for use of DORAs are patients with narcolepsy. As many as 90% of narcolepsy patients are are orexin ligand deficient and further antagonizing their orexin receptors could propagate their condition.[20]

Ultimately the goal of physicians is to alleviate patients suffering from insomnia by improving their ability to fall asleep and stay asleep for adequate time. Thus far, multiple clinical trials involving dual orexin receptor antagonists (suvorexant, lemborexant, and filorexant) have all yielded encouraging positive data with minimal side effects and no serious adverse events in

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patients with chronic insomnia. This represents a novel approach with unique promise to treating sleep-wake disorders.

Collectively, published research indicate that physicians and psychiatrists need to increase their awareness of new alternative mechanistic strategies for treating patients with sleep-wake disorders. Psychiatrists need to be able to properly select insomnia based on the diagnosis, patient profiles, and other comorbidities to achieve optimal outcomes.

Ultimately, chronic insomnia remains an ongoing problem, but significant new and novel therapeutic approaches involving the orexin antagonists are emerging that can increase sleep efficiency and maintenance in patients with with insomnia and related sleep disorders. General practitioners and psychiatrists must be made aware of the latest positive therapeutic opportunities, proper administration, and precautions in order to achieve optimal outcomes in the management of patients with chronic insomnia.

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