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Review Article

A review on orexin receptor antagonists in chronic insomnia: a revolutionary approach

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ABSTRACT

Chronic insomnia is a chronic sleep disorder characterized by the inability to fall asleep or stay asleep. Other than hyperarousal, altered circadian rhythms, and behavioral changes, it can also occur due to medical or psychiatric conditions. The use of benzodiazepines, Z-drugs, melatonin agonists, antihistamines, and sedative antidepressants as traditional treatment in chronic insomnia offer relief, but are also coupled with several limitations like tolerance, dependence, residual sedation, and disruption of normal sleep architecture. With the continuous revealing of the sleep neurobiology mystery, the orexin system has been pinpointed as a main regulator of wakefulness and arousal, thus making it a probable therapeutic target. Orexin receptor antagonists like suvorexant, lemborexant, and daridorexant inhibit the selective OX1R and OX2R pathways thereby decreasing the wakefulness and facilitating natural, continuous sleep. These medications have shown to enhance sleep by reducing the time to fall asleep, the number of times one wakes up and thereby increasing the total time spent during sleep, without impairing the normal sleep architecture. They are regarded as a breakthrough and more natural means of treating chronic insomnia because of their good safety profile and the low risk of next-day sedation they come with.

Keywords: Chronic insomnia, Orexin receptor antagonists, DORAs, SORAs, Suvorexant, Lemborexant, Daridorexant, Sleep–wake regulation, Hyperarousal, Pharmacotherapy

INTRODUCTION

Insomnia is one among the common sleep disorders with large number of adults being affected worldwide, leading to impairment of daily life and long-term health. It manifests itself through the inability to fall asleep, stay asleep, or obtain good sleep in spite of having an opportunity to sleep. The situation often brings about tiredness, inability to concentrate, changes in mood, and overall poor living conditions during daytime. Insomnia has become more common in different age groups and populations due to the changing lifestyle in modern times.[1,2]

Chronic insomnia, which is mainly characterized by the presence of the symptoms for at least three months, is a more complex and longer-lasting form of the disorder. It is very much linked to the increased physiological and cognitive arousal, circadian dysregulation, stress, and mental or physical health conditions coexisting with it. Chronic insomnia not only leads to poor quality of sleep, it also increases the incidence of heart diseases, diabetes, depression, anxiety, and weakened immune system. The complex nature of chronic insomnia illustrates the need for specific and efficient strategies for long-term treatment, on a case-to-case basis.[3,4]

The standard pharmacological treatments for sleeping disorders consist of benzodiazepines, non- benzodiazepine Z-drugs, antidepressants, antihistamines, and melatonin receptor agonists. But these cause dependence and tolerance issues, cognitive and psychomotor impairment, changes in sleep patterns and next-day sedation, all contribute to making these agents unsuitable for chronic use. These limitations are accentuating the need for a new generation of therapeutic options that would target the insomnia's underlying neurobiological mechanisms and also be safe.[5,6]

Neurobiological studies have shown the orexin system to be the major determinant of arousal and wakefulness in humans. Neurons that produce orexin are located in the hypothalamus and are responsible for keeping us awake, coordinating our sleep-wake transitions, and processing metabolic, emotional, and circadian signals.

Disruption or hyperactivity of this system has been cited as a strong contributor to the development of chronic insomnia, mainly through increased arousal and difficulty in sleep onset. So, this orexin receptor antagonism has been the reason behind the paradigm shift towards targeted pharmacological intervention.[7,8]

Orexin receptor antagonists are the most effective way to deal with chronic insomnia in a natural way. They directly act on the body's wake-promoting centers, instead of inducing merely a sleepy state. All orexin receptor blockers like suvorexant, lemborexant, and daridorexant have exhibited consistent success in sleep quality and next day performance, along with safety. It is fascinating to discuss their mechanisms of action, clinical benefits, limitations and the future potential they carry in the treatment of insomnia.[9,10]

CHRONIC INSOMNIA

Chronic insomnia is a sleep disorder characterized by delayed sleep onset, and/or impairment in maintenance of sleep, with the symptoms lasting for at least three nights a week, for a period of at least three months. The ongoing disruptions that come with chronic insomnia are very different from those that characterize transient or short-term insomnia and are the main cause of the significant negative effects that the person suffers during the day in terms of functioning, productivity, and even the overall quality of life.

Sufferers commonly have to endure long waiting times before sleep sets in, they wake up several times during the night, or they wake up early in the morning and feel that their sleep was not refreshing.[11]

The disorder comes about as a result of a multi-faceted merging of physiological, psychological, and behavioral factors. The central nervous system's heightened arousal, increased metabolic activity and abnormal regulation of sleep and wakefulness contribute heavily to the condition's existence.[12] Chronic insomnia has a strong relationship with a multitude of medical and psychiatric comorbidities, which can further cause sleep disruption. However, prolonged insomnia might be taking a toll on such conditions, creating a vicious cycle of interplay and worsening. The lifestyle factors such as sleeping at odd hours, too much time in front of the screen, and poor sleeping habits further enhance its chronicity.

The long-term consequences of chronic insomnia go beyond just fatigue and daytime sleepiness. The disturbance of sleep that is persistent has been linked to impaired cognitive performance, unstable moods, reduced immune function, and increased risk of developing metabolic disorders, hypertension, cerebrovascular and cardiovascular events. These long-term systemic effects make chronic insomnia a significant public health issue that needs to be detected and treated efficiently, as soon as possible.[13]

Because of its multifactorial nature and prolonged duration, chronic insomnia usually benefits from a mixture of therapeutic methods addressing behavioral, psychological, and pharmacological aspects.

The key for determining the right treatment is to understand the mechanisms involved in the pathogenesis of the disorder and through such knowledge, new therapeutic strategies like the orexin receptor antagonists have been created, which specifically target the neurobiological pathways involved in regulating arousal and wakefulness.

PATHOGENESIS OF CHRONIC INSOMNIA

The development of chronic insomnia is secondary to intricate interplay of several factors, including biological, psychological and behavioral, which eventually lead to a soldering state of heightened arousal. The primary mechanisms by which the underlying pathogenesis comes about are interconnected and manifold and can be summarized under the following sub-headings.

Hyperarousal theory

During hyperarousal state, patients display central and autonomic nervous system hyperactivation. Here, the cortical activity becomes heightened, metabolic rate becomes increased, heart rate becomes elevated and overall sympathetic tone gets increased. All these put together, contribute to the difficulty in initiating and maintaining sleep in such patients.[18]

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis

Chronic stress exposure leads to the HPA axis activation, with increased secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH),

and cortisol which reinforce and perpetuate the cycle of insomnia and hyperarousal.[19]

Orexin system overactivity

The orexin neuropeptides, produced in the lateral hypothalamus, are the main center of the wakefulness regulation. When the orexin pathway is overactive, wakefulness is prolonged and the transition to sleep becomes difficult. High levels of orexin keep arousal centers (the locus coeruleus, the raphe nuclei, and the tuberomammillary nucleus) active, thereby, hindering the onset of stable sleep.[20]

Circadian rhythm misalignment

Another major pathological factor is the disruption in the sleep-wake circadian cycle. Misalignment can be traced either to the body's internal clock (genetic clock abnormalities) or to the outside world (irregular sleep schedules, shift work). Changes in the suprachiasmatic nucleus (SCN) result in modified melatonin secretion and timing of the sleep drive, which in turn leads to delayed sleep onset, fragmented sleep, or early morning awakening.[21]

Cognitive and behavioral factors

Unhealthy cognitive patterns and poor sleep habits can be responsible for maintaining chronic insomnia. The preoccupation with sleep, the anxiety of not sleeping, and spending too much time in bed are some of the factors that lead to conditioned arousal. Anxiety at bedtime creates a loop in which forcing sleep worsens the inability to fall asleep. Poor sleep hygiene, irregular schedules, and heavy screen exposure make the situation worse.[22]

Neurotransmitter imbalance

A common finding in chronic insomnia is the imbalance between neurotransmitters promoting sleep (GABA, galanin, melatonin) and neurotransmitters keeping awake (orexin, norepinephrine, dopamine, serotonin, acetylcholine). The balance necessary for a healthy sleep can be disturbed by either an inadequate number of inhibitory signals or an overstimulation of excitatory signaling. Also, increased histamine activity can contribute to wakefulness that is hard to overcome.[23]

Genetic and familial predisposition

Polymorphisms in genes that control circadian rhythm (CLOCK, BMAL1, PER) and stress responses are linked to an increased risk of insomnia. Family history of insomnia is a strong predictor of the incidence of sleep problems, indicating genetic factor involvement in the development of chronic insomnia.[24]

Medical and psychiatric comorbidities

Chronic insomnia can be caused by medical or psychiatric conditions such as, chronic pain, depression, anxiety disorders and dementia. To illustrate, on the one hand, anxiety intensifies cognitive hyperarousal, while on the other hand, depression modifies circadian timing, and REM sleep architecture. Disorders like GERD, heart failure, and OSA, contribute to the sleep fragmentation, that occurs as a result of sleeping in separate bouts.[25]

Inflammation and immune dysregulation

There is a growing body of literature that underlines chronic insomnia as being perhaps the result of an underlying low-grade inflammation. Inflammatory cytokines (like IL-6 and CRP) play a central role in the regulation of sleep and in the excitability of the neurons. Furthermore, the inflammatory markers become even more pronounced by the lack of sleep, thus leading to a self-perpetuating cycle.[26]

CURRENT TREATMENTS FOR CHRONIC INSOMNIA

Cognitive behavioral therapy for insomnia

Cognitive behavioral therapy (CBT) for Insomnia is the most effective long-term therapy for chronic insomnia and is considered first-line treatment. CBT-I works with altering the patients' behaviors and cognitive processes that are the root cause of the persistent sleep hardships.

The techniques available in this treatment comprise sleep restriction, stimulus control, cognitive restructuring, relaxation training, and education regarding good sleep practices. CBT-I produces long-lasting improvements and is effective regardless of the patient's age and the number of disorders with which he or she is suffering.[27]

Sleep hygiene and lifestyle modifications

The enhancement of daily habits and the improvement of the environmental factors play a fundamental role. The most important strategies consist of keeping a fixed sleep schedule, not consuming caffeine or heavy meals at night, minimizing screen exposure before going to bed, and making a dark and quiet environment for sleeping and being physically active during the day. Limiting long naps and adjusting the bedroom temperature are practices that help in the reinforcement of the natural homeostatic and circadian rhythms.[28]

Pharmacotherapy

Pharmacotherapy is the term used for drug therapy that is frequently considered when it is difficult to manage the patient's condition with non-pharmacological measures only. Medications affect various neurotransmitter systems that are involved in sleep regulation.

Benzodiazepines

Benzodiazepines, like temazepam and triazolam, produce sedation by their action on GABA-A receptors. Even though they shorten sleep latency and prolong the total sleep time, they might modify sleep architecture through the reduction of slow-wave sleep. The risks associated with their use include tolerance, dependence, cognitive impairment, and rebound insomnia; thus, their use is restricted to short periods.[29]

Non-benzodiazepine hypnotics (Z-drugs)

Drugs such as zolpidem, zaleplon, and eszopiclone have the same primary action as benzodiazepines but are more tolerable due to selective targeting of GABA-A receptors. They are helpful in both sleep onset and maintenance types of insomnia, but impair next day functioning impairment, leading to an unusual sleep behavior and development of dependency if the drug is taken for a prolonged period of time.[30]

Melatonin and melatonin receptor agonists

Ramelteon, the melatonin receptor agonist (MT1/MT2), brings patients to sleep without the danger of addiction. Though it's able to maintain the quality and quantity of sleep and is considered safe for long-term use, it's less effective than other sleep-inducing drugs.[31]

Sedating antidepressants

Low doses of tricyclic antidepressants and sedating antidepressants are the mainstay medications for insomnia linked to mood disorders. Common side effects consist of anticholinergic symptoms, weight gain, and drowsiness during the day.[32]

Antihistamines

Antihistamines make people drowsy by interfering with H1 receptors. Their effectiveness is limited by the development of tolerance and adverse reactions like dry mouth, confusion, and reduced cognition.[33]

Antipsychotics

Atypical antipsychotics are sometimes used off-label for the treatment of severe insomnia, particularly when patients also have mental disorders. They facilitate sleep by inhibiting dopamine and serotonin receptors but are associated with adverse effects like weight gain, metabolic syndrome and movement disorders. These medications are not advisable for general insomnia treatment.[34]

Complementary and alternative therapies

Herbal supplements, valerian root, chamomile, ashwagandha, and lavender oil are some of the most popular. In spite of their mild nature, clinical evidence that supports their efficacy is limited and inconsistent.

On the other hand, light therapy along with meditation-based practices aligns the human body's internal cycles and mitigates stress-caused sleeping issues.[35]

Chronotherapy and light-based treatments

Bright light therapy particularly helps in the correction of the circadian rhythm misalignment. The amount of time of light exposure, has an effect on the suprachiasmatic nucleus, thus adjusting the secretion of melatonin. Chronotherapy, which involves a gradual shift of sleep timing, is effective in insomnia associated with circadian rhythm disturbances.[36]

Treatment of comorbid medical and psychiatric conditions

Secondary insomnia can be caused by disorders like anxiety, depression, pain, sleep apnea and GERD, to name a few. Treating the primary condition significantly enhances the sleep quality. For instance, chronic pain management with non-opioid analgesics or sleep apnea treatment with CPAP have the same result of normal sleep patterns restoration.[37]

LIMITATIONS OF CURRENT TREATMENTS FOR CHRONIC INSOMNIA

Accessibility and practical barriers to non-pharmacological therapies

CBT-I, though being the first-choice of treatment in chronic insomnia, is still not often offered in many parts of the world due to the unavailability of trained therapists, high cost, or long wait periods. The digital CBT-I methods are in pipeline, but might not be friendly for every patient. Lifestyle changes demand a lot from the patients in terms of commitment, and this can ultimately lead to reduced adherence and effectiveness.[38]

Limited long-term effectiveness

The efficacy of most traditional hypnotics, benzodiazepines, and Z-drugs among them, is confined to a short period. Tolerance has a diminishing effect on their efficacy and the patients who discontinue the use of the drug are likely to suffer from a recurrence of symptoms. Treatment with medication-free CBT-I is very effective but has the drawback of demanding tremendous compliance over a long period and also some patients may not be able to access it.

Risk of dependence, tolerance, and withdrawal

The medications that are widely used for the treatment of sleep disorders possess the highest risk of dependence. Long-term use of these drugs leads to tolerance, while

stopping the drugs can bring about withdrawal symptoms or rebound insomnia, hence making it difficult for the physician to prescribe them in chronic cases.[39]

Adverse effects and next-day impairment

The use of sedative-hypnotics will make patients less active during daytime, and they will be likely dozy, with poor concentration, slow thinking, dizziness and can have frequent falls, especially in elderly.

Some agents such as sedating antidepressants or antipsychotics, do more harm to patients by disturbing their metabolism, and may even lead to cardiovascular problems.

Disturbance of natural sleep architecture

Most of the traditional sleeping pills drastically impair the sleep cycle, by variably affecting the sleep stages. Even though the patients fall asleep faster, the sleep gained may be less restorative, thus leading to continuous fatigue, mood disorders, and decreased efficiency during the day.[40]

Limited efficacy in comorbid conditions

Insomnia patients that come together with depression, anxiety, chronic pain, neurodegenerative disorders, or disturbances in their circadian rhythms are often the ones that get the least help from the standard treatments. Here, the use of traditional hypnotics not only treat the underlying problem, but can additionally aggravate the comorbid conditions.

Safety concerns in vulnerable populations

Older people, pregnant women, those suffering from liver or kidney-related health issues, and patients taking several medications have limited options with regards to treatment, owing to drug interactions, high sensitivity and the risk of experiencing side effects. Hypnotics are mostly not allowed in such populations or only given with very strict monitoring.

RATIONALE FOR OREXIN RECEPTOR ANTAGONISTS' USAGE

Orexin receptor antagonists (ORAs), mark a distinctive and focused strategy of healing the chronic insomnia problem, helping to overcome the drawbacks of the conventional hypnotics.

Targeting the core neurochemical drive of wakefulness

The orexin system is responsible for wakefulness and prevents people from falling asleep at the wrong moment. The orexin-A and orexin-B peptides stimulate the OX1R and OX2R receptors in the brain's arousal centers which include locus coeruleus, tuberomammillary nucleus, and raphe nuclei.

Here, the receptors for orexin are blocked and this reduces arousal signaling, coaxing the person naturally to sleep.[41]

Physiological sleep induction approach

Orexin antagonists selectively affect the wake-promoting pathway to induce sleep. The resulting sleep is more physiological and closely resembles the natural sleep. Hence, the use of ORAs leads to normal sleep architecture, in turn leading to restoration of quality sleep.[42]

Reduced risks compared to traditional hypnotics

ORAs have a very low potential for drug dependence or rebound insomnia. Next day impairment is also less likely to occur and these drugs are considered to be safe for long-term administration and are preferred in elderly patients and in specific sleeping disorders where conventional sedatives cannot be used.[44,43]

Addressing limitations of current therapies

A lot of the insomnia treatments that are currently available are not really effective in treating sleeping onset and sleeping maintenance insomnia together. The DORAs have been confirmed to be better in both aspects, as they lower the total arousal and also normalize sleep-wake transitions.

Evidence from narcolepsy research

The idea of blocking the orexin pathway is based on the narcolepsy case studies, which is the clinical proof that, the orexin system is essential for the wakefulness control. By blocking these receptors, the power of the signaling system is reversed and this in turn promotes sleep, making it easier to fall asleep and maintain sleep longer.[45]

Potential for better safety in special populations

DORAs present a safe pharmacological option with fewer systemic side effects in elderly population, without any anticholinergic effects, cognitive impairment, drug interactions and with almost no depressive effects on respiration. Thus, they are suitable to be given to a wider group of patients.46

Favorable pharmacodynamic profile

By the selective inhibition of OX1R and OX2R receptors, the ORAs produce a sedation that is predictable and stable without impacting the other neurotransmitter systems. This minimizes the potential for mood changes, memory loss and the occurrence of complicated sleep-related behaviors noted with traditional hypnotics.[47]

OREXIN RECEPTOR PATHWAYS

The orexin system is a major player in the process of sleep and waking and also in the maintenance of energy balance

in the body. The orexin system comprises of two peptides namely orexin-A and orexin-B, which are produced in the lateral hypothalamus and act on OX1R and OX2R, the two G-protein–coupled receptors. Different receptor activation leads to the involvement of different neural circuits, which coordinate the wake-promoting pathways together.

Orexin neurons (driving force for arousal)

Orexin neurons are mainly located in the lateral hypothalamus and perifornical area. Wide distribution of projections activates the multiple brain nuclei promoting wakefulness. The great diffusion allows the influence of orexin signaling over the limbic system, brainstem, cortex, and autonomic centers.[48]

OX1R pathway (orexin receptor 1)

OX1R has a strong preference for orexin-A and is widely distributed in areas related to emotional arousal, stress, and reward. The main projection locations of OX1R are locus coeruleus, ventral tegmental area and amygdala. Signalling through OX1R increases the alertness, boosts the sympathetic nervous system's activity and leads to the maintenance of the wakefulness state. This pathway has a major role in the development of insomnia due to stress and hyperarousal.[49]

OX2R pathway (orexin receptor 2)

The OX2R receptor is the main mediator of sleep-wake state stability and binds to both orexin-A and orexin-B with similar affinity. It is mainly found in the tuberomammillary nucleus, dorsal raphe nucleus and other major arousal centers. OX2R activity ensures the smooth flow of sleep and wakefulness and blocks the unwarranted REM intrusion. The disorder of this pathway is intimately connected to narcolepsy, which underlines the importance of this pathway in wakefulness.[50]

Combined OX1R–OX2R signalling (dual pathway integration)

Both receptors are working together to keep a person awake. While OX1R boosts alertness and stress-related arousal, OX2R acts to keep the person awake and to prevent the person from going through the sleep stages.

The dual activation results in very powerful wakefulness effects, as the orexin system simultaneously activates the different neurotransmitter systems like noradrenaline, histamine, dopamine, serotonin, and acetylcholine systems. This merging of pathways turns into a perfectly synchronized arousal network.[51]

Intracellular signaling mechanisms

Both receptors, after receiving orexin peptides set off G-protein-mediated signaling cascades. This results in more calcium inside the cell, depolarization of the membrane, and more firing of the neurons.

The upstream effects are the activation of cAMP pathways, alteration of ion channel conductance, and the establishment of a lasting excitatory tone in the neurons that are targeted. These cellular happenings are conducive to maintaining wakefulness and alertness to a higher degree.[52]

Functional role in sleep-wake regulation

The orexin receptor pathways work as a stabilizing switch that keeps the transitions between sleep and wake states smooth and effortless. The activity of orexin signaling keeps the arousal systems engaged, hence sleeping is prevented. When this signaling is reduced, the sleep-hypnotizing centers are on the top. The system's bidirectional control is shown by the fact that, overactivity leads to insomnia by keeping the arousal state constant, while underactivity results in narcolepsy.

Targeting orexin pathways with therapeutics

DORAs block both OX1R and OX2R receptors to bring down wakefulness and promote sleep. By preventing the arousal that is mediated by orexin and not by enhancing sedation, these medications offer a more natural way of sleep induction. The use of selective OX2R antagonists is being studied for the purpose of being able to influence sleep stability only and not the emotion-arousal pathways which are controlled by OX1R.[53]

CLASSIFICATION OF OREXIN RECEPTOR ANTAGONISTS

Dual orexin receptor antagonists (DORAs)

DORAs inhibit the activity of both OX1 and OX2 receptors and thus, the whole orexin system, which in turn leads to a decrease in neuronal excitation and stabilizes the sleep–wake switch. So, patients fall asleep naturally with normal sleep architecture, making this their hallmark. DORAs lower hyperarousal, increase total sleep time, and enhance sleep maintenance through localized inhibition rather than overall CNS depression. Their even-handed mechanism resembles natural sleep induction, thus making them better than benzodiazepines and Z-drugs for chronic insomnia treatment.[54]

Examples include Suvorexant, Lemborexant, Daridorexant.

Selective orexin-2 receptor antagonists (SORAs-2)

The SORAs-2 are selective and inhibit only the OX2R receptor that is mainly responsible for maintaining alertness. By blocking OX2R, activity in arousal centers is heavily reduced, thus calming hyperarousal, without affecting the circuits of reward and emotion controlled by

OX1R. This promotes sleep onset, enhances sleep continuity and at the same time maintains normal REM/NREM ratios. SORAs-2 could lead to decreased probability of cataplexy and negative emotions experience, since OX1R remains active. They are being considered for the treatment of insomnia and hyperarousal associated with depressive states.55

Examples include Seltorexant (JNJ-42847922), TAK-925 and TAK-994 (early-stage inverse agonists).

Selective orexin-1 receptor antagonists (SORAs-1)

SORAs-1 selectively antagonize OX1R, the receptor through which stress-related arousal, emotional responsivity and reward via amygdala and ventral tegmental area are controlled. This decreases overactivation of glutamatergic transmission and hence the wakefulness induced by fear/anxiety. They are not agents for primary insomnia but can indirectly help in stress or anxiety-associated insomnia. SORAs-1 are considered a new approach in treating panic disorder, addiction and anxiety, by controlling emotional arousal without complete blocking of the OX2R-controlled wakefulness network.[56]

Examples include ACT-539313, JNJ-61393215.

Next-generation multi-target orexin modulators

These compounds represent the combination of orexin antagonism and histamine (H1) inhibition, muscarinic modulation or serotonergic influence. They work in coordination with various wake-promoting circuits, making sleep extremely robust for refractory insomnia. Besides the significant neurotransmitter system modulation, they mirror the circadian and sleep-homeostatic pathways through synergistic suppression of arousal. Multi-target agents intend to address situations where the sole use of pure orexin antagonism is inadequate.[57]

Examples include hybrid orexin-H1 antagonists (early research), multimodal ligands like HTL0018318 analogues.

Biased ligands and allosteric orexin modulators

Biased ligands selectively inhibit the specific intracellular signaling pathways like G-protein or β-arrestin pathways, thus allowing for the partial functioning of orexin and still keeping one asleep. This exactness diminishes the side effects and does not entirely block the physiological functions of orexin like metabolic control and emotional balance. Allosteric modulators are able to act at the non-orthosteric receptor sites that modify receptor response only under certain circumstances. The use of these agents can be thought of a more sophisticated method for regulating sleep with an increased safety margin and less daytime sedation.58

Examples include OX2R-biased β-arrestin pathway inhibitors (preclinical), selective allosteric OX2R modulators.

The key pharmacokinetic and clinical differences among currently available and investigational Orexin receptor antagonists are summarized in Table 1.

Table 1: The key pharmacokinetic and clinical differences among currently available and investigational orexin receptor antagonists.

Drug	Type	Approved adult dose	Half-life (t½)	Effect on sleep onset	Effect on sleep mainten-ance	Next-day sedation	Key clinical notes
Suvorex-ant	DORA	10–20 mg once nightly	~12 hours	Moderate	Good	Low–moderate	First approved DORA; avoid concomitant use with strong CYP3A inhibitors
Lembore-xant	DORA	5–10 mg once nightly	~17–19 hours	Significant	Significant	Low	Strong sleep-maintenance benefit
Daridore-xant	DORA	25–50 mg once nightly	~8 hours	Significant	Significant	Very low	Shorter half-life; better daytime functioning
Seltorex-ant	SORA (OX2)	Investigational	~2–3 hours	Moderate	Moderate	Minimal	Studied mainly in insomnia associated with depression
TAK-994	SORA (OX2)	Investigational	Short	Significant	Significant	Minimal	Development discontinued due to safety concerns
ACT-539313	SORA (OX1)	Investigational	Not establis-hed	Mild	Mild	Minimal	Potential utility in stress and anxiety related hyperarousal, sleep benefit is indirect

CLINICAL EFFICACY

Improvement in sleep onset by reducing the sleep onset latency with effectiveness in both acute insomnia and chronic insomnia.

Better sleep maintenance by reducing wake after sleep onset (WASO) leading to deeper and more stable sleep cycles, with overall improvement in quality of night-time rest.

Increased total sleep time leading to continuous and consolidated sleep along with increased sleepiness during the night.[59]

Preservation of natural sleep architecture and hence supporting the physiological sleep, leading to a more profound and revitalizing rest.

Lower risk of next-day sedation compared to non-selective drugs.

Effective across diverse patient populations including elderly and those with disorders like sleep apnea due to absence of CNS depressive effects.

In summary, they provide reliable and continuous sleep enhancement in different clinical situations.[60]

SAFETY PROFILE

ORAs are generally regarded as safe because their selectivity chooses to interfere with the orexin wakefulness system instead of the whole CNS system. Hence, this leads to the reduction of the risks that traditional sleeping pills would cause, like respiratory depression, dependence, tolerance, and severe next-day impairment. The use of ORAs is associated with negligible cognitive or psychomotor effects, and clinical studies have shown very low rates of dextrose-induced sedation in the morning, thus they are suitable for long-term usage. Reduced incidence of side effects mainly in the at-risk groups like elderly, results in improved patient compliance and therapeutic outcomes.

On the contrary, not all of the safety advantages of ORAs are positive ones because they too can cause adverse effects, though minimal, like headache, drowsiness, vivid dreams, or fatigue. But these are usually temporary and dose related. There are still some rare occurrences of sleep paralysis, hypnagogic hallucinations, and REM-related experiences, which are usually to some extent connected to the therapy, occurring with some frequency in patients who are on their first doses in the course of treatment. It is recommended that precautions are taken with patients who have severe liver problems and amongst those on strong CYP3A inhibitors, because drug metabolism might be significantly altered. However, ORAs are considered to have a strong safety limit when compared to benzodiazepines and Z-drugs, who were the only ones with long- term risks and poor tolerance.[61,62]

FUTURE DIRECTIONS

Future research aspires to develop even more selective OX1R or OX2R antagonists with greater efficacy, quicker onset, and fewer side effects, tailored to different patient sleep disturbance patterns. The role of ORAs may be extended to their use in the treatment of insomnia associated with neurodegenerative diseases, PTSD, depression, and chronic pain, thus exploring their potential far beyond primary insomnia management.[64,65] Long-term clinical trials are necessary to ascertain the safety of chronic ORA use in various populations with respect to cognitive, metabolic, and psychological effects.

Also, pharmacogenomic integration could potentially aid in the detection of orexin pathway variations specific to a patient, thus allowing for personalized dosing and consequently better treatment outcomes.[63] Combination of ORAs with behavioral therapy or low-dose sedatives for the treatment of complex or treatment-resistant insomnia, can further increase the benefits of drug therapy and decrease the adverse effects of drugs.

CONCLUSION

ORAs are a big step forward in chronic insomnia treatment as they provide a targeted, physiologic way to sleep regulation. In comparison to traditional hypnotics, they do not cause generalized central nervous system depression, but rather induce and maintain sleep through selective inhibition of orexin-mediated wakefulness, thus reducing the sleep onset latency and improving the total sleep time, simultaneously preserving the natural sleep architecture. Their good safety profile, low potential for addiction, and possibly being suitable for different patient groups contribute to their clinical value. The long-term data and individual treatment approaches are still developing but the current evidence is pointing towards ORAs as a promising and even revolutionary therapeutic option. The ongoing research on better formulations, broader applications, and longer-term benefits will further determine their position in the insomnia management, in the near future.

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