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REVIEW ARTICLE

Review of Dual Orexin Receptor Antagonists on Treatment of Insomnia and Beyond

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ABSTRACT

Insomnia is a sleep disorder that not only causes daytime impairment but is also associated with increased health risks. Besides treatment with cognitive behavioral therapy, pharmacologic options remain limited with the potential significant adverse effects that must be carefully monitored and weighed against the benefits. The orexin system plays a crucial role in sleep-wake regulation and since the development of dual orexin receptor antagonists (DORAs), increasing research studies have shown their benefit on improving both sleep onset and sleep maintenance without significant adverse events. The current three approved DORAs, suvorexant, lemborexant, and daridorexant, showed significant reduction in wakefulness without compromising patient safety. In addition to circadian regulation, the orexin axis also extends to the arousal and reward pathway, specifically involving dopaminergic neurons. There is emerging data on targeting the orexin system in the treatment of dementia, delirium, mood and anxiety disorders, menopause, substance use disorders and obstructive sleep apnea. Available evidence demonstrates that dysregulation of the orexin system is associated with conditions such as dementia, delirium, and vasomotor symptoms in menopause; meanwhile, inhibition of orexin receptors showed promising preliminary data on modulating mood and anxiety disorders, substance use and eating disorders. This scoping review highlights not only the efficacy of orexin antagonists in treatment of insomnia but also explores the emerging data on implications beyond insomnia and identifies current gaps.

Introduction

Insomnia is one of the most common sleep disorders. More than one in ten Americans have been diagnosed with chronic insomnia based on the Sleep Prioritization Survey in 2024 conducted by the American Academy of Sleep Medicine (AASM)[1] Global prevalence of insomnia is estimated to be 852 million adults (global prevalence of 16.2%)[2]. According to the International Classification of Sleep Disorders, chronic insomnia is defined as an inadequate amount of sleep despite having the opportunity to do so. It is further characterized by difficulty initiating sleep, maintaining sleep, or rising prior to intended wake time with daytime impairment in functioning. Insomnia is primary or secondary to other conditions such as medical illnesses, psychiatric disorders, prescription or over-the-counter medications, substance use, or other underlying sleep disorders such as restless leg syndrome or obstructive sleep apnea. The sleep disturbance is present for at least 3 nights per week for at least 3 months. The impact of insomnia is well described resulting in impaired social, family, occupational, or academic performance. Symptoms include daytime fatigue, difficulty concentrating, mood irritability, memory impairment, behavioral problems, weakened immunity, cardiovascular disease, metabolic syndrome, and increased risk of fatal injuries and motor vehicle deaths.[3,4]

Guidelines by the American Academy of Sleep Medicine and the American College of Physicians recommend cognitive behavioral therapy for insomnia (CBT-I) as first line treatment for insomnia.[5,6] Multiple evidence-based studies have repeatedly demonstrated its effectiveness and long lasting benefits as it focuses on treating the maladaptive thoughts and behaviors associated with insomnia using cognitive restructuring, stimulus control, sleep restriction and sleep hygiene.[7] If patients have persistent insomnia despite CBT-I, or in the setting of acute insomnia requiring short-term treatment, the AASM recommends pharmacological treatments.[8] All of the recommended medications were graded as weak given the scarcity of robust clinical trials and heterogeneity in the data but not due to these medications' ineffectiveness. The AASM guideline recommends that clinical decisions should be tailored to individual cases for appropriateness. Pharmacologic treatments were categorized as follows: orexin receptor antagonists, benzodiazepine receptor agonists (Z-drugs or Z-hypnotics), benzodiazepines, melatonin agonist, heterocyclic antidepressant, anticonvulsants, and over-the-counter medications. The recommended benzodiazepine receptor agonists are zolpidem, zaleplon, and eszopiclone. Benzodiazepines include triazolam and temazepam. Melatonin agonist includes ramelteon. Heterocyclic antidepressant includes doxepin.

The purpose of this review article is to discuss the class of medications known as dual orexin receptor antagonists (DORAs) and their effects on treating insomnia and their additional benefits. There is emerging clinical data on the role of targeting the orexin system in treatment of Alzheimer's disease, delirium, mood and anxiety disorders, menopause, substance use and eating disorders, and obstructive sleep apnea. Although data is currently sparse, available studies have shown promising results and uncovered further knowledge gaps that are worth exploring.

Neurophysiology of Orexin and Orexin Antagonists

Orexin (hypocretin) is a neuropeptide that is secreted in the lateral hypothalamus and perifornical region in the brain. It plays an essential role in the sleep wake cycle in conjunction with feeding pattern, energy, reward, cognition, and mood. Orexin A (hypocretin-1) and orexin B (hypocretin-2) are derived from a common precursor known as prepro-orexin. Orexin A binds to orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R) meanwhile orexin B only binds to OX2R. The orexin receptors send

excitatory signals most specifically to monoaminergic and cholinergic nuclei in the brain stem and hypothalamic regions. These include locus coeruleus, tuberomammillary nucleus, raphe nuclei, laterodorsal and pedunculopontine tegmental nuclei, and ventral tegmental region.[9] The studies of orexin most notably stemmed from narcolepsy type I patients, as these patients lack the excitatory neuropeptides in the hypothalamus. It was reported that on average, only 10% of orexin neurons were seen in narcolepsy type I patients compared to the normal 70,000 orexin neurons in a healthy counterpart. The main hypothesis for the degeneration of the orexin neurons is attributed to autoimmune-mediated destruction.[10] It has been identified that the human leukocyte antigen (HLA) DQB1*0602 is linked to narcolepsy in the process of immune-mediated attack. The loss of this excitatory norepinephrine signaling to motor neurons with concurrent increased inhibitory response results in patients with narcolepsy losing muscle tone, termed as cataplexy.[11]

Dual orexin receptor antagonists (DORAs) are a class of medications that were approved in recent years, with Suvorexant in 2014, Lemborexant in 2019, and Daridorexant in 2022. They are Food and Drug Administration (FDA) approved to treat chronic insomnia. Unlike other hypnotics listed above, DORAs act to inhibit the wakefulness property of the orexin neurons to promote sleepiness, in contrast to the inhibitory GABA modulating property of benzodiazepines and Z-drugs or the antihistamine and melatonin pathway in doxepin and ramelteon. Suvorexant was the first DORA approved for the treatment of insomnia in 2014. In two randomized trials, suvorexant was shown to improves sleep onset and sleep maintenance as measured by polysomnography and self-reported outcomes.[12,13] Sleep latency and wakefulness after sleep onset (WASO) of suvorexant had a dose-dependent effect compared to placebo.[14] There was similar efficacy between men and women.[15] Long-term treatment with suvorexant was safe and well tolerated.[16] Lemborexant, approved in 2019, demonstrated significant improvement in latency to persistent sleep (LPS) and WASO. It was effective in a wide range of patients including older adults. Phase III trials showed improvements in sleep parameters compared to placebo and zolpidem.[17-19] Daridorexant was approved in 2022 after two landmark multicenter, randomized, double-blinded, placebo-controlled trials and was shown to improve sleep maintenance and daytime functioning and addressing residual symptoms such as fatigue and impaired cognition. Daridorexant is effective in reducing WASO and improving total sleep time (TST). It has a good safety profile with minimal daytime sedation after use. It has a low risk of dependency in contrast to benzodiazepines.[20] With long-term use it remains efficacious with no induced drowsiness, withdrawals, or rebound insomnia.[21]

Emerging Data on DORAs Beyond Insomnia Treatment

Alzheimer's disease

Alzheimer's disease (AD) is described as a progressive neurodegenerative disorder due to accumulation of amyloid-beta (Aβ) plaques derived from amyloid precursor protein (APP) and hyperphosphorylated tau proteins that cause neurofibrillary tangles. Buildup of these plaques and tangles lead to impaired neuronal signaling and inflammation, exhibiting cognitive decline, memory loss, and behavioral changes. It was previously shown that Aβ rises during wakefulness and falls during sleep. However, the dysregulation of the circadian rhythm in Alzheimer dementia increases the risk of Aβ deposition. In orexin knockout mice, the decrease in wakefulness was observed to have a reduction in amyloid pathology.[22] Furthermore, increased levels of orexin correlated with worsened cognitive impairment in Alzheimer's. Specifically, Zhou and colleagues demonstrated that suvorexant not only restored circadian rhythm in Alzheimer mice (induced by APP genetic expression), but it also

showed improvement in memory and cognition through performance in mazes and a reduction of Aβ deposition in the hippocampus and cortex.[24]

Orexin antagonists have been well tolerated in Alzheimer's patients with insomnia improving total sleep time and nighttime awakening.[24] Despite several different proposed mechanisms, including bidirectional positive feedback loop of Alzheimer, circadian disruption, and glymphatic drainage, orexin is without a doubt a major player and a current target of interest.[25] To determine whether suvorexant may have a preventative role in Alzheimer's disease, Lucey and colleagues conducted a proof-of-concept study on 38 healthy patients (45-65) randomized into placebo vs suvorexant 10mg vs suvorexant 20mg. Cerebrospinal fluid (CSF) was sampled every 2 hours for 36 hours, and there was a significant decrease of 10-15% in phosphorylated tau-threonine-181 in the suvorexant 20mg group but not tau-serine-202 or tau-threonine-217.There was a significant decrease in amyloid beta by about 10-20% in the 20mg group as well compared to placebo.[26] In summary, further investigations are warranted to explore orexin antagonism as a treatment for the sleep disturbances associated with Alzheimer's disease but also its neuroprotective role in modifying neurodegeneration.

Overall, clinical and animal studies support the use of DORAs to enhance sleep quality in patients with AD with comorbid sleep and circadian sleep-wake rhythm disorders. Preliminary results suggest these medications may have benefits beyond sleep regulation. They may have a neuroprotective role affecting amyloid-β and tau pathologies.[27] To investigate the effects and potential mechanisms of suvorexant in alleviating circadian rhythm sleep-wake disorders (CRSD), Hu and colleagues utilized a photothermal displacement-induced CRSD model of rats treated with suvorexant to investigate its impact on cognitive function, the Brain and Muscle Arnt-Like 1(BMAL1)/ NLR family pyrin domain containing 3 (NLRP3) axis-related genes, the microglial marker IBA1, Aβ levels, and the expression of inflammatory factors. BMAL1 is a transcription factor that acts on the clock gene to maintain circadian homeostasis, while NLRP3 inflammasomes regulate the innate inflammatory cascades in response to pathogen and cellular stress. The suvorexant group was found to upregulate the anti-inflammatory pathway in levels of BMAL1, IL-10, CD206, and TGF-β in CRSD rats, and downregulate the levels of NLRP3, IL-1β, Aβ1-40, Aβ1-42, IL-6, TNF-α, and iNOS. In addition, suvorexant rats were observed to have increased swimming speed, number of crossing and time spent in target quadrant in the quadrant maze test, indicating improvement in cognition and performance. When short hairpin RNA was used to knock down the expression of the BMAL1 gene, the effects of suvorexant were reversed suggesting that BMAL1 may play a role in how suvorexant influences cognitive impairment in CRSD rats. Thus, suvorexant attenuates cognitive impairment in CRSD and appears to improve cognitive function through the BMAL1/NLRP3 axis and it regulates microglia activation.[28] Further investigation is needed to explore orexin antagonism not only as a symptomatic treatment for sleep disturbances, but also for its broader implications in modifying AD neurodegeneration, emphasizing mechanisms of action and long-term outcomes.

Psychiatric Disorders

Preliminary studies show that orexin antagonists are promising therapeutic agents for psychiatric disorders due to the involvement of the orexin system in regulating arousal, stress, mood, and reward pathways. Overactivation of the orexin system has been linked to heightened anxiety and the stress response. Orexin antagonists may alleviate these symptoms by promoting normal sleep and reducing increased arousal. In a review of pre-clinical and clinical investigations on the role of the orexin system in fear and anxiety-related behavior in response to aversive stimuli, orexin signaling in the amygdala, bed nucleus of the stria terminalis, paraventricular nucleus of the thalamus,

locus coeruleus and prefrontal cortex has been implicated.[29] Human studies are limited with preliminary data indicating that orexin receptor antagonists are anxiolytic in experimental models of anxiety. Given this emerging evidence of the potential role of orexin antagonists in management of anxiety, further human studies are warranted.

Han and colleagues reviewed the efficacy of selective OX2R antagonists (SORA2s) and DORAS in the treatment of chronic insomnia and they reviewed the beneficial role of selective OX1R antagonists (SORA1s) for anxiety and substance use disorders. Patients with panic-related anxiety exhibited elevated CSF orexin-A levels and patients with depression had low CSF orexin-A levels.[30] In several mouse studies, OX2R and dual OX1/2R showed dose dependent antidepressant-like effects. Suvorexant showed improvement in severity of anxiety and depression in patients with insomnia at weeks 2 and 4. The level of cortisol, a stress hormone, also significantly decreased by the end of Nakamura's study.[31] OX1R was a major potential target as several mouse studies showed attenuation of panic-like behaviors. In contrast in a small meta-analysis, Uğurlu found that the use of an orexin antagonist only had a significant effect on core symptoms of depression by weeks 4-6 and no significant effect in weeks 2-3. Preliminary data suggests the antidepressant effects of orexin antagonists act on different pathways for mood regulation other than improvement in sleep. The above findings suggest that orexin antagonism may be a potential target as an adjunct to other antidepressant or anxiolytic treatments.[32]

Dysregulation of the orexin system is implicated in depression, anxiety, and substance use disorders. In a systemic review, Kishi and colleagues identified 21 studies examining the effects of DORAs for chronic insomnia with comorbid psychiatric disorders. Several clinical trials and cohort studies showed improvement of sleep in patients with concomitant insomnia and psychiatric disorders. Comorbid psychiatric disorders in these studies included trauma, bipolar disorder, major depressive disorder, schizophrenia, adjustment disorder, eating disorder, and anxiety. The authors found that several cohort studies showed significant baseline improvement in comorbid psychiatric disorders without any adverse effects of the psychiatric disorder. Studies demonstrated that DORAs showed improvements in mental illness severity, alleviation of depression and anxiety and substance dependence. One phase 3 clinical trial of suvorexant showed increased suicidal ideation at the higher dose (30/40mg) and lower suicide risk with the lower dose. This was not observed with lemborexant. However, it is interesting to note that in the suvorexant post-marketing study, the incidence of adverse drug reactions was higher in patients with psychiatric disorders, including somnolence, insomnia, headache, and dizziness. It is unclear if this is attributed to confounding variables such as other psychotropic medications or the ongoing management of the underlying comorbid psychiatric disorder.[33]

Hyperarousal and insomnia are common symptoms of major depressive disorder. Orexin antagonists by promoting sleep and reducing arousal may have a role in alleviating these symptoms. Furthermore, orexin activity is thought to contribute to the dysregulation of mood related neurocircuitry. To evaluate the efficacy of orexin receptor antagonists in the treatment of major depression, Meshkat and colleagues conducted a systemic review of Seltorexant, a selective OX2R antagonist. They reviewed 5 randomized clinical trials involving 498 participants. Seltorexant significantly reduced depression scores as measured by the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale. However, there was a nonsignificant decrease in depressive symptoms as measured by the Quick Inventory of Depressive Symptomatology Self-Report Score compared to placebo.[34] Multiple selective investigational selective orexin antagonists are currently underway in preclinical studies and are needed to determine whether these agents can augment current treatment of mood disorders.[35]

Menopause

Menopause is characterized by significant physiological changes associated with reduced estrogen and cessation of ovarian function. It is estimated that 40-60% of perimenopausal and postmenopausal women experience sleep disturbances associated with vasomotor symptoms such as hot flashes and night sweats, affecting 50-72% of menopausal women in the United States. A previous study had shown that in the postmenopausal state with reduced estrogen level, there was an increase in plasma orexin-A level. Interestingly, postmenopausal women receiving hormonal replacement therapy had a normal orexin-A level compared to the control group.[36] Administration of orexin-A in castrated female rats primed with estradiol and progesterone appeared to induce luteinizing hormone secretion, suggesting orexin's role in the hypothalamic-pituitary-gonadal axis. Orexin has been shown to upregulate the autonomic nervous system and thermogenic response with increase in heart rate and body temperature. This may further support why postmenopausal women have increased cardiovascular morbidity and mortality. In converse, hormonal replacement with estrogen is cardioprotective, implicating the inhibitory effect of estrogen on orexin. It is proposed that this increased level of orexin dysregulates the sleep-wake cycle and thermoregulation. This is demonstrated in Federici and her colleagues' mouse model that had ovariectomy-induced postmenopausal state with observed increase in orexin level and a 6-7 °C increase in tail skin temperature, which was then attenuated after DORA administration.[37]

Rahman and colleagues conducted a double-blind, randomized, placebo-controlled trial of suvorexant on 54 patients who experienced vasomotor-associated insomnia with suvorexant vs placebo within 30 minutes of bedtime. The suvorexant group was initiated on 10mg for one week and increased to 20mg in a blinded protocol. At the end of the 4-week study period, the adjusted difference to baseline Insomnia Severity Index score was significantly reduced in the suvorexant group with mean of -8.1 compared to the placebo group with mean of -5.6 ($p = 0.04$). Secondary endpoints of WASO, TST, and sleep efficiency were not significantly different. However, subjective reports of nighttime vasomotor symptoms were significantly improved in the suvorexant group by three folds ($p=0.005$). Daytime vasomotor symptoms were not noted to be significantly different. This can potentially be explained by the bedtime administration of suvorexant, which has a half-life of 12 hours on average. Once the antagonistic effect wears off, the rise in orexin level throughout the day can result in the return of vasomotor symptoms. Although these secondary endpoints did not show significance, this study could be limited in setting of smaller statistical power and study duration of 4 weeks as WASO, TST, and sleep efficiency were trending toward a significant difference. This was the first of its studies showing the potential of utilizing DORAs in the treatment of vasomotor-associated insomnia.[38]

Delirium

Delirium is an acute neuropsychiatric syndrome characterized by disturbances in attention, cognition, and consciousness. Delirium is often categorized as hyperactive (agitation, restlessness), hypoactive (lethargy, reduced responsiveness), or mixed subtypes. These states may involve dysregulated arousal mechanisms in the brain. Acute delirium, especially in post-operative or hospitalized settings, is associated with short-term risk and increased long-term mortality.[39] Risk factors for delirium include sepsis, polypharmacy, sensory impairment, acute illness, immobility, and environmental factors in vulnerable patients such as the elderly or cognitive impaired patients. Current treatment remains supportive care with frequent orientation and maintaining a normal sleep-wake cycle. Unfortunately, no effective pharmacological treatment has been adapted.

The role of orexin antagonists in the treatment of delirium is an area of emerging interest but remains largely theoretical and under investigation. The orexin system, located in the hypothalamus, plays a significant role in maintaining wakefulness and regulating transitions between sleep and wakefulness. Evidence suggests that orexin hyperactivity may contribute to the hyperarousal and sleep-wake disturbances seen in delirium. Singh and colleagues performed a systematic review and meta-analysis on the effectiveness of DORAs on the prevention of delirium. Ten studies including three randomized trials were identified and pooled. They found that patients who received DORA prophylaxis had a significantly lower delirium incidence with an odds ratio of 0.23 (95% CI: 0.12 - 0.46) although length of hospital stay, time to delirium onset, and mortality were not different.[40] In hyperactive delirium, DORAs may reduce excess arousal and irritability by dampening orexin signaling. In hypoactive delirium orexin activity may be dysregulated and DORAs may stabilize the arousal system and normalize alertness.

The preliminary data suggests that DORAs may have a role in preventing delirium or reduce the severity of delirium. In a meta-analysis performed by Pontirolli and colleagues, they reviewed 3 randomized control trials and 9 observational studies with 3,547 patients and found that suvorexant reduced delirium incidence to 14.12% compared to 26.1% in control. The addition of ramelteon to suvorexant furthered significantly reduced incidence to 25.71% compared to 39.14% in control. There was no significant difference in mortality, hospital stay, or time to delirium. Interestingly, duration of mechanical ventilation was reduced by 4.26 hours with suvorexant.[41] Hatta and colleagues conducted a randomized clinical trial to determine whether suvorexant reduced delirium in 203 older adults after hospitalization. Although there was a reduction in delirium it was not statistically significant (17% in suvorexant vs 26% in placebo).[42] Oldham's group is currently investigating the use of suvorexant in delirium symptom burden on postoperative days 1 to 3 in patients who underwent heart surgery.[43] They reviewed 30 different studies (i.e., 4 case reports/series, 22 retrospective cohort studies, 3 clinical trials, and 1 clinical effectiveness project) and determined that although DORAs may have a role in preventing delirium, the data is inconclusive.

With respect to the physiological mechanism of how DORAs may prevent delirium, Han and colleagues, used a mouse model performing laparotomy under sevoflurane and assessed delirium-like behaviors. Hypothalamic orexin A levels and midbrain dopamine concentrations were elevated along with increased tyrosine hydroxylase (TH) expression in the ventral tegmental area (VTA). Administration of the DORA suvorexant via intraperitoneal injection reduced the activation of VTA dopamine neurons, decreased TH expression, and lowered dopamine levels in these mice.[44] Although the pathophysiology of delirium is multifactorial and complex, including neuroinflammation, neurotransmitter imbalance, and oxidative stress, the disruption of the sleep-wake regulation has a vital role.[45] In AD or neurodegenerative patients, as outlined above, disruption in the wake promoting neurons, such as orexin are prone to cognitive impairment and delirium. This further strengthens the need for more studies to understand the role that the neuropeptide orexin plays in delirium.

In summary, the following mechanisms may account for the role of DORAs in delirium management. Orexin antagonists may regulate the arousal system reducing agitation or reduced responsiveness. Delirium is strongly associated with disrupted sleep and circadian rhythms. DORAs help regulate a normal sleep wake schedule. While not directly anti-inflammatory, DORAs may indirectly reduce neuroinflammation by mitigating hyperarousal and promoting normal sleep which in turn reduces inflammation in the brain. Finally, by improving sleep and mitigating hyperarousal, DORAs reduce the severity of

cognitive disturbances in delirium. DORAs may have limitations. There is limited evidence for use with delirium, and they could potentially worsen hypoactive delirium by causing more sedation.

Substance Use and Eating Disorders

The orexin system plays a crucial role in substance use disorders (SUDs) due to its involvement in reward processing, drug-seeking behaviors, stress responses, and relapse. It has been observed that 70% of people in detoxification programs struggle with sleep impairments, and sleep loss has also been associated with addictive behavior and relapse. Fragale and colleagues reviewed the role of the orexin system in drug addiction and the potential role of DORAs. The orexin system was associated with morphine addiction and OX1R antagonists have been shown to attenuate addiction motivation for alcohol, cocaine, opioids, and nicotine. Furthermore, increased orexin cell numbers and activity increased addiction behavior. Increased orexin expression is also associated with drug withdrawal. The orexin system is also associated with stress regulation and blocking orexin receptors is associated with reduced stress levels.[46] This was demonstrated in Fragale's mouse studies showing an increased orexin mRNA in alcohol addicted rats as well as an increase in orexin-expressing neurons in rats who were motivated by cocaine, morphine, or fentanyl. Subsequently, blocking OX1R attenuates their drug seeking behaviors. In OX1R knockout mice, opioid withdrawal symptoms appeared to be dampened as well.

Studies have shown that the orexinergic system cooperates with the dopaminergic system in addiction. Orexin causes the release of dopamine in the ventral tegmental area (VTA) that plays a role in addictive behaviors. Previously orexinergic neurons were also found to have mu opioid receptors that likely act as a target for opioid dependence as well.[47] As such, orexin antagonist has become a new class of medication with the potential to attenuate the reinforcing properties of drug addiction. A patient case was reported in 2024 utilizing suvorexant in a 31-year-old male otherwise healthy patient who had concomitant insomnia and alcohol dependence disorder. He was prescribed suvorexant 20mg, and no other alcohol cessation pharmacotherapy, at 8PM every night for 13 weeks. His self-reported craving on the Obsessive-Compulsive Drinking Scale reduced from 44 out of 56 to 3 out of 56. He unfortunately was lost to follow-up, but this case demonstrates the potential role of DORAs in modulating addiction.[48] Currently, investigational selective OX1R antagonists are being studied for treatment of substance use disorders including SB-334867 in rodent models and C4X3256 in humans currently in Phase 1 clinical trials.[49,50]

Clinical inquiry is currently being made regarding the orexin system's role in eating disorders and as a potential target for modulating feeding patterns, reward system, and motor hyperactivity. Studies have observed an association between orexin and feeding encouragement. Increased orexin levels were found in mice exposed to a high fat diet.[51] It is proposed that DORA may play an essential role in interrupting the positive feedback loop in binge eating disorder.[52] Conversely, patients with anorexia nervosa were found to have lower plasma orexin level compared to the control group. In addition, these anorexia nervosa patients were also found to have a negative association on a cognitive Wisconsin Card Sorting Test, which supports the current available evidence on orexin's role in cognition as highlighted in the foregoing section.[53]

Sleep Apnea

Several studies have evaluated the use of DORAs for treatment of insomnia in patients with obstructive sleep apnea (OSA). In a systematic review and meta-analysis on the effects of DORAs on sleep architecture and respiratory parameters in patients with OSA, Yeh and colleagues reviewed four randomized placebo-controlled trials. From this analysis of 126 patients total, DORAs significantly improved TST by 27.46 minutes and

sleep efficiency by 5.59% without impacting REM sleep or the apnea-hypopnea index (AHI).[54] Boof and colleagues conducted two randomized, double-blind placebo-controlled two-period crossover study comparing daridorexant to placebo for patients with mild to moderate OSA. In the daridorexant group, there was more respiratory events (apneas and hypopneas) during TST compared to placebo; however, this was due to a longer TST in the daridorexant group. Daridorexant did not increase OSA severity but did shorten WASO and decreased sleep onset latency. Daridorexant was well tolerated in patients with mild to moderate OSA.[55,56] Khullar and colleagues conducted two multicenter, randomized, double-bling placebo-controlled studies evaluating the sleep parameters in participants with mild to severe OSA who were administered lemborexant for 8 nights. Lemborexant improved TST and sleep efficiency regardless of OSA severity.[57] Cheng and colleagues conducted a double-blind, two-period crossover, placebo-controlled study on the respiratory safety of lemborexant in adults with moderate to severe OSA. Lemborexant demonstrated respiratory safety and was well tolerated.[58] Thus, these agents improved sleep duration and did not worsen OSA.

There is data that higher doses of DORAs are safe for treating insomnia in OSA. In a randomized, double-blind, placebo-controlled, 2-period crossover study of 26 patients with suvorexant 40mg (double the recommended max dose of 20mg) compared to placebo, there was no clinically significant respiratory effects in patients with mild to moderate OSA as assessed by mean AHI and SpO2.[59] In a single-center, prospective, nonrandomized, uncontrolled, unblinded study in Japan by Mieno and colleagues, suvorexant 15mg was evaluated in patients with severe OSA by first and second night polysomnography with suvorexant being given on the second night. They found that the AHI between the first and second night was not significant, and suvorexant increased TST, decreased mid-night awakenings, increased REM percentage, and shortened REM latency.[60] Overall, DORAs are well-tolerated and none of the studies had observed changes in oxygen desaturation. Further and more robust studies are recommended to evaluate severe sleep apnea and its relationship with dose and duration. Nonetheless, DORAs are promising agents to be used in OSA patients with concomitant insomnia.

Future Direction

Although there are three FDA approved DORAs, several are currently in the investigational stage. Seltorexant is a selective OX2R antagonist currently in Phase 3 trial. Vornorexant is a DORA being investigated for insomnia and sleep apnea currently in phase 2 and 3 trials. Nivasorexant is a selective OX1R antagonist currently being investigated for addiction and anxiety. JNJ-48816274 is an OX2R antagonist for sleep quality in insomnia. NCT06823752 is a DORA in phase 2 clinical trial assessing its effect on tau and Aβ proteins. There are several OX2R agonists, first of its kind, currently in clinical trials for treatment of narcolepsy type 1, type 2, and idiopathic hypersomnia, including Oveporexton (TAK-861), ORX750, and TAK-994. It has been proposed that orexin may potentially play a role in augmenting the disease process of Parkinson's Disease as well through promoting brain-derived neurotrophic factor that is usually reduced in the substantia nigra found in Parkinson's Disease.[61] Although this, along with several potential treatment indications mentioned in this review article, were performed in smaller-scale models and trials, the orexin system has shifted the paradigm in clinical management through translational science.

The above preliminary studies show the novel uses of orexin antagonists beyond their initial role in the treatment of insomnia. The implications of these agents will allow for practitioners to do personalized medicine understanding the individual differences in orexin system dysfunction to guide targeted use of orexin antagonists, utilize combination treatments where orexin antagonists

will be combined with other medications to address insomnia with other comorbid disorders, and the expanded indications orexin antagonists to treat a broader range of medical and psychiatric conditions.

Conclusion

Since the discovery of orexin, research studies have increasingly identified its extensive involvement in multiple important biological processes that govern and regulate humans' sleep-wake cycle, feeding, reward system, mood, and behaviors. Since the approval of the three dual orexin receptor antagonists, increasing studies and explorations have demonstrated promising results in the efficacy of orexin antagonists in a multitude of medical conditions either as monotherapy or as an adjunct. Above all, the minimal adverse effect and excellent safety profile compared to other conventional sedatives or hypnotics are advantageous in the use of elderly population. Currently there is no concern of dependence or tolerance with long-term use of DORAs. No withdrawal symptoms or rebound insomnia were described in the 12 months clinical trial either. As further orexin research and data become available, the orexin system remains a therapeutic target of interest that may shift from the treatment of insomnia to the treatment of cognition, mood, behavior, and beyond.

Conflict of Interest:

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