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Review Article

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Emerging and upcoming therapies in insomnia

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ABSTRACT

Insomnia, commonly treated with benzodiazepine (BZD) receptor agonists, presents challenges due to associated serious side effects such as abuse and dependence. To address these concerns, many researches have been conducted to develop and advance both pharmacological and non-pharmacological interventions. Dual orexin receptor antagonists (DORAs), which include suvorexant, daridorexant and lemborexant, have recently been approved by United States Food and Drug Administration (US FDA) as a novel pharmacotherapeutic alternative. Unlike BZD receptor agonists that act as positive allosteric modulators of the gamma-aminobutyric acid type A subunit alpha 1 receptor, DORAs function by binding to both orexin receptor types 1 and 2, and inhibiting the action of the wake-promoting orexin neuropeptide. These drugs induce normal sleep without sleep stage change, do not impair attention and memory performance, and facilitate easier awakening. However, more real-world safety information is needed. Selective orexin-2 receptor antagonists (2-SORAs) is under clinical developments. This review provides an overview of the mechanism of action in relation to insomnia, pharmacokinetics, efficacy and safety information of DORAs and SORA. According to insomnia management guidelines, the first-line treatment for chronic insomnia is cognitive behavioral therapy for insomnia (CBT-I). Although it has proven effective in improving sleep-related quality of life, it has several restrictions limitations due to a face-to-face format. Recently, prescription digital therapy such as Somryst® was approved by US FDA. Somryst®, a smartphone app-based CBT-I, demonstrated meaningful responses in patients. However, digital limitations may impact scalability. Overall, these developments offer promising alternatives for insomnia treatment, emphasizing safety, efficacy, and accessibility.

Keywords: Insomnia; Dual Orexin Receptor Antagonists; Cognitive Behavioral Therapy, Digital Health

INTRODUCTION

Good quality sleep significantly influences various aspects of human health, including nerves, cognition, immunity, and proper growth [1]. The 21st century has ushered in profound changes in the lifestyles of contemporary individuals, affecting sleep quality

and patterns. The proliferation and overuse of personal devices increase screen exposure particularly in the evening and right before bedtime. Concurrently, the rise of online communication through social media has been associated with heightened anxiety and stress before sleep. Decreased physical activity, extended daylight hours, and diminished exposure to natural light can also lead to sleep disorders [2]. In a 2022 Gallup survey, only 32% of Americans reported excellent or very good sleep, 35% answered good sleep, and 33% indicated fair or poor sleep [3]. Trouble falling asleep were reported by 14.5% of United States (US) adults in 2020 [3].

Insomnia is associated with serious distress, irrational thoughts, and bedtime rituals [4]. Chronic sleep deprivation leads to a variety of detrimental health diseases, such as cardiovascular diseases, diabetes, impaired mood and cognitive function including Alzheimer's disease [5]. Sleep disorders are also risk factors for mental disorders [6,7]. Insomnia is also recognized as a major social costly public health issue [8]. One study found that individuals with moderate and severe insomnia had 75% larger mean total healthcare costs and 72% larger mean lost productivity costs [9].

Despite its significance, insomnia remains inadequately treated, and the available treatments for insomnia are limited. There is a growing need for development and updating of new drugs to address insomnia. Therefore, this paper will provide an overview of the pharmacokinetic information, efficacy, and side effects of recent approved therapies and upcoming new drug for insomnia treatment, especially, orexin receptor antagonists. In addition, prescription digital therapy will be introduced briefly.

LIMITATIONS OF TRADITIONALLY USED AND MARKETED INSOMNIA DRUGS

Benzodiazepine (BZD) receptor agonists are the most commonly used mediations for insomnia, encompassing both BZDs and non-BZD receptor agonists such as Z-drugs (zopiclone, zolpidem, zaleplon). Although BZDs and Z-drugs have different chemical structures, they share the same binding site and, consequently, exhibit the same pharmacodynamic action as positive allosteric modulators of gamma-aminobutyric acid type A (GABA-A) subunit alpha 1 receptor. This action induces sleep by causing a broad inhibition of central nervous system (CNS) activity [10].

Z-drugs are the most wildly used medications for insomnia. Although their drug response is very effective, concerns are increasing due to the side effects. The use of Z-drugs approximately doubles the risk of being involved in a motor vehicle accident [11,12]. These drugs can lead to dependence [13] in addition to next-day cognitive, memory, psychomotor and balance impairments [14]. And thus, the US Food and Drug Administration (FDA) has issued warnings regarding the use of Z-drugs, taking into consideration the increased risk of complex sleep behaviors like sleepwalking and sleep driving in conditions such as parasomnias and sleep-related disorders [15].

Among various BZDs, 5—quazepam, estazolam, flurazepam, triazolam, and temazepam—have been approved and prescribed for insomnia. However, quazepam and estazolam are considered unsuitable for treating insomnia due to their long elimination half-life exceeding 15 hours [16,17]. BZDs have similar but slightly more serious side effects compared with

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Z-drugs, including next-day hangover effects, cognitive or memory impairment, the rapid development of tolerance, rebound insomnia upon discontinuation, increased risk of car accidents or falls, and a substantial potential for abuse and dependence [18,19]. A considerable proportion of individuals who are prescribed BZDs becomes chronic users. Furthermore, BZDs are implicated in approximately 5–10% of car accidents, although the rate in individual studies varies from 1% to 65% [11].

RECENTLY MARKETED INSOMNIA DRUGS

Orexin: new target for insomnia treatment

Orexin, also known as hypocretin, is a pair of excitatory neuropeptide hormones with approximately 50% sequence homology [20], named hypocretin 1 and 2 [21], or orexin A and B, respectively [22]. Orexin A and orexin B are exclusively produced in lateral hypothalamic neurons [20] and are released by neurons in the tuberal region of the hypothalamus that also release glutamate [23,24]. Orexin exerts its physiological effects in the brain by activating 2 G-protein-coupled receptors known as orexin receptor type 1 (OX1R) and type 2 (OX2R). Orexin neurons synthesize prepro-orexin, which is processed to yield orexin A and orexin B. Orexin B exhibits 5 to 10 times higher selectivity for OX2R than for OX1R, whereas orexin A shows similar affinity for both receptors.

OX1R exhibits approximately 2–3 times lower affinity for orexin B compared to orexin A, while OX2R binds to both orexin A and orexin B with similar affinity [22,25]. Orexin neurons co-release glutamate and dynorphin, with glutamate binding to glutamate receptors and dynorphin binding to kappa opioid receptors and mu opioid receptors. Orexin neurons are involved in wakefulness by expressing GABA and galanin. Furthermore, the ventrolateral preoptic nucleus (VLPO) in the hypothalamus inhibits orexin neurons, which in turn indirectly inhibits the VLPO [26]. Secondly, orexin neurons influence neurons in the tuberomammillary nucleus (TMN) that promote wakefulness by co-releasing histamine and GABA. Orexin neurons both directly stimulate TMN neurons and indirectly release inhibition. Lastly, orexin neurons stimulate neurons in the locus coeruleus (LC) to trigger norepinephrine release and promote arousal. The effects on the LC are primarily mediated by OX1R, while the effects on the VLPO and TMN by orexin neurons are mainly mediated by OX2R [27]. In the regulation of sleep/wake control, orexin neurons receive projections from various brain regions, including the hypothalamus, basal forebrain, limbic system, and brainstem [28,29]. In this manner, the release of neurotransmitters such as acetylcholine, histamine, norepinephrine, and serotonin by the aforementioned wake-promoting centers helps to stabilize the state of arousal [26].

Introduction of dual orexin receptor antagonists (DORAs)

DORAs, which work by binding to both OX1R and OX2R, inhibit the activity of the wake-promoting orexin neuropeptide (**Fig. 1**), offering an alternative to the traditionally employed positive allosteric GABA-A receptor modulators. DORAs exhibit a distinct action mechanism from GABA modulators, leading to differences in efficacy and side effects. Firstly, whereas GABA modulators alter both sleep stages and the brain's activity network during specific sleep stages, DORAs induce somnolence consistent with normal sleep [30]. The possible explanation for this is that, while GABA modulators alter cortical activity, DORAs inhibit the activity of orexin peptides. Orexin signaling, characterized by slower neuropeptide release, dispersion, and clearance compared to fast neurotransmitters, suggests a role as a

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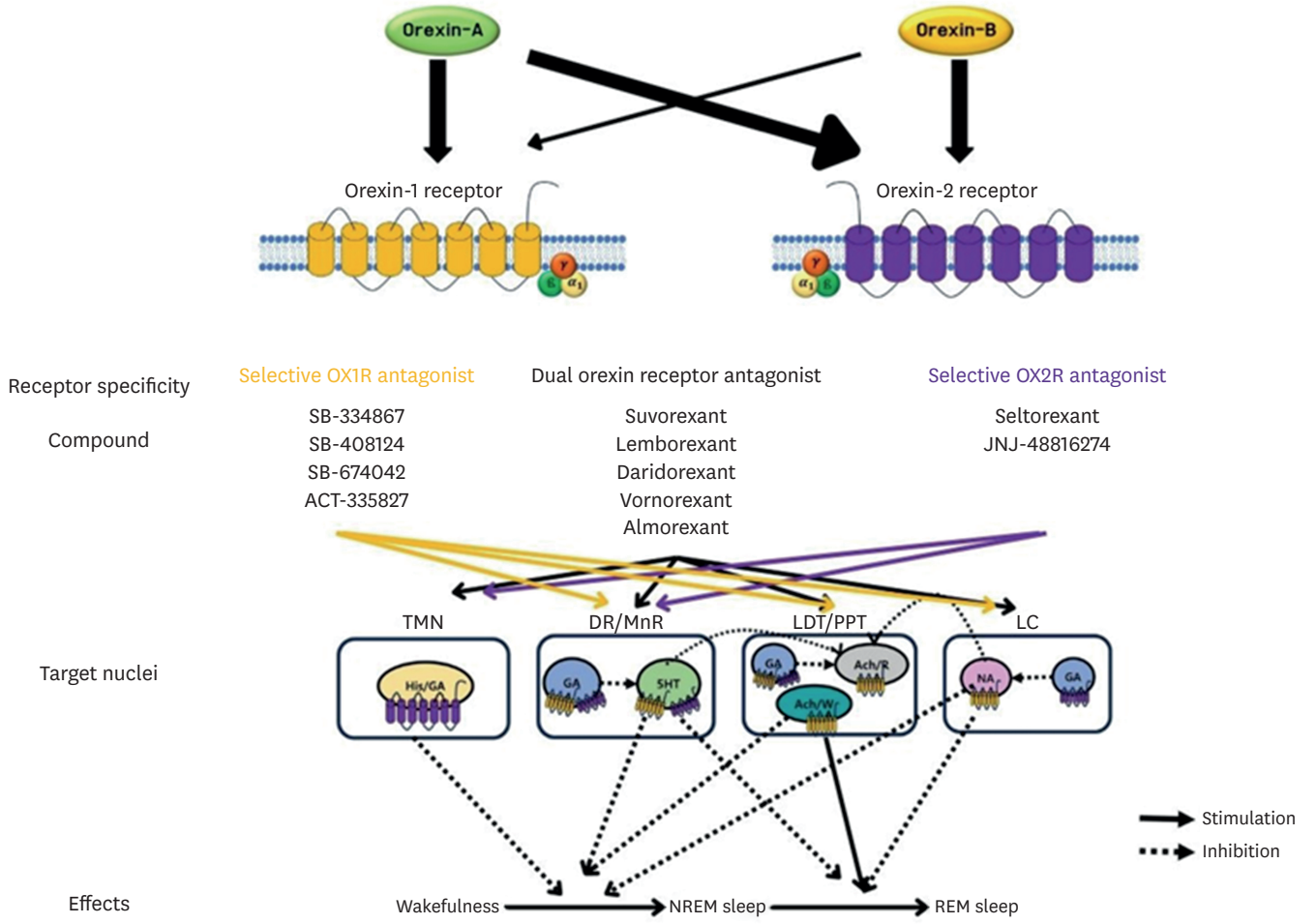

Figure 1. Mechanism of action of orexin antagonists. Orexin A and B act on the orexin receptor. Orexin B exhibits 5 to 10 times higher selectivity for OX2R than for OX1R, whereas orexin A shows similar affinity for both receptors. Orexin receptors are diversely located in the central nervous system, and LC mainly expresses OX1R, TMN and paraventricular nucleus exclusively express OX2R, while DR, basal forebrain, and cortical express both receptors. This orexin regulates wake/sleep transition by activating a variety of neurons and putative interneurons. Cholinergic neurons that are active during wake/REM sleep have the potential to inhibit NREM, while REM-on cholinergic neurons have the potential to induce REM sleep. In addition, serotonergic and noradrenergic neurons interact with REM-on neurons to activate interbrain reticular formation. Gamma-aminobutyric acid-ergic interneurons inhibit cholinergic neurons in the PPT and serotonergic neurons in the raphe. In addition, orexin receptor antagonists are listed. Dual orexin receptor antagonists bind to OX1R and OX2R is suggested to contribute to the suppression of REM sleep. Selective OX2R antagonists has been proposed to facilitate wakefulness and inhibit NREM. Meanwhile, selective OX1R antagonists is not directly indicated for sleep.
OX1R, orexin receptor type 1; OX2R, orexin receptor type 2; LC, locus coeruleus; TMN, tuberomammillary nucleus; DR, dorsal raphe; REM, rapid eye movement; NREM, non-rapid eye movement; PPT, pedunculopontine tegmental nucleus; 5HT, serotonergic neurons; Ach, cholinergic neurons; Ach/R, REM-on cholinergic neurons; Ach/W, Wake/REM-on cholinergic neurons; GA, gamma-aminobutyric acid-ergic neurons; His, histaminergic neurons; LDT, laterodorsal tegmental nucleus; NA, noradrenergic neurons.

wakefulness regulator rather than a carrier of rapid information in the CNS. Secondly, unlike GABA modulators, DORAs do not impair attention and memory performance in rats and monkeys [31] possibly due to the absence of a direct synaptic effect of orexin antagonists on fast neurotransmitter release. However, this effect needs confirmation in long-term and large cohort studies. Thirdly, DORAs facilitate easier awakenings than GABA modulators and cause less functional impairment in locomotor tasks in various animal [32,33]. The auditory discrimination system, crucial for arousability by external stimuli, operates downstream and is independent on orexin signaling.

Now, suvorexant, daridorexant and lemborenxant have been approved by US FDA and will be introduced in this article.

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Table 1. Orexin receptor antagonists for insomnia

Characteristics	Drugs	Major target receptors	Inhibition constant	Recommended dose (mg)	Tmax (hr)	Onset (min)	Vd (L)	CL/F (L/h)	Active metabolites	Metabolism	$T_{1/2}$ (hr)	Duration of action (hr)	Indication	Reference
Marketed drugs	Suvorexant	OX1R OX2R	Ki: 0.55 nM (OX1R) 0.35 nM (OX2R)	15–20 (dose reduction with moderate CYP3A inhibitor)	2	30	49	N/A	-	CYP3A CYP2C19	12	7	Sleep onset and maintenance	[34-36]
	Daridorexant	OX1R OX2R	Kb: 0.52 nM (OX1R) 0.78 nM (OX2R)	25–50	1–2	30	31	5	-	CYP3A4	8	7	Sleep onset and maintenance	[47,94,95]
	Lemborexant	OX1R OX2R mainly	Ki: 4.8 nM (OX1R) 0.61 nM (OX2R)	5–10	1–3	30	1,970	22.7	M4 M9 M10 (major circulating metabolite)	CYP3A CYP2B6	17–19	7	Sleep onset and maintenance	[67,69]
Drugs in development	Vornorexant	OX1R OX2R	N/A	N/A	2.5–3	60	N/A	N/A	M3	N/A	1.32–3.25	N/A	N/A until now	[76]
	Seltorexant	OX2R selective	Ki: 8.0 nM	N/A	0.5–1.5	N/A	N/A	N/A	-	CYP3A4	2–3	N/A	N/A, target indication: Sleep onset	[81,96]

Tmax, time to peak drug concentration; Vd, volume of distribution; CL/F, oral clearance; $T_{1/2}$, elimination half-life; N/A, not applicable; OX1R, orexin receptor type 1; OX2R, orexin receptor type 2; Ki, inhibition constant; CYP3A, cytochrome P450 3A.

Suvorexant

Suvorexant, the first DORA, gained approval from the US FDA in 2014 for the treatment of primary insomnia. Receptor-ligand structures showed that suvorexant reversibly blocks the binding of orexin A and orexin B at the orthosteric site of both OX1R and OX2R resulting in the inhibition of the activation of OX1R and OX2R, leading to the suppression of wakefulness [34]. Suvorexant exhibits binding affinities of 0.55 nM and 0.35 nM for human OX1R and OX2R, showing high selectivity for OX1R and OX2R [35]. Preclinical studies in various species demonstrated reduced wakefulness during active phases and increased rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep upon oral administration of suvorexant [25].

1) Pharmacokinetics

Pharmacokinetic profile of DORAs is listed and compared in **Table 1**.

The absolute bioavailability of suvorexant is 62%. The median time to reach the maximum concentration (Tmax) of suvorexant was approximately 2 hours [36]. Accumulation ratios for the area under the concentration-time curve (AUC) and maximum observed concentration (Cmax) were increased in a less than dose-proportional manner over the range of 10–80 mg due to decreased absorption [37]. When administered with high-fat meals, Tmax was delayed by 1.5 hours, but there was no clinically significant change in AUC and Cmax. Protein binding exceeds 99%, primarily to human serum albumin and α1-acid glycoprotein [36].

Metabolism primarily occurs in the liver via cytochrome P450 3A (CYP3A), with minimal contribution from CYP2C19. A hydroxy-suvorexant, a major circulating metabolite, is pharmacologically inactive. Elimination half-life is 12 hours [36]. Suvorexant is eliminated primarily as metabolites with less than 1% of dose recovered in feces and urine as suvorexant, and 66% in feces and 23% in urine [36]. Ketoconazole, a strong CYP3A inhibitor, increased

suvorexant AUC by 2.79-fold and diltiazem, moderate CYP3A inhibitors, increased AUC by 2.05-fold [38]. Consequently, co-administration with strong or moderate CYP3A4 inhibitors is not recommended [36,38]. Suvorexant is a weak inhibitor of CYP3A and the intestinal P-glycoprotein (P-gp) following consecutive, multiple dose administration. Due to P-gp inhibition, co-administration of suvorexant and digoxin resulted in a slight increase in digoxin levels. When co-administering suvorexant and digoxin, clinicians should monitor the digoxin concentrations [36].

Age, race, and renal impairment do not appear to have a clinically significant effect on suvorexant pharmacokinetics [39]. In individuals with moderate hepatic impairment (Child-Pugh category 7 to 9), the terminal half-life increased from 15 hours in healthy subjects to 19 hours [39]. It has not been studied in patients with severe hepatic impairment, and its use is not recommended in these patients.

The AUC and Cmax in female are increased by 17% and 9% compared to male following administration of suvorexant 40 mg [36]. Oral clearance is inversely related body mass index (BMI). In obese female (BMI > 30 kg/m^2), the AUC and Cmax increased by 31% and 17%, respectively, compared to nonobese female (BMI < 25 kg/m^2) [36].

2) Clinical efficacy in insomnia

In early phase II studies, suvorexant showed dose-related efficacy as measured by the latency to persistent sleep (LPS) and wake after sleep onset (WASO) in a dose range of 10–80 mg over two 4-week periods [40]. In 3 phase III studies, in an administered dose range of 15–40 mg, suvorexant improved the LPS as objectively measured by polysomnography, and self-reported total sleep time (sTST), and subjective sleep quality, as well as the Insomnia Severity Index score during the 3 months [41,42].

3) Safety

The most common adverse events (AEs) (more than 2%) were somnolence, dizziness, headache, and nightmare [41,42]. Female are more likely to experience AEs than males at similar dosages; however, the AE profile was similar between the male and female groups [43].

In the assessment of next-morning residual effects of suvorexant on driving performance, there was no statistically significant change [44]. However, 5 females out of a total 52 subjects (4 non-elderly on suvorexant; one elderly on placebo) prematurely stopped their driving tests due to somnolence, suggesting clinically meaningful impaired driving performance. Patients should be advised not to drive and engage in other activities requiring full mental alertness until fully awake [44].

Long-term use of suvorexant for chronic insomnia did not result in physical dependence or withdrawal syndrome after one year of chronic treatment cessation [42]. No evidence of rebound insomnia was observed following treatment discontinuation at Month 3, Month 6 or Month 12 [42]. In a study to evaluate the abuse potential in recreational polydrug users, suvorexant (40, 80 and 150 mg) produced similar effects as zolpidem (15 and 30 mg) on subjective ratings of drug liking [45]. And thus, as with other hypnotics, care should be taken with suvorexant the patients with a history of addiction or abuse due to risk of misuse or abuse.

Daridorexant

1) Pharmacokinetics

According to FDA labels, Bioavailability of daridorexant is 62%. Its plasma exposure is dose-

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proportional at the therapeutic doses [46]. The pharmacokinetic profiles of daridorexant are similar following a single dose and multiple doses, with no clinically relevant accumulation [47]. The average Tmax of daridorexant was approximately 1.0 hour, indicating rapid absorption [47]. In healthy subjects, a high-fat and high-calorie meal delayed the Tmax by 1.3 hours and decreased the Cmax by 16%, but did not affect the AUC [48].

Daridorexant is highly bound to plasma proteins (99.7%) and has a blood to plasma ratio of 0.64. Daridorexant undergoes extensive metabolism and is primarily metabolized by CYP3A4 (89%). Other CYP enzymes individually contribute to less than 3% of metabolic clearance of daridorexant. The major human metabolites of daridorexant do not contribute to its pharmacodynamic effect [49]. The primary route of daridorexant excretion is via feces (approximately 57%), followed by urine (approximately 28%) primarily as metabolites with trace amounts of parent drug found [49]. The terminal elimination half-life of daridorexant is approximately 8 hours [47]. This represents the shortest half-life among available DORAs, and whether this contributes to a reduced risk of next-day functional impairment remains to be elucidated.

The pharmacokinetics of daridorexant are not affected to a clinically significant extent by sex, race, body size, mild-to-severe kidney impairment (not on dialysis) or mild liver impairment [50-52]. But following a 25 mg dose of daridorexant in patients with moderate liver impairment (Child-Pugh score 7–9), there was an increase of 1.6- and 2.1-fold in the exposure to unbound daridorexant and half-life, compared with healthy subjects [53]. The pharmacokinetics of daridorexant have not been studied in patients with severe liver impairment [53].

2) Clinical efficacy in insomnia

The maximum pharmacodynamic effects were observed approximately 2 hours post-administration, returning to baseline levels within 4–10 hours post-dose [47]. In subjects with insomnia disorder at doses of 5, 10, 25, and 50 mg, daridorexant demonstrated a substantial and dose-dependent improvement in objectively evaluated sleep initiation and maintenance compared to placebo, without dosage-limiting safety concerns [54]. In 2 phase III studies, daridorexant 50 mg significantly reduced WASO and LPS from baseline, and improved sTST and Insomnia Daytime Symptoms and Impacts Questionnaire compared to placebo at Month 1 and 3 [55].

3) Safety

In 2 phase III studies, daridorexant was generally well tolerated in patients with insomnia disorder with minimal reported side effects [55]. The overall incidence of AEs was similar across all treatment groups (38% with daridorexant 50 mg, 38% with daridorexant 25 mg and 34% with placebo), showing no evidence of dose dependency. The most common AEs (more than 2%) were nasopharyngitis, headache, somnolence, fatigue, etc., and they were mild in severity. Despite the low incidence, suicidal ideation was reported in one patient receiving daridorexant 25 mg and one receiving daridorexant 10 mg; both patients had pre-existing conditions (paranoid schizophrenia and depression, respectively). Cataplexy-like symptoms or complex sleep behaviors were not reported [55].

In the assessment of next-morning residual effects of daridorexant on driving performance, conducted 9 hours after first dose, driving performance was impaired [56]; patients should be cautioned about driving and engaging in other hazardous activities after administration of daridorexant.

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The safety and tolerability of daridorexant in older adults were comparable to those in younger adults [50]; thus, no dose reduction is recommended in elderly patients.

In the 12-month extension study, there were no new safety or tolerability concerns, nor was there evidence of dose dependency in the frequency of AEs [57]. This supports relatively safe chronic use in chronic insomnia while The European guideline for the treatment of insomnia recommends BZDs and Z-drugs for the short-term (≤ 4 weeks) treatment of insomnia [58]. No evidence of rebound insomnia was observed during the run-out periods or the extension study [55]. Thus, daridorexant can be discontinued without down-titration. Daridorexant did not produce signs of withdrawal or dependence upon discontinuation in animal studies and clinical trials [59]. In a human abuse potential study involving recreational sedative drug users, daridorexant 50 mg, 100 mg and 150 mg exhibited greater drug-liking effects than placebo in a dose-dependent manner [60]. Patients with a history of substance abuse should be closely monitored.

Lemborexant

Lemborexant received approval for the treatment of adult insomnia from the US FDA in 2019 and from Pharmaceuticals and Medical Devices Agency in Japan in 2020 [61].

Similar to suvorexant, lemborexant is a reversible competitive antagonist binding to both OX1R and OX2R; however, lemborexant exhibits higher affinity or activity for OX2R than OX1R [62]. OX1R inhibits the onset of REM sleep, while the OX2R predominantly plays a role in suppressing the initiation of NREM sleep and also contributes to some extent to the regulation of REM sleep [63]. Therefore, lemborexant increases NREM sleep compared to zolpidem and placebo [64]. Lemborexant diminishes wakefulness by modulating orexin-mediated wake drive.

Unlike other orexin receptor antagonists with slower dissociation kinetics, lemborexant rapidly binds and dissociates from orexin receptors [62]. These characteristics suggest a shorter action duration, i.e., promoting sleep onset and reducing the risk of daytime sleepiness [65].

1) Pharmacokinetics

The bioavailability of lemborexant is at least 87% [66]. The Tmax of lemborexant is 1 to 3 hours. The administration of high-fat and high-calorie meal has been found to delay the Tmax by 2 hours. The distribution volume of Lemborexant is extensive, measuring 1,970 L. Although Lemborexant is bound to approximately 94% of proteins *in vitro*, the specific protein to which it binds in plasma has not been identified [67].

Lemborexant undergoes extensive metabolism primarily by CYP3A4 and, to a lesser extent, by CYP3A5 [68]. Metabolism via CYP3A yields M4, M9, and M10, with the predominant circulating metabolite being M10. M10 is pharmacologically active, binding to orexin receptors with comparable affinity. However, its contributions to the sleep-promoting effects are likely low due to limited brain penetration by P-gp. M10 has the potential to induce CYP3A and CYP2B6, weakly inhibit CYP3A [69].

Following oral administration, 57.4% of the dose is recovered in the feces, while 29.1% is found in the urine. Less than 1% of the recovered dose in the urine remains unchanged [69]. Lemborexant has a long effective half-life of 17–19 hours; however, in the earlier elimination phase, it appears to be more rapidly cleared than suvorexant [69], contributing reduced next-day effects.

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The age, sex, race/ethnicity, BMI, or renal impairment didn't have the clinically significant effects on the pharmacokinetics of lemborexant [66]. Lemborexant exposure was increased in mild and moderate hepatic impairment supporting recommendation of dose adjustment. It has not been studied in the patients with severe hepatic impairment, so it's use is not recommended.

2) Clinical efficacy in insomnia

In a recent meta-analysis comparing various insomnia treatments, including suvorexant, zolpidem, zopiclone, eszopiclone, trazodone, flunitrazepam, estazolam, triazolam, brotizolam, temazepam, and ramelteon, lemborexant emerged as the most effective treatment in 3 out of 4 objectively measured outcomes assessed by polysomnography, such as TST, LPS, and sleep efficiency at 4 weeks [70]. Lemborexant exhibited similar efficacy to suvorexant in subjective measurements of WASO, sTST, and sleep onset latency (SOL) at 4 weeks. These demonstrating significant advantages in sleep onset and maintenance. In addition, the sustained effects of lemborexant over a period of 12 months suggest that lemborexant may provide long-term benefits to subjects with chronic insomnia [71].

3) Safety

The safety profile of lemborexant, regarding serous AEs and withdrawals due to AEs, was broadly similar to that of other insomnia drugs [70]. Lemborexant did not show significant morning residual effects or a meaningful association with next-day functional impairment and it posed a significantly lower risk of dizziness and postural discomfort compared to BZD receptor agonists [70,72]. Due to the potential risk of impaired driving ability the following day, individuals sensitive to lemborexant effects should be prescribed lower doses [72].

Lemborexant did not induce withdrawal signs or symptoms upon drug discontinuation [73], suggesting that lemborexant does not lead to physical dependence. In a human abuse potential study conducted in recreational sedative abusers, lemborexant 10 mg, 20 mg, and 30 mg produced responses such as drug liking, take drug again that were statistically similar to those produced by 30 mg zolpidem and 40 suvorexant [74]. Therefore, individuals with a history of abuse or addiction to alcohol or other drugs should be carefully monitored.

PIPELINE DRUGS OF OREXIN RECEPTOR ANTAGONISTS UNDER CLINICAL DEVELOPMENT FOR INSOMNIA IN 2023

Several drugs for insomnia are currently under clinical development. Investigational drugs by category are as follows (clinicaltrials.gov).

- $GABA_A$ receptor positive allosteric modulators: Lorediplon (GF-015535-00), Zuranolone (SAGE-217), EVT-201
- DORAs: Vornorexant (ORN-0829, TS-142)
- Selective OX2 receptor antagonist (2-SORA): Seltorexant (MIN-202, JNJ,42847922, JNJ-922)
- Melatonin receptor agonists: Piromelatine (Neu-P11)
- Nociceptin receptor agonists: Sunobinop (IMB-115, IT-1315, S-117957, V-117957)

DORAs and 2-SORAs will be introduced below.

DORAs under clinical development

Vornorexant (ORN-0829, TS-142)

Vornorexant, the investigational DORA, known by the development code names ORN-0829 or

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TS-142, is under development by Taisho Pharmaceutical Co. for the treatment of insomnia and sleep apnea [59,75]. Designed with a short half-life and duration of action to reduce next-day effects, such as residual sedation [75], vornorexant is currently undergoing phase III trials (clinicaltrials.gov).

1) Pharmacokinetics

The vornorexant AUC increased proportionally with dose [76]. No cumulative effect was observed with repeated administration of vornorexant at doses of 10–30 mg showing almost similar concentration-time profiles on Day 1 and Day 7. Vornorexant was rapidly absorbed with a Tmax of 0.5–3 hours. In food intake, Tmax was delayed to 1.5–4 hours although no effects on Cmax and AUC of vornorexant.

Vornorexant was extensively metabolized into various metabolites [76]. However, the unchanged form was predominant in plasma followed by M3 (less than one fifth of vornorexant concentration levels) with a dehydrogenated oxazinane ring and then M1 (less than one tenth of vornorexant) with a hydroxylated methylphenyl moiety. Although Tosho Co. didn't publish, they suggested that M1 and M3 is active but less potent antagonistic activity against OX1 and OX2 compared to vornorexant.

The elimination half-life of vornorexant ranged from 1.32 to 3.25 hours, indicating rapid elimination and possibility of reduced next-day effects [76].

There was no significant difference in vornorexant exposure between non-elderly and elderly individuals [76].

2) Clinical efficacy in insomnia

In a phase II clinical trials in insomnia patients administered dose of 5 mg, 10 mg and 30 mg, vornorexant improved LPS, WASO, and self-reported measures of sleep onset, awakening, and sleep quality [77].

3) Safety

In phase I and phase II trials, all AEs were mild or moderate and none were serious [76,77]. Until now, suicide attempts or suicidal ideation were not observed [76,77]. In a phase II trial, in order to evaluate the risk of next-day residual effects, Karolinska Sleepiness Scale (KSS), Digit Symbol Substitution Test (DSST) were assessed [77]. There was no significant change in KSS or DSST scores between vornorexant and placebo, suggesting that the occurrence rate of next-day residual effects may be low when vornorexant is administered at a dose range of 5–30 mg [77].

Introduction of 2-SORAs

SORA, a selective antagonist of human orexin receptors, exerts its effects by selectively binding to either OX1R or OX2R, in contrast to a comprehensive DORA that inhibits both receptors. The activation of OX2R has been proposed to facilitate wakefulness and inhibit NREM, whereas the activation of both receptors is suggested to contribute to the suppression of REM sleep [78]. Therefore, 2-SORA can offer a more tailored sleep profile by preserving the normal sleep architecture [79]. Meanwhile, 1-SORAs, which is not directly associated with sleep, is in development for treatment of addictive behavior and stress-related disturbances [80]. Therefore, it will not be covered in this article.

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JNJ-48816274 and seltorexant (JNJ-42847922) were developed as 2-SORA by Janssen Pharmaceuticals. While JNJ-48816274 is no longer being studied (clinicaltrials.gov), seltorexant is under development and has clinical data, which will be introduced here.

Seltorexant (JNJ-42847922/MIN-202)

Seltorexant is a selective, high-affinity OX2R antagonist, exhibiting a 100-fold greater selectivity compared to OX1R, with negligible affinity for other receptors, transporters, or ion channels [79].

1) Preclinical characteristics

Following oral administration of seltorexant in mice, rapid occupancy and clearance of OX2R binding sites in the brain were observed. This resulted in a reduction of SOL and an extension of NREM sleep duration while minimizing its impact on REM sleep. The sleep-promoting effects persisted upon repeated administration, and after discontinuation, returned to baseline levels. Notably, this compound showed no effects in OX2R knockout mice, confirming the specificity of its mediation in sleep response through OX2R [79].

2) Pharmacokinetics

Seltorexant exhibits rapid absorption with a Tmax ranged from 0.5 to 1.5 hours, and a short duration characterized by a half-life of 2 to 3 hours [81]. This profile suggests it is ideal for sleep induction. Seltorexant exposure at doses ranging from 10 mg to 80 mg showed an increase that was less than dose-proportional [79]. It is known to be metabolized by the CYP3A4 and shows moderate CYP inhibition.

In vivo positron emission tomography imaging in animals revealed that [^{18}F] Seltorexant has demonstrated exceptional binding specificity for OX2R, along with suitable blood-brain barrier penetration, and brain uptake [82]. Pretreatment with competitive P-gp inhibitor cyclosporin increased brain uptake, suggesting a potential interaction with P-gp.

3) Clinical efficacy for insomnia

Seltorexant is currently undergoing phase III clinical trials for treatment for major depressive disorder and phase II trials for insomnia treatment. Here, clinical efficacy for only insomnia will be covered.

In a dose-ranging phase II study with dose ranging from 5 mg to 20 mg, seltorexant resulted in a prolonged TST, and shorter LPS and WASO compared to placebo [83]. The study also reported a persistent reduction in the time to REM onset and an increase in the total duration of REM sleep, confirming seltorexant as a promising candidate for the treatment of insomnia.

4) Safety

In a phase III trials, headaches, somnolence, nausea were the most common AEs [84]. In a meta-analysis, seltorexant had fewer AEs than BZDs and Z-drugs [85]. Seltorexant appeared to be a well-tolerated drug, but data on other important outcomes including AE were limited, making firm conclusions impossible.

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EMERGING PRESCRIPTION DIGITAL COGNITIVE BEHAVIORAL THERAPY

According to the most recent guidelines, cognitive behavioral therapy for insomnia (CBT-I) is the first-line treatment for chronic insomnia [86,87]. The limitations of pharmacological treatments for insomnia, such as the potential for dependency and resistance with long-term use, support the use of medications only for short-term relief. Not only has CBT-I shown beneficial effects on insomnia symptoms, but it has also proven effective in reducing depression, anxiety, chronic pain, and improving sleep-related quality of life [88]. CBT-I has traditionally been delivered in a face-to-face format by trained therapists, which, however, comes with drawbacks. Cases exist where patients may not fully grasp the treatment or face geographical constraints. a need that has become particularly acute due to many restrictions in face-to-face healthcare interactions mandated as a result of the COVID-19 pandemic. Moreover, the limited number of trained experts can result in long waiting times. Despite robust empirical evidence, CBT-I has not been widely adopted in clinical settings [89]. With recent developments in technology, an innovative solution has been developed to deliver digital CBT-I. Until now, as digital CBT-I, Somryst® and NightWare™ are approved by US FDA. Unlike CBT-I, NightWare™ was approved for sleep disturbance for psychiatric condition such as post-traumatic stress disorder. By utilizing a biosensor within a smartwatch, the NightWare™ system can incorporate a sophisticated app that vibrates the user's arm when it detects they are having a nightmare [90]. Due to lack of space, Somryst® will be briefly introduced.

Somryst®

Somryst®, which received approval in April 2019 is the first approved prescription digital therapeutic for chronic insomnia. Developed by Pear Therapeutics, Inc., Somryst® follows the approval of reSET® and reSET-O® in 2023. It is a mobile application designed for smartphone or tablet, offering CBT-I for adults aged 22 and older with chronic insomnia. Somryst® incorporates 3 key therapeutic components to address the symptoms of chronic insomnia: tailored sleep restriction and consolidation, stimulus control, and personalized cognitive restructuring. These components align with standard CBT-I provided in a face-to-face context [91].

Its effectiveness in treating chronic insomnia is reported in 2 clinical studies [92,93]. After treatment with Somryst®, over 40% of patients no longer met the criteria for chronic insomnia, and more than 60% showed clinically meaningful responses to insomnia without AE. Additionally, the therapy offers advantages such as flexible treatment timing, overcoming geographical and logistical barriers to treatment access. It excels in providing treatment in individual environments, particularly crucial for conditions prone to stigmatization, such as substance use disorder, suicidal impulses, or depression. The therapy's personalization based on observed patient responses, outcomes, progress, or other metrics is advantageous. Somryst® allows treatment adjustments as needed, and clinicians can review key progress parameters before face-to-face or virtual meetings with patients.

Somryst® uses sleep restriction, a technic that limits the time a patient spends in bed to generally match the amount of time they sleep. However, this treatment approach can increase the risks of excessive daytime sleepiness for some patients whose pathophysiology may be worsened by sleep restriction [93]. Therefore, Somryst® should not be used in following conditions: any disorder exacerbated by sleep restriction (e.g., bipolar disorder, schizophrenia, other psychotic spectrum disorders), untreated obstructive sleep apnea, parasomnias, epilepsy, individuals at high risk of falls, pregnant female, individuals with any

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other unstable or degenerative illness judged to be worsened by sleep restriction delivered as part of CBT-I [91].

CONCLUSIONS

When compared to GABA modulators, the beneficial effects of DORAs, a newly approved class, on the onset and maintenance of sleep have been demonstrated from data on pharmacokinetics, efficacy and safety. In addition, it was proved to lower risk of next-morning sleepiness, cognitive function, and rebound insomnia.

A 2-SORA including seltorexant, is under clinical developments. Seltorexant selectively binds to OX2R, providing advantages in residual effects and associated side effects due to its rapid absorption and short elimination profile [85] although it needs to be confirmed in phase III.

US FDA approved digital therapy like Somryst® have demonstrated significant improvements in insomnia, mental health, and cost-effectiveness, making them valuable alternatives with benefits such as sustained efficacy and reduced risk of adverse effects in the evolving landscape of insomnia therapeutics.

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