Evidence-based insomnia treatment strategy using novel orexin antagonists: A review

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INTRODUCTION

1.1 Insomnia disorder

Insomnia is one of the most common sleep disorders. Approximately 35% of the general population has at least one of the symptoms of insomnia. In addition to nighttime sleep onset and/or maintenance difficulties, the diagnostic criteria for insomnia disorder include daytime dysfunction. Patients with insomnia frequently present with fatigue, daytime sleepiness, and/or difficulties with attention, concentration, and memory. Thus, the treatment goal was to alleviate nighttime sleep difficulties and daytime dysfunction. Nonpharmacological treatments, such as cognitive-behavioral therapy, are initially recommended for patients with chronic insomnia. Although these are effective and vital therapeutic modalities for adult patients, pharmacotherapy might be required when the initial approach is ineffective in terms of...
symptom patterns, treatment goals, past therapeutic responses, or patient preference. It is crucial to select an insomnia medication from the perspective of efficacy and safety. The appropriate drug selection depends on patient symptoms including difficulty initiating and maintaining sleep, and/or early morning awakening with the inability to return to sleep. In recent years, pharmacologic treatment options for insomnia have expanded as new drugs with diverse mechanisms of action have been approved. Therefore, physicians may choose the optimal drugs for individual patients based on a balance between safety and efficacy. Hence, it is essential to examine fundamental treatment strategies in terms of evidence-based medicine (EBM).

1.2 Current pharmacological treatment for insomnia

The major categories of drugs approved by the United States (US) Food and Drug Administration (FDA) for the treatment of insomnia disorder include benzodiazepine receptor agonists (BZDs), non-BZDs (Z-drugs), melatonin receptor agonists, orexin receptor antagonists, and barbiturates. Of these, BZDs and Z-drugs are most commonly administered to patients with insomnia. Short-acting BZDs or Z-drugs might improve difficulty in initiating sleep but may not necessarily ameliorate sleep maintenance problems or early morning awakening. The FDA issued box warnings regarding the potential risk of physical dependence associated with these drugs and sleep-related complex behavior while not fully awake. The Japanese Pharmaceuticals and Medical Devices Agency issued an alert concerning prolonged BZD and Z-drug administration. Physical dependence has been observed even at therapeutic doses especially during long-term use. The gamma-aminobutyric acid type A (GABA_A) receptors are the targets of BZDs and Z-drugs, and they regulate inhibitory neurotransmission in the brain. Therefore, these drugs may also be anxiolytic, anticonvulsant, muscle relaxant, and amnestic. They might induce dependency, tolerance, and cognitive (memory and learning) impairment. Some of these effects are particularly problematic when these drugs are used for long term and when administered to elderly individuals. It is now widely accepted that BZDs and Z-drugs are somewhat effective for patients with insomnia. However, because the prevalence of chronic insomnia disorder is approximately 5%–10%, the efficacy of insomnia drugs should be improved.

Ramelteon is a melatonin receptor agonist. Its mechanism is distinct from that of BZDs and Z-drugs. Ramelteon was approved in the US in 2005 and Japan in 2010 for improving sleep initiation difficulty. Melatonin is secreted by the pineal gland and acts mainly on the melatonin receptors in the suprachiasmatic nucleus. The melatonin level shows diurnal variation. It gradually increases in the evening, peaks during the night, and decreases between morning and noon. Although it lacks the safety concerns peculiar to BZDs and/or Z-drugs, ramelteon is only indicated for the treatment of insomnia characterized by sleep onset difficulty. It is not recommended for the management of sleep maintenance difficulties.

1.3 Trends in pharmacological treatment for insomnia—orexin receptor antagonist

The dual orexin receptor antagonists (DORAs), suvorexant and lemborexant, were recently developed and approved for insomnia treatment. Their pharmacological mechanism of action differs from that of GABAergic drugs. DORAs promote sleep and inhibit wakefulness by competitively blocking orexin neurotransmission. The orexin neuropeptides orexin-A and orexin-B are critical upstream controllers of most wakefulness-promoting neurotransmitters including acetylcholine, histamine, norepinephrine, and serotonin. They bind to the G-protein-coupled orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R). Suvorexant and lemborexant are known as DORAs since they bind to both OX1R and OX2R. Orexin neurons occur exclusively in the lateral hypothalamic area but broadly project to the cerebral cortex, brainstem, and basal forebrain. Orexin helps to establish and maintain the sleep-wake cycle. Hence, drugs targeting the orexin receptors are expected to have comparatively fewer nonspecific effects. Lemborexant binds specifically to OX1R and OX2R, but not to receptors for GABA_A, prostaglandins D2 and E2, serotonin, noradrenaline, histamine, acetylcholine, dopamine, galanin, and corticotropin-releasing factor. The goal of this review was to propose an EBM-based strategy for the insomnia medication use of lemborexant and suvorexant according to the results of studies on clinical efficacy and safety.

1.4 What is evidence-based medicine?

EBM is a criterion for selecting treatment methods in various clinical practice guidelines. The level of evidence is set according to study reliability. Systematic reviews and meta-analyses are research tools with the highest evidence level followed by randomized controlled trials (RCTs). Systematic reviews qualitatively integrate the outcomes of more than one RCT for a particular disorder or drug. Pairwise and network meta-analyses quantitatively evaluate summarized evidence. Network meta-analyses compare drugs not previously evaluated in head-to-head RCTs and would, therefore, provide comparison data. If RCT1 compares Drug A with placebo and RCT2 compares Drug B with placebo, then comparisons could be made between Drugs A and B via the placebo. In practice, it is difficult to conduct RCTs on all drugs of interest. Hence, network meta-analyses furnish reliable evidence and compare certain intervention modalities in a cost-effective and time-efficient manner.

2 SUMMARIES OF META-ANALYSIS OUTCOMES

2.1 Suvorexant

Suvorexant was approved in the US and Japan in 2014. In phase 3 Studies 028 (NCT01097616) and 029 (NCT01097629), relative to the
placebo, suvorexant improved total sleep time (TST), subjective total sleep time (sTST), latency to onset of persistent sleep (LPS), subjective sleep onset latency (sSOL), objective wake time after sleep onset (sWASO), and insomnia severity index (ISI) scores. However, at some evaluation points, certain sleep parameters were inconsistent between the phase 3 studies. In Study 029, sSOL of the 20/10-mg suvorexant group was numerically different from that of the placebo group at 1 week, 1, and 3 months after administration. In contrast, sSOL was different from that of placebo only at 1 week and 3 months after administration in Study 028. Despite the similarity between these study protocols, two possible explanations for this inconsistency have insufficient statistical power and sample size. For this reason, a meta-analysis was conducted to perform problem-based investigations. A meta-analysis of placebo-controlled RCTs (four studies; 3076 subjects) revealed that sSOL significantly improved in the suvorexant group compared with that in the placebo group at 1 week, 1, and 3 months after administration (Tables 1 and 2). Moreover, in the suvorexant group, sTST was prolonged by 20.16 minutes, sSOL was shortened by 7.62 minutes, sWASO was shortened by 7.75 minutes, ISI was improved by 1.35 points, LPS was shortened by 10.82 minutes, and WASO was shortened by 25.32 minutes compared with those in the placebo group at 1 month (all values are weighted mean differences). Suvorexant showed superior efficacy to placebo in other meta-analyses. Zheng et al quantitatively compared the efficacy of medications for insomnia and demonstrated that of all FDA-approved drugs, suvorexant was associated with the greatest improvement in WASO. However, lemborexant was not included in this analysis.

The major adverse event in the phase 3 trials (ie, Study 029) was somnolence. The incidence of this adverse effect was 3.1% in the placebo group and 8.4% in the suvorexant group. For suvorexant, the relative risk of somnolence was 2.05-3.53 compared with the placebo in the meta-analysis.

In a double-blind, randomized, crossover study comparing 20-mg suvorexant, 10-mg zolpidem, and placebo, electroencephalography (EEG) was performed. After zolpidem administration, the theta- and alpha-wave densities were reduced during the rapid eye movement (REM) sleep and non-REM sleep compared with those after placebo administration in healthy subjects. In contrast, only an increase in theta-wave density during REM sleep was observed in response to suvorexant administration. Therefore, both suvorexant and placebo had roughly similar effects on EEG. Early-onset REM sleep was the most common adverse event throughout the study. Its incidence was 23.5% for suvorexant, 5.9% for zolpidem, and 5.6% for placebo.

### 2.2 Lemborexant

Lemborexant was approved as a novel DORA in the US in 2019 and in Japan and Canada in 2020. In phase 3 Study 304 (SUNRISE-1; NCT02783729), 5- and 10-mg lemborexant were compared with placebo or 6.25-mg zolpidem tartrate extended release (zolpidem ER; not yet approved in Japan). Both 5- and 10-mg lemborexant groups showed significantly improved TST, sTST, LPS, sSOL, WASO, sWASO, sleep efficacy (SE), and subjective sleep efficacy (sSE) compared with the placebo group. Lemborexant also significantly improved TST, LPS, sSOL, WASO, and SE compared with the zolpidem ER group. In phase 3 Study 303 (SUNRISE-2; NCT02952820), 5- and 10-mg lemborexant were compared with placebo for 6 mo. The 5- and 10-mg lemborexant groups showed significantly improved TST, sTST, LPS, sSOL, WASO, sWASO, sleep efficacy (SE), and subjective sleep efficacy (sSE) compared with the placebo group. Lemborexant also significantly improved TST, LPS, sSOL, WASO, and SE compared with the zolpidem ER group. In phase 3 Study 303 (SUNRISE-2; NCT02952820), 5- and 10-mg lemborexant were compared with placebo for 6 mo. The 5- and 10-mg lemborexant groups showed significantly improved TST, sTST, LPS, sSOL, WASO, sWASO, sleep efficacy (SE), and subjective sleep efficacy (sSE) compared with the placebo group. Lemborexant also significantly improved TST, LPS, sSOL, WASO, and SE compared with the zolpidem ER group.

| TABLE 1 Efficacy and safety of sleep medicines compared with placebo according to meta-analysis results |
|--------------------------------------------------------|----------------|----------------|----------------|
| **Efficacy** | **Suvorexant 20 mg/15 mg** | **Lemborexant 5 mg**<sup>21</sup> | **Lemborexant 10 mg**<sup>21</sup> |
| Subjective assessment | | | |
| sTST | | | |
| sSOL | | | |
| sWASO | | | |
| Sleep quality | | n/a | n/a |
| ISI | | | |
| Objective | **TST** | n/a | n/a | n/a |
| **assessment** | **LPS** | | | |
| WASO | | | |
| SE | | n/a | n/a |
| Safety | Somnolence | | |
| | | | |
| **Note:** | | | |
| -: statistically significant difference compared with the placebo in the efficacy assessment; ○: statistically significant difference compared with the placebo in the safety assessment; ●: no statistically significant difference compared with the placebo in the safety assessment. n/a, not applicable; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake time after sleep onset; LPS, objective latency to persistent sleep; TST, objective total sleep time; WASO, objective wake time after sleep onset; ISI, insomnia severity index; SE, sleep efficacy. | | | |
| aIncluded 40-mg suvorexant. | | | |
improved sTST, sSOL, sWASO, and sSE compared with the placebo group.\(^2^6\) In both trials, lemborexant improved ISI compared with the placebo.\(^2^5,2^6\) Somnolence was the major adverse event during the phase 3 studies, and its incidence increased with drug dosage.

A network meta-analysis of lemborexant, suvorexant, zolpidem ER, and placebo was performed based on the results of phase 3 studies on lemborexant and suvorexant (four trials; 3237 subjects) at 1 week and 1 month after administration.\(^2^1\) Here, we examined treatment efficacy at 1 week to compare rapid symptomatic improvement. In the network meta-analysis, lemborexant doses (5- and 10-mg), other drugs, and placebo were compared. The 10-mg lemborexant group presented with considerably improved sTST and sWASO relative to the 5-mg lemborexant group after 1 week of administration, bearing in mind that 5 mg is also an effective dose (Table 3). There were no significant differences in the somnolence risk ratio between the 5- and 10-mg lemborexant groups. Nevertheless, the somnolence risk ratio was higher in the 10-mg lemborexant group than in the placebo group (Table 4). Therefore, it is reasonable to consider increasing the lemborexant dose to 10 mg when 5 mg is insufficient from the efficacy perspective while monitoring for adverse reactions such as somnolence.

Significant improvements in sSOL, sTST, and sWASO at 1 week and 1 month after treatment were observed in the 5- and 10-mg lemborexant, 20-mg suvorexant, and 6.25-mg zolpidem ER groups compared with those in the placebo group (Tables 3 and 5).\(^2^1\) The exception was sSOL at 1 month zolpidem ER administration (Table 5).\(^2^1\) Additionally, as objective parameters, significant improvements in WASO, as well as LPS at 1/2 day and 1 month, were observed in the 5- and 10-mg lemborexant, suvorexant, and zolpidem ER groups compared with those in the placebo group. The exception was LPS at 1 month zolpidem ER treatment. There were no significant differences in the clinical trial discontinuation rates among the placebo, 5-mg lemborexant, 10-mg lemborexant, and suvorexant groups (Table 4). Moreover, the discontinuation rates associated with adverse events did not significantly differ from the placebo in the 5-mg lemborexant, 10-mg lemborexant, suvorexant, or zolpidem ER groups.

At 1 week, sSOL significantly improved in the 5- and 10-mg lemborexant groups compared with that in the suvorexant group (Table 3). Two possible explanations are the kinetics of the orexin receptor (OXR) subtypes and changes in the drug plasma level. The risk of somnolence did not statistically differ between the 5- and 10-mg lemborexant groups (Table 4). In contrast, the risk ratio for discontinuation caused by adverse events was higher in the 10-mg lemborexant group than in the suvorexant group.\(^2^1\) Thus, the balance between efficacy and safety must be considered when the lemborexant dose is increased.

Table 1 summarizes the results of meta-analysis comparing insomnia treatment with placebo for efficacy and safety. Although 5- or 10-mg Lemborexant and 20-mg suvorexant improve difficulty in sleep initiation, the effect size is greater for the former.\(^2^1\) Moreover, 5- and 10-mg lemborexant and 20-mg suvorexant improve difficulty in sleep maintenance. Nevertheless, the effect size is greater for 10-mg lemborexant than for 5-mg lemborexant or 20-mg suvorexant. Furthermore, 10-mg lemborexant not only has superior efficacy but also carries a greater relative risk of discontinuation caused by adverse events than 20-mg suvorexant. Somnolence risk was associated with 10-mg lemborexant and 20-mg suvorexant.

### 3 | Pharmacological Characteristics of Lemborexant and Suvorexant

The clinical characteristics of lemborexant and suvorexant can be attributed in part to their pharmacological and pharmacokinetic properties. Here, we review their drug characteristics potentially related to clinical efficacy and safety that were identified by in vitro assessments and pharmacokinetic studies.

Preclinical studies showed that OX1R and OX2R play distinct roles in sleep/wake regulation. A study on orexin receptor-deficient mice indicated that OX2R controls sleep and wakefulness.\(^2^7\) However, it is presumed that OX1R has similar functions because the severity of narcolepsy-like symptoms was higher in OX1R- and OX2R-deficient mice than in OX2R-deficient mice.\(^2^8\) Moreover, OX1R might suppress REM sleep onset, whereas OX2R activation is required for the transition from wakefulness and non-REM sleep and may participate in REM sleep control.\(^2^8\)

Although both suvorexant and lemborexant are DORAs, they have unique in vitro effects against orexin receptor subtypes. An in vitro study on receptor selectivity showed that lemborexant

### Table 2: List of studies in Table 1

| Article | Study method | Number of studies | Drug | Dosage |
|---------|--------------|-------------------|------|--------|
| 1) Kishi et al\(^2^0\) | Meta-analysis | Safety: Three studies | 2809 | Suvorexant Placebo |
| 2) Kishi et al\(^2^1\) | Meta-analysis | Efficacy: Four studies | 3076 | Suvorexant Placebo |
|  | Meta-analysis | Four studies | 3237 | Lemborexant |
|  |  |  |  | Suvorexant |
|  |  |  |  | Zolpidem extended-release |
|  |  |  |  | Placebo |

**Table 2** List of studies in Table 1

- **Article:** The studies included in the meta-analysis.
- **Study method:** The method used for the study.
- **Number of studies:** The number of studies included in the meta-analysis.
- **Drug:** The drugs compared in the meta-analysis.
- **Dosage:** The dosages of the drugs compared in the meta-analysis.
**TABLE 3**  Network meta-analysis of efficacy assessments by subjective endpoints (week one)

| Subjective Endpoint | LEM10 | LEM5 | SUV20/15 | ZOL6.25 | PLA |
|---------------------|-------|------|----------|---------|-----|
| **sSOL**            | -0.03(-0.15, -0.09) | -0.18(-0.44, -0.10) | 0.09(-0.11, 0.29) | -0.30(-0.46, -0.14) |       |
|                     | 0.21(-0.37, -0.13)  | -0.48(-0.60, -0.36) | -0.21(-0.33, -0.10) | -0.30(-0.46, -0.14) |       |
|                     | 0.51(-0.63, -0.39)  | -0.58(-0.70, -0.45) | 0.01(0.05, 0.18)    | -0.42(-0.59, -0.25) |       |
|                     | -0.16(-0.32, -0.06) | 0.18(0.08, 0.25)     | 0.28(0.13, 0.23)    | 0.14(-0.03, 0.01)   |       |
| **sTST**            | -0.24(-0.36, -0.12) | 0.01(-0.16, 0.18)    | 0.08(-0.13, 0.28)   | 0.09(-0.11, 0.29)   |       |
|                     | -0.21(-0.33, -0.10) | 0.09(-0.08, 0.18)    | -0.34(-0.46, -0.23) | -0.09(-0.07, 0.25)  |       |
|                     | 0.16(-0.32, 0.01)   | 0.18(0.08, 0.25)     | 0.23(0.13, 0.42)    | 0.30(0.22, 0.43)    |       |
| **sWASO**           | 0.16(-0.32, 0.01)   | 0.18(0.08, 0.25)     | 0.23(0.13, 0.42)    | 0.30(0.22, 0.43)    |       |

Note: LEM5, 5-mg lemborexant group; LEM10, 10-mg lemborexant group; SUV20/15, 20 mg/15-mg suvorexant group; ZOL6.25, 6.25-mg extended-release zolpidem group; PLA, placebo group; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake time after sleep onset. Statistically significant differences are in bold text.

**TABLE 4**  Network meta-analysis of safety assessments measured by risk ratio

| Safety Assessment | LEM10 | LEM5 | SUV20/15 | ZOL6.25 | PLA |
|-------------------|-------|------|----------|---------|-----|
| All causes        | 1.27(0.97, 1.65) | 1.06(0.70, 1.60) | 0.51(0.26, 0.99) | 1.90(1.03, 3.49) |     |
| Discontinuation   | 1.34(0.89, 2.00) | 0.53(0.29, 0.99) | 0.96(0.71, 1.30) | 3.118(0.945, 10.286) |   |
| due to adverse    | 0.67(0.37, 1.24) | 1.01(0.76, 1.35) | 1.30(1.00, 1.30) | 1.03(1.00, 1.05) |    |
| events            | 1.28(0.98, 1.68) | 1.72(0.61, 4.83) | 0.74(0.33, 2.02) | 0.945(0.945, 1.046) |  |
| Somnolence        | 1.73(0.83, 3.59) | 0.34(0.10, 1.10) | 0.45(0.23, 2.06) | 0.61(0.33, 1.10) |    |
|                   | 1.28(0.85, 3.84) | 1.04(0.45, 2.43) | 1.84(0.52, 5.95) | 0.61(0.33, 1.10) |    |
|                   | 1.71(0.78, 3.76) | 1.06(0.29, 3.86) | 2.72(0.84, 8.79) | 2.16(0.67, 6.97) |    |
|                   | 4.66(1.54, 14.13) | 2.58(0.57, 11.71) | 2.05(1.17, 3.57) | 2.05(1.17, 3.57) |    |

Note: LEM5, 5-mg lemborexant group; LEM10, 10-mg lemborexant group; SUV20/15, 20 mg/15-mg suvorexant group; ZOL6.25, 6.25-mg extended-release zolpidem group; PLA, placebo group. Statistically significant differences are in bold text.
|          | sSOL     | sTST     | sWASO    |
|----------|----------|----------|----------|
| LEM10    | -0.07(−0.23, -0.09) | -0.27(−0.50, -0.27) | -0.43(−0.60, -0.29) |
| LEM5     | -0.21(−0.43, 0.02)  | -0.37(−0.53, -0.21) | -0.35(−0.48, -0.22) |
| SUV20/15 | 0.03(−0.24, 0.30)  | 0.01(−0.23, 0.23)  | -0.35(−0.54, -0.16) |
| ZOL6.25  | -0.19(−0.41, 0.02) | -0.16(−0.32, 0.01) | -0.38(−0.55, -0.20) |

Note: LEM5, 5-mg lemborexant group; LEM10, 10-mg lemborexant group; SUV20/15, 20-mg/15-mg suvorexant group; ZOL6.25, 6.25-mg extended-release zolpidem group; PLA, placebo group; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake time after sleep onset. Statistically significant differences are in bold text.
nonelderly healthy adults after 9 hours had no clinically meaningful residual effect on next-morning driving.33,34

Given these results, receptor-binding profiles and pharmacokinetic properties may have a certain impact on clinical outcomes, although the pharmacodynamics, protein binding rate, permeability of blood-brain barrier, and orexin levels in individuals must be comprehensively considered.

### 5 | STRATEGY FOR INSOMNIA MEDICATIONS

American and Japanese clinical practice guidelines for the treatment of chronic insomnia indicate statements on the practice of sleep medicine.9,35 However, because these guidelines make no reference to lemborexant, here, we discuss the clinical significance and propose an EBM-based strategy for insomnia medications.

Relative differences in the receptor-binding and pharmacokinetic properties of lemborexant and suvorexant might partially account for their differences in terms of clinical efficacy and safety. Lemborexant rapidly binds to human OXRs. Moreover, the network meta-analysis demonstrated that patients administered lemborexant improved sleep initiation and nighttime sleep maintenance compared with patients administered suvorexant. In view of the balance between clinical efficacy and safety and the unique pharmacology of DORAs, 5-mg lemborexant is suggested as the most suitable first-line drug.

In cases where 5-mg lemborexant is ineffective, escalation to 10 mg may be considered but with caution as it could increase the incidence of somnolence. According to the network meta-analysis, 10-mg lemborexant had a somnolence risk ratio comparable with that of 5-mg lemborexant but higher than that of placebo. However, 10-mg lemborexant showed greater efficacy than 5-mg lemborexant.21 The risks of falling/loss of balance were similar between the 10-mg lemborexant and placebo groups. Nevertheless, elderly patients undergoing this therapy should be closely monitored. In addition, the results of Study 303 indicated that lemborexant is efficacious for patients with a history of depression.36

For patients complaining of difficulty maintaining sleep, suvorexant may be considered.9 However, according to the network meta-analysis, suvorexant was associated with a higher somnolence risk.

### TABLE 6  In vitro parameters of lemborexant and suvorexant to human OXR

| Receptor | LEM | SUV |
|-----------|-----|-----|
| IC<sub>50</sub> and K<sub>i</sub> values | | |
| IC<sub>50</sub>, nM | hOX1R | 6.1 ± 1.4 | 8.8 ± 2.5 |
| RBA | hOX2R | 2.6 ± 0.4 | 12.0 ± 2.8 |
| | hOX1R | 4.8 ± 1.4 | 1.4 ± 0.2 |
| K<sub>r</sub>, nM | FDSS Ca<sup>2+</sup> Imaging Assay | hOX2R | 0.61 ± 0.1 | 2.2 ± 0.3 |

| Binding and dissociation kinetic parameters | |
| --- | --- |
| K<sub>on</sub> (L/nmol/min) | hOX2R | 0.0496 ± 0.001 | 0.0052 ± 0.0002 |
| K<sub>off</sub> (1/min) | hOX2R | 0.0626 ± 0.0014 | 0.0164 ± 0.0011 |
| Dissociation half-life (min) | | 11.1 ± 0.4 | 42.2 ± 3.1 |

Note: Data are expressed in mean ±SEM; RBA, receptor-binding assay; FDSS, functional drug screening system; LEM, lemborexant; SUV, suvorexant; IC<sub>50</sub>, half-maximal inhibitory concentration; K<sub>r</sub>, inhibition constant; RBA, receptor-binding assay; K<sub>on</sub>, association rate constant; K<sub>off</sub>, dissociation rate constant.

### FIGURE 1  Time course of plasma suvorexant and lemborexant levels after repeated administration over 14 days.39

Data from Study 003<sup>31</sup> for SUV and Study 003<sup>29</sup> for LEM. Abbreviations: C<sub>max</sub>, maximum drug concentration; LEM, lemborexant; SUV, suvorexant.

![Graph showing plasma concentrations of lemborexant (LEM) and suvorexant (SUV) over time.](image-url)
ratio than placebo (Table 4). It has been reported that suvorexant prevents delirium in elderly patients with insomnia after emergency transport or during hospitalization. Therefore, suvorexant may be administered in accordance with comorbidities and insomnia.

Potential drug interactions must be taken into consideration during drug selection. According to the package insert in the US, lemborexant is contraindicated in patients being administered moderate-to-strong cytochrome P450 3A (CYP3A) inhibitors. However, in Japan, these patients may be administered 2.5-mg/d lemborexant. In the US, patients being administered weak CYP3A inhibitors may take 5-mg/d at the maximum lemborexant. Suvorexant is not recommended for co-administration with drugs that strongly inhibit CYP3A in both the US and Japan. For patients being treated with moderate CYP3A inhibitors, the recommended suvorexant dose is 5 mg/d in the US and 10 mg/d in Japan.

In cases where orexin receptor antagonists are ineffective, an alternative therapeutic strategy is ramelteon administration as it binds to the melatonin receptor. Moreover, BZDs and Z-drugs may be considered in cases where lemborexant, suvorexant, and ramelteon have limited efficacy. However, in all cases, the balance between safety and efficacy must be considered in the selection and administration of BZDs or Z-drugs.

6 | CONCLUSIONS

In the present review, we examined the pharmacological and pharmacokinetic features of lemborexant and suvorexant based on evidence obtained from the meta-analyses. In practice, it is difficult to recommend any single uniform treatment method for insomnia patients with various possible causes. However, we propose algorithms for the treatment of insomnia using these drugs because lemborexant has not yet been recommended in clinical practice guidelines. The network meta-analysis disclosed that 5-mg lemborexant is a viable initial treatment option and may be followed by the administration of 10-mg lemborexant and suvorexant. The insomnia treatment protocol could be applied based on the strategy presented herein and adjusted according to the patient background and therapeutic objectives.

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CONFLICT OF INTEREST

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KN and MM designed the original study, developed the protocol, and performed the data analysis of lemborexant (funded by Eisai Co., Ltd.). KT, KS, MO, IN, and NI contributed to the original study of the network meta-analyses. MN, MK, TT, and KM prepared the manuscript. All authors were involved in the decision to submit this article for publication, contributed to the interpretation, reviewed the manuscript, and approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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