Lemborexant Clinical Application Chinese Expert Consensus Post-print

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Abstract

Insomnia is the most common sleep disorder, which significantly impairs patients' quality of life and work performance, and is associated with somatic diseases, mental disorders, and other conditions. Lemborexant, as a novel hypnotic agent, is the first dual orexin receptor antagonist (DORA) approved for marketing in China. However, there is currently a lack of relevant guidelines for its clinical application in the country. To address this gap, the Chinese Sleep Research Society, the Sleep Medicine Professional Committee of Guangdong Medical Doctor Association, and the Hospital Pharmacy Management Professional Committee of Guangdong Hospital Association convened domestic experts in pharmacy and clinical medicine to formulate the "Chinese Expert Consensus on Clinical Application of Lemborexant,"based on advances in domestic and international research and incorporating China' s first real-world study of lemborexant. This consensus elaborates on the pharmacological effects, pharmacokinetics, indications, and clinical application methods of lemborexant, and after multiple rounds of discussion, revision, and voting, 17 recommendations were ultimately developed to provide comprehensive and standardized references and guidance for the clinical use of lemborexant.

Full Text

Preamble

Expert Consensus on the Clinical Application of Lemborexant in China

Chinese Sleep Research Society, Sleep Medicine Professional Committee of Guangdong Medical Doctor Association, Pharmacy Administration Committee of Guangdong Province Hospital Association

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Abstract Insomnia is the most common sleep disorder, significantly impairing patients' quality of life and occupational performance, and is associated with physical illnesses and mental disorders. Lemborexant, a novel hypnotic agent, is the first dual orexin receptor antagonist (DORA) approved for marketing in China. However, standardized guidelines for the clinical application of lemborexant are currently lacking in China. Therefore, the Chinese Sleep Research Society, the Sleep Medicine Professional Committee of Guangdong Medical Doctor Association, and the Pharmacy Administration Committee of Guangdong Province Hospital Association convened domestic experts in pharmacy and clinical medicine to develop the *Expert Consensus on the Clinical Application of Lemborexant in China*, based on domestic and international research progress and China' s first real-world study of lemborexant. This consensus elaborates on the pharmacological effects, pharmacokinetics, indications, and clinical application methods of lemborexant. After multiple rounds of discussion, revision, and voting, 17 recommendations were ultimately formulated to provide comprehensive and standardized references and recommendations for the clinical application of lemborexant.

[**Keywords**] Lemborexant; Insomnia; Dual orexin receptor antagonist; Clinical application

1. Consensus Development Methods

The multidisciplinary expert panel consisted of 12 pharmacists and 20 clinicians (including specialists in psychiatry, neurology, and sleep medicine). A literature search was conducted on topics related to the clinical application of lemborexant across PubMed, Embase, Cochrane Library, Wanfang Data, and CNKI databases, using search terms including "DORA," "lemborexant," "insomnia," and "莱博雷生" (lemborexant). The search period covered database inception through April 30, 2025. Based on the search results, the lead authors compiled evidence-based medical evidence, integrated China' s current diagnostic and treatment status with clinical practice experience, and formulated recommendations for the clinical application of lemborexant.

Evidence quality assessment and recommendation grading followed the *Guiding Principles for the Development/Revision of Clinical Diagnosis and Treatment Guidelines in China (2022 Edition)* issued by the Chinese Medical Association, adopting the Oxford Centre for Evidence-Based Medicine evidence level grading system (Table 1 , Table 2). Expert group members first graded the quality of evidence for included literature, then graded the strength of recommendations accordingly. For some key areas where evidence in existing literature was insufficient, the expert group supplemented judgments based on clinical experience. For each recommendation's direction and strength, expert group members voted, requiring support from at least 80% of members with a coefficient of variation <15% to finalize the recommendation. This expert consensus underwent three expert meetings to form the initial draft, followed by three rounds of revision, then submission to all editorial board members for review and discussion. After two additional rounds of modification, the final version was completed.

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2. Mechanism of Action and Pharmacokinetic Characteristics of Lemborexant

2.1 Mechanism of Action

The orexin system (also known as the hypocretin system) promotes and maintains wakefulness through projections from the hypothalamus to the cortex and multiple wake-promoting neurotransmitter nuclei (noradrenaline, acetylcholine, histamine, serotonin, and dopamine). Orexins are neuropeptides synthesized in the lateral hypothalamic area, divided into orexin A and orexin B, which play roles in various physiological functions including sleep-wake rhythm, thermoregulation, energy metabolism control, and feeding behavior [8]. Orexin neurons project extensively to different brain regions, including the tuberomammillary nucleus, locus coeruleus, dorsal raphe nucleus, and median raphe nucleus. By activating orexin receptors, they excite wake-promoting neurons such as noradrenergic, cholinergic, and histaminergic neurons to maintain the awake state and regulate the sleep-wake cycle [9-13], playing a central role in maintaining

wakefulness and inhibiting both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep [14-15]. The role and mechanism of orexin receptors in the sleep-wake system are illustrated in Figure 1 [Figure 1: see original paper].

There are two orexin receptor subtypes: Orexin Receptor-1 (OX1R) and Orexin Receptor-2 (OX2R). OX1R is associated with sleep state transitions, while OX2R is associated with cortical arousal, primarily functioning in NREM sleep initiation and partially regulating REM sleep [16-17]. Orexin A binds to both OX1R and OX2R but with higher affinity for OX1R; orexin B selectively binds to OX2R; OX2R has equivalent affinity for both orexin A and B [1,8-19]. DORAs reduce arousal drive and prolong both REM and NREM sleep by competitively binding to OX1R and OX2R, thereby blocking orexin effects. Lemborexant exhibits antagonistic activity against both OX1R and OX2R, with slightly higher affinity for OX2R. Lemborexant binds to and dissociates from orexin receptors relatively quickly [20-21]. A schematic diagram of lemborexant' s mechanism for suppressing hyperarousal is shown in Figure 2 [Figure 2: see original paper].

2.2 Pharmacokinetic Characteristics

2.2.1 Absorption: Lemborexant is rapidly absorbed orally, with time to peak concentration (tmax) of 1-3 hours under fasting conditions [22]. Food delays lemborexant absorption.

2.2.2 Distribution: Lemborexant is highly lipophilic, easily distributing to adipose tissue, liver, brain, and other lipid-rich organs, with extensive distribution throughout the body and an apparent volume of distribution (Vd) of 1,970 L. Lemborexant has high protein binding (94% plasma protein binding) [22], resulting in low free drug concentrations.

2.2.3 Metabolism: Lemborexant' s half-life (t1/2) varies by dose, with mean effective half-life (t1/2eff) of 17 hours and 19 hours following 14 days of continuous dosing with 5 mg and 10 mg, respectively [22-23]. After multiple doses reaching steady state, morning lemborexant plasma concentration is equivalent to 27% of maximum concentration (Cmax) [24]. Approximately 53%-57% of the area under the curve (AUC) is cleared 8-9 hours post-dose [24-25].

Lemborexant is primarily metabolized by CYP3A4, with minor metabolism by CYP3A5. Most conversion by CYP3A4 yields M4, M9, and M10 metabolites, predominantly M10 [26]. Although M4, M9, and M10 have orexin receptor affinity comparable to lemborexant, their pharmacodynamic effects remain dominated by lemborexant due to significantly lower plasma concentrations and blood-brain barrier permeability [24,27]. Lemborexant is a weak P-gp substrate, while M10 is a P-gp substrate.

2.2.4 Excretion: Lemborexant is eliminated 57.4% through feces and 29.1% through urine [22].

Studies show no significant differences in lemborexant pharmacokinetics across age, sex, race, ethnicity, or BMI [25].

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3. Clinical Applications

3.1 Insomnia Disorder

The short-term efficacy of lemborexant for insomnia disorder has been validated in clinical trials. A one-month multicenter randomized controlled Phase III trial (SUNRISE 1) used polysomnography (PSG) to compare lemborexant' s short-term efficacy and safety against placebo and 6.25 mg zolpidem tartrate extended release (ZOL ER) [28]. Compared with placebo and ZOL ER, lemborexant significantly reduced latency to persistent sleep (LPS) and wake after sleep onset (WASO), while improving sleep efficiency (SE). Unlike ZOL ER, lemborexant shortened REM latency and prolonged REM duration without affecting NREM duration [29]. A meta-analysis showed lemborexant 10 mg was superior to suvorexant 15 mg or 20 mg and ZOL ER in subjective time to sleep onset (sTSO) at week 1 [21]. This advantage changed by week 4, when lemborexant demonstrated superior PSG objective measures including total sleep time (TST), LPS, and SE compared with suvorexant, BZRAs, NBZDs (including zolpidem, eszopiclone, zopiclone), and ramelteon, with no significant difference in WASO compared with suvorexant [30]. Another meta-analysis showed lemborexant provided optimal improvement in WASO and TST, superior to suvorexant, daridorexant, and melatonin receptor agonists (including ramelteon, tasimelteon) [31]. The PROEM study demonstrated lemborexant effectiveness rates of 36.0%, 56.5%, and 60.4% at weeks 1, 2, and 4, respectively, in Chinese populations [6]. Correspondingly, real-world studies abroad found lemborexant significantly improved objective sleep parameters (TST, WASO) and subjective sleep parameters [subjective sleep onset latency (sSOL) reduction, subjective wake after sleep onset (sWASO) reduction, subjective total sleep time (sTST) extension, subjective sleep efficiency (sSE) improvement] in insomnia patients at week 4 [32]. Subgroup analyses showed lemborexant efficacy across different genders [33], races [34], and ages [35].

Long-term efficacy of lemborexant for insomnia disorder was also validated in clinical trials. A 12-month global multicenter randomized controlled Phase III trial (SUNRISE 2) used sleep diaries to compare lemborexant versus placebo in improving sSOL and sWASO [36]. At 6 months, 45.5% and 44.9% of patients receiving lemborexant 5 mg and 10 mg, respectively, reported sSOL improvement of $ $20 minutes, while 35.0% and 30.0% reported sWASO improvement of $ $60 minutes. This efficacy persisted through month 12. Additionally, lemborexant groups showed significant improvements in sSE, sTST, sleep quality, and morning alertness compared with placebo.

[Recommendation 1] Lemborexant is indicated for short-term ($ $4 weeks$) and long-term ($12 months) treatment of insomnia disorder with difficulty initiating

and/or maintaining sleep. (Grade A recommendation, Level I evidence)

3.2 Insomnia Associated with Mental Disorders

3.2.1 Anxiety and Depression-Related Insomnia: Anxiety and depression frequently co-occur with insomnia. A subgroup analysis of a randomized controlled trial (RCT) showed that at 6 months, lemborexant shortened sSOL, increased sSE, and prolonged sTST in insomnia patients receiving antidepressant/anxiolytic medications, with improvements similar to the overall population and no new safety signals [37]. Lemborexant treatment reduced Athens Insomnia Scale (AIS) scores, with significant improvements in sleep induction, nocturnal awakenings, sleep quality, well-being, daytime function, and sleepiness, while significantly reducing mean concomitant BZD dosage [38]. In real-world studies, insomnia patients with comorbid depression showed a 67.1% response rate to lemborexant, while the anxiety group showed a 64.6% response rate; diazepam-equivalent doses of BZDs decreased significantly after lemborexant initiation without adverse events [39]. Lemborexant treatment may reduce BZD-related risks [40].

Additional studies explored lemborexant' s effects on anxiety and depressive symptoms in insomnia patients. The PROEM study showed significant reductions in Insomnia Severity Index (ISI), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7) scores in insomnia patients [6]. A retrospective study further found that after 8 weeks of lemborexant treatment, PHQ-9 and GAD-7 scores decreased significantly, with a treatment response rate (ISI<8) of 87.5% [41]. Age, concomitant medications, and lemborexant 10 mg/d were independent factors affecting efficacy.

[**Recommendation 2**] Lemborexant can be used to treat anxiety and depression-related insomnia. (Grade C recommendation, Level III evidence)

3.2.2 Other Mental Disorder-Related Insomnia: Insomnia commonly occurs with mental disorders other than anxiety and depression, requiring consideration of other medications. A systematic meta-analysis indicated DORAs (lemborexant and suvorexant) showed similar efficacy for insomnia associated with mental disorders as for primary insomnia, but did not stratify by mental disorder type [42]. In mental disorder patients (including major depressive disorder, bipolar disorder, and schizophrenia) previously using other sedative-hypnotics (including BZDs, suvorexant, lamotrigine, mirtazapine, trazodone, and antipsychotics), switching to lemborexant significantly reduced mean AIS scores from baseline, with no significant change in Epworth Sleepiness Scale (ESS) scores, significant improvement in Perceived Deficits Questionnaire-5 (PDQ-5) scores, and decreased diazepam-equivalent doses [40]. Lemborexant treatment may reduce concomitant psychotropic medication types and dosages. A retrospective study of mental disorder patients discharged from rehabilitation wards found median psychotropic medication types decreased from 2 at admission to 1 at discharge, with significantly increased lemborexant dosing and decreased doses

of antipsychotics, BZRAs, antidepressants, suvorexant, lamotrigine, and valproate [43].

[Recommendation 3] Lemborexant can be used to treat mental disorder-related insomnia (e.g., bipolar disorder, schizophrenia). (Grade C recommendation, Level III evidence)

3.3 Insomnia Associated with Neurological Disorders

3.3.1 Alzheimer's Disease-Related Insomnia: Alzheimer's disease patients frequently exhibit sleep disturbances, particularly irregular sleep-wake rhythm disorder. Consolidating nocturnal sleep and daytime wakefulness represents the primary treatment goal for sleep-wake rhythm disorders. Due to safety concerns, the American Academy of Sleep Medicine advises against sedative-hypnotics in Alzheimer' s disease patients. Recent evidence suggests dysfunctional orexin systems may play a role in the neuropathology of sleep-wake rhythm disorders [44-45]. Orexin system-targeted therapies like DORAs may improve sleep in Alzheimer' s disease patients [46-47]. A multicenter RCT showed lemborexant-treated mild-to-moderate Alzheimer' s disease patients had less agitation than placebo, with reduced daytime sleep episode duration in the 5 mg group, low post-treatment adverse event incidence, and no reports of serious adverse events or new safety issues [48]. Lemborexant treatment did not cause cognitive deterioration in irregular sleep-wake rhythm disorder and Alzheimer' s disease patients.

[Recommendation 4] Lemborexant is indicated for treating circadian rhythm sleep-wake disorder and insomnia associated with Alzheimer' s disease. (Grade B recommendation, Level II evidence)

3.3.2 Post-Stroke Insomnia: Post-stroke insomnia has high incidence due to factors including reduced melatonin levels, physical discomfort, and hospital environment [49]. No studies have examined lemborexant in post-stroke insomnia patients. However, suvorexant, another DORA, was found to have no affinity for γ-aminobutyric acid receptors (GABAR) [50-51], with significantly lower delirium and somnolence rates compared with GABAR agonists in acute stroke patients [52]. Studies show sedative-hypnotics including BZDs, suvorexant, lamotrigine, mirtazapine, trazodone, and antipsychotics can be safely and effectively switched to lemborexant, with successful conversion potentially improving sleep onset and maintenance [53]. Lemborexant has demonstrated good safety and efficacy in multiple RCTs [54]. Therefore, lemborexant' s potential advantages over traditional GABAR agonists for post-stroke insomnia warrant further investigation.

3.3.3 Delirium-Related Insomnia: Delirium patients frequently experience sleep disturbances and insomnia. However, sedative-hypnotics (e.g., BZDs) are generally not recommended for delirium with insomnia, limiting treatment options. Two retrospective studies showed lemborexant achieved 78.6% effectiveness for insomnia in cancer patients with delirium [55] and 95.3% effectiveness

for insomnia in patients with delirium after deep sedation for pancreatobiliary endoscopy [56], without significantly worsening delirium.

[Recommendation 5] Lemborexant can be used to treat delirium-related insomnia. (Grade C recommendation, Level III evidence)

No evidence exists for lemborexant use in sleep disorders associated with other neurological diseases such as Parkinson' s disease, epilepsy, autoimmune encephalitis, or neuromuscular disorders.

3.4 Insomnia Associated with Respiratory Disorders

3.4.1 Obstructive Sleep Apnea (OSA)-Related Insomnia: Some sedative-hypnotics carry respiratory depression risks, representing serious safety concerns for OSA patients. Studies found lemborexant 10 mg did not increase apnea-hypopnea index (AHI) in mild OSA patients, with no impact on peripheral oxygen saturation (SpO2) during REM and NREM sleep, proportion of SpO2<90% events lasting >30 seconds, or TST percentage during SpO2 declines [57]. Additionally, lemborexant 10 mg did not increase AHI or reduce SpO2 in moderate-to-severe OSA patients; mean AHI on days 1 and 8 was similar between lemborexant 10 mg and placebo groups across REM sleep, NREM sleep, total sleep period, and different OSA severity subgroups [58]. Lemborexant also showed no significant effects on SpO2 and AHI in healthy individuals of different ages [59].

Studies also examined lemborexant' s effects on sleep parameters in OSA patients. Compared with placebo and ZOL ER, mild OSA patients treated with lemborexant 5 mg and 10 mg showed significantly increased TST percentage and SE, decreased LPS and WASO, increased REM sleep, and shortened REM latency [60]. Additionally, lemborexant 5 mg and 10 mg increased NREM sleep compared with placebo.

[Recommendation 6] Lemborexant is indicated for treating insomnia associated with OSA of varying severity. (Grade A recommendation, Level I evidence)

3.4.2 Chronic Obstructive Pulmonary Disease (COPD)-Related Insomnia: COPD patients frequently experience sleep disturbances such as difficulty initiating sleep. BZDs carry respiratory depression risks, complicating insomnia management in COPD populations. A multicenter, two-stage crossover RCT in adults with moderate-to-severe COPD found no significant difference in least squares mean SpO2 between lemborexant 10 mg and placebo after single dosing (Day 1); after multiple doses (Day 8), lemborexant 10 mg showed significantly higher SpO2 than placebo [61]. Additionally, TST percentage and mean AHI were similar between groups after single and multiple dosing when analyzed by SpO2 thresholds (<90%, 85%, or 80%). Both single and multiple lemborexant 10 mg dosing did not adversely affect SpO2 or AHI in moderate-to-severe COPD subjects, with significantly shorter LPS and WASO and higher SE compared with placebo.

[**Recommendation 7**] Lemborexant is indicated for treating COPD-related insomnia. (Grade B recommendation, Level I evidence)

3.5 Nocturia-Related Insomnia

Nocturia affects sleep quality and health-related quality of life. When prescribing sedative-hypnotics for elderly insomnia patients with nocturia, adverse effects such as fall-related fractures must be avoided. A study enrolled insomnia patients (AIS $ 6)*withincreasednocturiaepisodes*($2) unresponsive to medication or behavioral therapy. After 4 weeks of lemborexant treatment, AIS total score decreased from 11.4 to 7.8, nocturia episodes decreased from 3.4 to 2.3, single void volume increased from 182.5 mL to 225.3 mL, continuous sleep time extended from 105.3 to 174.8 minutes, and Nocturia Quality of Life Questionnaire (N-QOL) total score improved significantly from 49.6% to 64.8% [62].

[**Recommendation 8**] Lemborexant can be used to treat nocturia-related insomnia. (Grade C recommendation, Level III evidence)

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4. Safety and Usage Considerations

4.1 Contraindications

Lemborexant is contraindicated in narcolepsy [22]. Loss of orexin neurons is associated with narcolepsy, and decreased orexin has become a diagnostic criterion for type 1 narcolepsy [14-15].

4.2 Usage Considerations

4.2.1 Dosing Regimen: Food delays lemborexant absorption. When administered with food (during or immediately after meals), lemborexant tmax is delayed by approximately 2 hours, Cmax decreases by 23%, and 24-hour area under the curve (AUC0~24h) increases by 18% [63].

The safe and effective dose range for lemborexant is 2.5-10 mg/d. Dose-ranging studies of 1-25 mg showed significant sleep changes from baseline at doses $ $2.5 mg [64]. A review showed lemborexant 10 mg was slightly superior to 5 mg in sleep parameters including sSOL, sWASO, sTST, sleep quality scores, and morning alertness scores, while sSE and ISI scores were comparable between doses [65], indicating 10 mg is slightly better than 5 mg for improving sleep onset difficulty, reducing nocturnal awakenings, improving sleep continuity, increasing TST, improving subjective sleep quality, and enhancing morning alertness. Both doses showed equivalent effects on improving sleep quality and insomnia severity.

[**Recommendation 9**] Patients should take lemborexant on an empty stomach for optimal effect. (Grade B recommendation, Level I evidence)

[**Recommendation 10**] The therapeutic dose of lemborexant for adult insomnia is 2.5-10 mg/d, with initial dose not exceeding 5 mg/d. Dose should be individualized based on patient response and tolerability, with a maximum recommended dose of 10 mg/d. (Grade B recommendation, Level I evidence)

[**Recommendation 11**] Lemborexant should be taken immediately before bedtime, not more than once nightly. Patients should ensure at least 7 hours in bed after taking lemborexant to reduce risks of adverse effects such as somnolence and next-day functional impairment. (Grade B recommendation, Level II evidence)

4.2.2 Drug Interactions: Concomitant lemborexant and alcohol increases cognitive impairment risk. A Phase I RCT showed that while lemborexant did not significantly worsen alcohol' s effects on postural stability at 2 hours post-dose, it significantly negatively impacted cognitive performance at 0.5, 2, and 6 hours when combined with alcohol, specifically affecting attention, sustained attention, memory quality, and memory retrieval speed. Additionally, alcohol increased lemborexant Cmax by 35% and 72-hour AUC (AUC0~72h) by 70%; Cmax of major metabolites M4, M9, and M10 decreased by 17%-33%, but M9 exposure (AUC) increased by approximately 26% after 9 hours. Pharmacokinetic analysis showed alcohol significantly increased lemborexant plasma exposure, partially explaining the increased negative cognitive effects.

CYP3A4 inhibitors or inducers interact with lemborexant, increasing adverse effect risk or reducing efficacy (Table 3). Co-administration with itraconazole (strong CYP3A4 inhibitor) increased lemborexant Cmax 1.4-fold and AUC0-∞ 3.7-fold; with fluconazole (moderate CYP3A4 inhibitor) increased Cmax 1.6-fold and AUC0-∞ approximately 4-fold; with rifampin (strong CYP3A4 inducer) decreased both Cmax and AUC0-∞ by >90% [66]. Physiologically-based pharmacokinetic modeling indicated weak CYP3A4 inhibitors increased lemborexant exposure by less than 2-fold.

Lemborexant may induce CYP2B6. Co-administration with CYP2B6 substrate bupropion decreased bupropion Cmax and AUC0-∞ by 49.9% and 45.5%, respectively [66-67].

In vitro interaction studies showed lemborexant and its metabolite M10 have time-dependent inhibition of CYP3A but do not inhibit other CYP isoenzymes or transporters. Long-term lemborexant use may inhibit CYP3A4 in a time-dependent manner, increasing plasma concentrations of drugs primarily metabolized by CYP3A4 (e.g., antipsychotic clozapine), potentially causing excessive sedation and somnolence; clinicians should monitor patients when co-prescribing [68]. However, lemborexant did not significantly affect exposure of CYP3A4 substrate midazolam [66].

Co-administration with famotidine decreased lemborexant Cmax by 27% and delayed tmax by 0.5 hours, but did not affect overall exposure (AUC) or lemborexant' s improvement in sSOL, supporting combined use [69]. Oral contraceptives (OC) co-administration had no clinically relevant effect on lemborexant

steady-state pharmacokinetics, with adverse events consistent with known safety profiles, supporting combined use without dose adjustment [70].

[Recommendation 12] Alcohol should be avoided during lemborexant treatment. (Grade B recommendation, Level I evidence)

[Recommendation 13] Lemborexant should be avoided with moderate-to-strong CYP3A4 inducers or inhibitors (including grapefruit juice). When used with weak CYP3A4 inhibitors, lemborexant maximum dose should not exceed 5 mg/d, not more than once nightly. Potential effects on CYP2B6 substrates (e.g., bupropion) should be noted. (Grade B recommendation, Level I evidence)

4.2.3 Medication Switching: Lemborexant can reduce or replace BZRA use [71-72]. A retrospective study showed lemborexant reduced mean diazepam-equivalent BZD dose by 2.8 mg in mental disorder patients [73]. When switching from other sedative-hypnotics to lemborexant, two methods can reduce rebound insomnia and withdrawal symptoms from abrupt discontinuation [74-75]: direct switching or cross-tapering (Figure 3 [Figure 3: see original paper]). Direct switching (rapid conversion) involves discontinuing all BZRAs while initiating lemborexant (e.g., replacing 1 BZRA tablet directly with 1 lemborexant tablet). Cross-tapering involves initiating lemborexant while gradually reducing BZRAs (e.g., decreasing BZRAs by 10%-25% weekly or biweekly).

In a U.S. randomized, open-label, multicenter study, 81.1% of subjects successfully switched directly from immediate-/extended-release zolpidem to lemborexant with good tolerability [76]. Another study showed 97.8% of patients successfully switched directly from NBZD monotherapy (zolpidem, zopiclone, or eszopiclone), suvorexant monotherapy, suvorexant combined with BZRAs, or ramelteon to lemborexant, with 82.2% maintaining lemborexant treatment at 12 weeks [53]. Retrospective cohort data showed 70.1% of patients successfully switched (using only lemborexant or no hypnotics) after 6 months [77].

Studies show both direct switching and cross-tapering from BZRAs to lemborexant proceed smoothly [53,76,78-79], making direct switching a viable option for insomnia patients dissatisfied with current treatment. However, the *Chinese Insomnia Disorder Diagnosis and Treatment Guidelines (2nd Edition)* [1], *European Clinical Practice Guidelines for Switching or Deprescribing Hypnotic Medications for Chronic Insomnia (2025)* [74], and *American Alliance for Sleep Clinical Practice Guideline on Switching or Deprescribing Sedative-Hypnotic Medications for Insomnia (2023)* [79] recommend cross-tapering when switching from BZRAs to DORAs.

[Recommendation 14] Lemborexant is suitable as an alternative medication for reducing or discontinuing BZD receptor agonist hypnotics; switching can employ direct replacement or cross-tapering methods. (Grade A recommendation, Level I evidence)

4.2.4 Discontinuation: No evidence indicates rebound insomnia or withdrawal effects after long-term (1 year) lemborexant discontinuation [79]. The

American Alliance for Sleep Clinical Practice Guideline states lemborexant typically does not require special tapering measures upon discontinuation [79]. An RCT showed that after 1 year of lemborexant treatment, subjects' sleep remained significantly better than baseline during the 2-week discontinuation period; WASO and SOL worsened compared with double-blind treatment end but remained superior to baseline [80].

If insomnia improves significantly or serious adverse events occur during lemborexant treatment, discontinuation may be considered. Patients should be informed that sleep may temporarily worsen. Sleep quality and other potential symptoms should be closely monitored for two weeks before discontinuation; otherwise, no additional measures appear necessary.

[Recommendation 15] Lemborexant is relatively safe during discontinuation or switching and does not require special tapering measures. (Grade B recommendation, Level I evidence)

4.3 Adverse Effects

4.3.1 Common Adverse Effects: Common lemborexant adverse effects include somnolence, fatigue, headache, and dizziness. Next-day somnolence is the most common adverse effect, typically occurring during the first few days of treatment, with incidence increasing dose-dependently. Data showed somnolence incidence of 1.6%, 8.6%, and 13.1% in placebo, lemborexant 5 mg, and lemborexant 10 mg groups, respectively; extending time in bed to >7 hours reduces risk [36]. Headache incidence did not correlate completely with dose, occurring in 6.2%, 6.4%, and 4.9% of placebo, lemborexant 5 mg, and lemborexant 10 mg groups, respectively [28].

4.3.2 Effects on Daytime Function: Lemborexant has relatively minimal effects on next-day postural stability and cognitive function. Modified multiple sleep latency test results showed possible next-day residual effects with lemborexant 5 mg and 10 mg [81]. Compared with zolpidem, lemborexant did not affect postural stability or cognitive function upon awakening, while zolpidem significantly increased body sway and reduced cognitive function [5]. No significant difference in body sway was observed between placebo and lemborexant groups, while zolpidem significantly increased body sway [28]. In mid-night awakening patients, zolpidem significantly increased body sway compared with lemborexant; lemborexant 5 mg and 10 mg showed no change in auditory awakening threshold compared with placebo, and lemborexant 5 mg showed no statistical difference in cognitive performance [82]. In morning awakening patients, lemborexant 5 mg and 10 mg showed no difference from placebo in body sway or cognitive performance, while zolpidem significantly increased body sway.

Lemborexant has relatively minimal impact on driving ability. Compared with zopiclone, lemborexant did not impair next-day driving performance, while approximately 50% of zopiclone subjects showed impaired driving [83]. Next-day performance approximately 9 hours after lemborexant 2.5 mg, 5 mg, and 10

mg appeared as safe as placebo, with no significant driving impairment at any dose, while zopiclone increased driving impairment [84]. Network meta-analysis also suggested lemborexant 2.5-5 mg caused less driving impairment than zolpidem [85]. Repeated dosing (maximum follow-up 10 days) caused fewer residual effects than as-needed dosing. Note that as a central nervous system depressant, lemborexant doses exceeding recommendations or combined use with other CNS depressants (e.g., BZRAs, tricyclic antidepressants, opioids, alcohol) may increase next-day functional impairment risk.

Although lemborexant has a relatively long t1/2, next-morning residual effects are not prominent, likely due to rapid nighttime clearance resulting in limited residual blood concentrations the next day and competitive displacement by rising endogenous orexin concentrations in early morning [86].

4.3.3 Serious Adverse Effects: Lemborexant occasionally causes sleep paralysis, hypnagogic hallucinations, and cataplexy-like symptoms [87]. Compared with controls, lemborexant-treated patients experienced more frequent nightmares and may develop complex sleep behaviors including sleepwalking and sleep-driving; lemborexant should be discontinued immediately if complex sleep behaviors occur [22]. Meta-analysis showed no significant difference in sleep paralysis and hallucination risk between lemborexant and placebo groups [87].

Clinical studies suggest lemborexant may increase suicidal ideation or behavior, with incidence of 0.3% and 0.4% in 5 mg and 10 mg groups, respectively, compared with 0.2% for placebo [22]. Post-marketing FDA Adverse Event Reporting System (FAERS) data showed no significant association between DORAs and suicide parameters (suicidal ideation, depression suicide, suicidal behavior, suicide attempts) [88]. Depressed patients using lemborexant require assessment for suicidal tendencies and whether existing tendencies worsen, with prescribing of the lowest effective dose recommended [89]. If insomnia symptoms remain unresolved after 7-10 days of treatment, underlying psychiatric disorders should be re-evaluated.

4.3.4 Drug Overdose: No lemborexant overdose cases have been reported clinically. Studies reported no toxicity after 7.5 times the recommended dose, with only dose-dependent increased somnolence risk [22]. No specific antidote exists for lemborexant overdose. Overdose management should provide supportive care while monitoring for complex sleep behaviors, sleep paralysis, and other specific risks.

4.3.5 Dependence and Abuse Potential: Animal studies show lemborexant has no physical dependence or abuse reinforcement effects, with subjective effects differing from known drugs of abuse (e.g., zolpidem). Lemborexant showed no cross-generalization with zolpidem-trained rats, while suvorexant showed cross-generalization. Lemborexant showed no toxic effects in animals, while suvorexant showed behavioral toxicity. Somatic dependence and self-administration studies in rats and monkeys showed no somatic dependence or increased abuse reinforcement effects [90].

Long-term lemborexant use carries low abuse risk, with most patients not experiencing rebound insomnia, withdrawal symptoms, or dependence after discontinuation [91]. Similar to suvorexant and daridorexant, lemborexant appears to have no tolerance issues. In a one-month study, patient response at study end was equivalent to study start [16].

Overall evidence shows lemborexant treatment-emergent adverse events (TEAEs) occur at low rates, mostly mild or moderate, without major treatment impact. However, safety and efficacy monitoring remains necessary during treatment. Monthly assessment of sleep status and daytime function is recommended, with detailed efficacy, dependence tendency, and comorbidity progression evaluation every 6 months. If good sleep can be maintained, dose reduction should be attempted [36].

4.4 Patient Education

Patients should receive education about lemborexant, understanding that the medication experience more closely approximates normal sleep to build trust. Patients should be instructed to take lemborexant on an empty stomach before bedtime with adequate time in bed and avoid alcohol. Patients should be helped to recognize common adverse effects such as daytime somnolence, dizziness, and nightmares/abnormal dreams, and informed that daytime somnolence and dizziness typically become tolerable after one week. Patients should be advised to avoid driving, working at heights, or operating dangerous machinery when experiencing functional impairment. Sleep hygiene education should be provided to establish good sleep habits and avoid caffeine-containing tea and beverages before bedtime.

4.5 Special Populations

4.5.1 Hepatic Impairment: Lemborexant is not recommended for severe hepatic impairment (Child-Pugh Class C) [93]. Lemborexant has not been studied in severe hepatic impairment; given its primary hepatic metabolism, accumulation risk exists in severe impairment. Maximum recommended dose is 5 mg for moderate hepatic impairment, not more than once nightly. Phase I trials in mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment showed similar tmax medians across groups [93]. Compared with healthy subjects, lemborexant Cmax and AUC0-∞ increased by 58% and 25% in mild impairment and 22% and 54% in moderate impairment, respectively. Drug clearance decreased by 20% and 35% in mild and moderate impairment, respectively. TEAEs were mild with no serious TEAEs. Single-dose 10 mg lemborexant exposure was similar to healthy subjects in mild impairment but increased in moderate impairment, with good tolerability.

[**Recommendation 16**] No dose adjustment is needed for mild hepatic impairment (Child-Pugh Class A); maximum recommended dose is 5 mg/d for moderate hepatic impairment (Child-Pugh Class B), not more than once nightly;

lemborexant is not recommended for severe hepatic impairment (Child-Pugh Class C). (Grade B recommendation, Level I evidence)

4.5.2 Renal Impairment: No dose adjustment is needed for mild, moderate, or severe renal impairment. Compared with healthy subjects (n=8), severe renal impairment patients [estimated glomerular filtration rate 15-29 $mL \cdot min^{-1} \cdot (1.73 m^2)^{-1}$, n=8] showed similar tmax and Cmax after single 10 mg lemborexant, with AUC0-t and AUC0-∞ increased 1.5-fold and metabolite exposure increased 1.4-1.5-fold [94]. Given no clinically meaningful pharmacokinetic changes from renal impairment, no dose adjustment is required.

[Recommendation 17] No dose adjustment is needed for renal impairment patients using lemborexant. (Grade B recommendation, Level I evidence)

4.5.3 Pregnancy: No safety data exist for lemborexant use in pregnant women. Animal reproductive studies showed oral lemborexant during organogenesis caused toxicity only at >139 times the maximum recommended human dose based on AUC, manifesting as decreased maternal body weight and food consumption, reduced fetal weight, increased stillbirths, skeletal variations (cervical ribs, reduced femur length), and external and visceral malformations (omphalocele, cleft palate, membranous ventricular septal defect) [22]. A case report described a 37-year-old woman taking lemborexant 10 mg daily from gestational week 12 through postpartum days 2-6, delivering a 2,889 g male infant via planned cesarean section [95]. The infant was in good condition without abnormalities, suggesting possible safety from mid-pregnancy onward, though evidence remains insufficient. In principle, lemborexant is not recommended during pregnancy; if benefits clearly outweigh risks, cautious use with close monitoring may be considered in the second trimester. Further studies are needed to evaluate lemborexant safety in pregnancy.

4.5.4 Lactation: Animal studies show lemborexant and its metabolites are present in lactating rat milk, suggesting possible excretion in human milk [22]. In healthy lactating women ($ $18 years) receiving single 10 mg lemborexant, mean cumulative total excretion in milk over 240 hours (10 days) was 0.174% (n=8), with approximately 70% excreted within 24 hours post-dose [96]. For a 6 kg infant, this corresponds to a daily dose of 0.00290 mg/kg [coefficient of variation (CV) 54.5%], with a relative infant dose (RID, proportion of maternal daily dose) of 1.96% (CV 63.1%). Another case report showed RID of 1.21%. RID <5% is considered safe [95]. These studies confirm trace lemborexant amounts in human milk with low infant exposure unlikely to be clinically significant. However, studies did not directly assess lemborexant concentrations in infants and had small sample sizes; further research is needed to clarify safety and tolerability in breastfed infants. Given current data, lemborexant should be used cautiously in lactating women, with monitoring for excessive sedation in breastfed infants if used.

4.5.5 Children and Adolescents: No extensive clinical data exist for lemborexant use in populations <18 years. Use is contraindicated under age 18

or only permitted cautiously at specialized centers with ethics approval and guardian consent.

4.5.6 Elderly: Lemborexant demonstrates significant efficacy in improving sleep disturbances in elderly patients with minimal next-day residual effects and good tolerability, making it a suitable treatment option for elderly insomnia. Insomnia is more common in the elderly, and BZRAs pose safety concerns including cognitive and psychomotor impairment, postural instability, falls, and traffic accident risk. BZDs are not recommended for elderly insomnia in the Beers Criteria. Three clinical trials with post-hoc analyses in elderly subjects (women $ $55 years, men $ $65 years) showed lemborexant was superior to ZOL ER and zopiclone in improving sleep disturbances and effects on postural stability, next-day driving performance, memory, and attention upon awakening [97]. Lemborexant was well tolerated in subjects $ $65 years, with no serious adverse events reported and safety results consistent with the overall study population; caution is advised regarding driving and operating machinery during treatment.

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5. Summary and Outlook

Lemborexant is a novel hypnotic agent that antagonizes dual orexin receptors, demonstrating good therapeutic efficacy for primary insomnia, mental disorder-related insomnia (anxiety, depression, bipolar disorder, schizophrenia), Alzheimer' s disease-related insomnia, OSA- or COPD-related insomnia, and nocturia-related insomnia, with good overall tolerability, few and mild adverse effects, no negative impact on respiratory parameters, and low risk of somnolence and daytime functional impairment. Lemborexant holds promise for providing new therapeutic prospects for various insomnia types, though current clinical and long-term safety studies remain limited. More high-quality clinical studies are needed to provide evidence-based support.

This consensus represents the views of participating experts for guiding clinical practice and is not legally binding. Consensus content reflects the current understanding in this field and will be updated promptly as new clinical evidence emerges.

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References

[1] ZHANG B. Chinese Insomnia Disorder Diagnosis and Treatment Guidelines [M]. 2nd ed. Beijing: People' s Medical Publishing House, 2025: 147.

[2] HOC T V, LEE H C. Clinical and polysomnographic characteristics of Asian patients with comorbid insomnia and obstructive sleep apnea [J]. Sci Rep, 2025, 15(1): 11529. DOI: 10.1038/s41598-025-96825-7.

[3] HERTENSTEIN E, BENZ F, SCHNEIDER C L, et al. Insomnia-a risk factor for mental disorders [J]. J Sleep Res, 2023, 32(6): e13930. DOI: 10.1111/jsr.13930.

[4] KRYSTAL A D. Insomnia medications: History, characteristics, and guidelines for optimal use in clinical practice [J]. J Sleep Res, 2023, 32(6): e14084. DOI: 10.1111/jsr.14084.

[5] MOLINE M, ZAMMIT G, YARDLEY J, et al. Lack of residual morning effects of lemborexant treatment for insomnia: summary of findings across 9 clinical trials [J]. Postgrad Med, 2021, 133(1): 71-81. DOI: 10.1080/00325481.2020.1823724.

[6] LI X, ZHENG S, JIAN W, et al. Reported OUTCOMES for LEMborexant treatment in Chinese patients with insomnia (PROEM): a real-world study [C]//SLEEP 2025, the 39th Annual Meeting of the Associated Professional Sleep Societies, LLC (APSS). Seattle, Washington, USA, 2025.

[7] CHEN Y L, YANG K H, WANG X Q, et al. Guiding principles for the development/revision of clinical diagnosis and treatment guidelines in China

(2022 edition) [J]. National Medical Journal of China, 2022, 102(10): 697-703. DOI: 10.3760/cma.j.cn112137-20211228-02911.

[8] CHIEFFI S, CAROTENUTO M, MONDA V, et al. Orexin system: the key for a healthy life [J]. Front Physiol, 2017, 8: 357. DOI: 10.3389/fphys.2017.00357.

[9] NEVÁREZ N, DE LECEA L. Recent advances in understanding the roles of hypocretin/orexin in arousal, affect, and motivation [J]. F1000Res, 2018, 7: F1000FacultyRev-F1000Faculty1421. DOI: 10.12688/f1000research.15097.1.

[10] Ardeljan A, Hurezeanu R. Lemborexant [J]. Am J Health Syst Pharm, 2020, 77(17): 1358-61.

[11] HOYER D, ALLEN A, JACOBSON L H. Hypnotics with novel modes of action [J]. Br J Clin Pharmacol, 2020, 86(2): 244-249. DOI: 10.1111/bcp.14180.

[12] FRONCZEK R, LAMMERS G J, BALESAR R, et al. The number of hypothalamic hypocretin (orexin) neurons is not affected in Prader-Willi syndrome [J]. J Clin Endocrinol Metab, 2005, 90(9): 5466-5470. DOI: 10.1210/jc.2005-0296.

[13] THANNICKAL T C, MOORE R Y, NIENHUIS R, et al. Reduced number of hypocretin neurons in human narcolepsy [J]. Neuron, 2000, 27(3): 469-474. DOI: 10.1016/s0896-6273(00)00058-1.

[14] MIEDA M, HASEGAWA E, KISANUKI Y Y, et al. Differential roles of orexin receptor-1 and-2 in the regulation of non-REM and REM sleep [J]. J Neurosci, 2011, 31(17): 6518-6526. DOI: 10.1523/JNEUROSCI.6506-10.2011.

[15] PEYRON C, FARACO J, ROGERS W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains [J]. Nat Med, 2000, 6(9): 991-997. DOI: 10.1038/79690.

[16] FULLER M C, CARLSON S F, GRANT C, et al. A comprehensive review of lemborexant to treat insomnia [J]. Psychopharmacol Bull, 2024, 54(1): 43-64.

[17] COLEMAN P J, GOTTER A L, JOSEPH HERRING W, et al. The discovery of suvorexant, the first orexin receptor drug for insomnia [J]. Annu Rev Pharmacol Toxicol, 2017, 57: 509-533. DOI: 10.1146/annurev-pharmtox-010716-104837.

[18] BEUCKMANN C T, SUZUKI M, UENO T, et al. In vitro and in silico characterization of lemborexant (E2006), a novel dual orexin receptor antagonist [J]. J Pharmacol Exp Ther, 2017, 362(2): 287-295. DOI: 10.1124/jpet.117.241422.

[19] SAKURAI T, AMEMIYA A, ISHII M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior [J]. Cell, 1998, 92(4): 573-585. DOI: 10.1016/s0092-8674(00)80949-6.

[20] KISHI T, NISHIDA M, KOEBIS M, et al. Evidence-based insomnia treatment strategy using novel orexin antagonists: a review [J]. Neuropsychopharmacol Rep, 2021, 41(4): 450-458. DOI: 10.1002/npr2.12205.

[21] KISHI T, NOMURA I, MATSUDA Y, et al. Lemborexant vs suvorexant for insomnia: a systematic review and network meta-analysis [J]. J Psychiatr Res, 2020, 128: 68-74. DOI: 10.1016/j.jpsychires.2020.05.025.

[22] FDA. DAYVIGO (Lemborexant): highlights of prescribing information [EB/OL]. [2025-05-08]. https://www.accessdata.fda.gov/drugsatfda_{docs}/label/2025/212028s011lbl.pdf.

[23] LANDRY I, HALL N, ALURI J, et al. Effect of alcohol coadministration on the pharmacodynamics, pharmacokinetics, and safety of lemborexant: a randomized, placebo-controlled crossover study [J]. J Psychopharmacol, 2022, 36(6): 745-755. DOI: 10.1177/02698811221080459.

[24] LALOVIC B, MAJID O, ALURI J, et al. Population pharmacokinetics and exposure-response analyses for the most frequent adverse events following treatment with lemborexant, an orexin receptor antagonist, in subjects with insomnia disorder [J]. J Clin Pharmacol, 2020, 60(12): 1642-1654. DOI: 10.1002/jcph.1683.

[25] LANDRY I, NAKAI K Y, FERRY J, et al. Pharmacokinetics, pharmacodynamics, and safety of the dual orexin receptor antagonist lemborexant: findings from single-dose and multiple-ascending-dose phase 1 studies in healthy adults [J]. Clin Pharmacol Drug Dev, 2021, 10(6): 681-690. DOI: 10.1002/cpdd.915.

[26] MANO Y, UENO T, HOTTA K. Establishment of a simultaneous assay for lemborexant, a novel dual orexin receptor antagonist, and its three metabolites, and its application to a clinical protein binding study [J]. J Pharm Biomed Anal, 2020, 187: 113359. DOI: 10.1016/j.jpba.2020.113359.

[27] UENO T, ISHIDA T, ALURI J, et al. Disposition and metabolism of [14C] lemborexant in healthy human subjects and characterization of its circulating metabolites [J]. Drug Metab Dispos, 2021, 49(1): 31-38. DOI: 10.1124/dmd.120.000229.

[28] ROSENBERG R, MURPHY P, ZAMMIT G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial [J]. JAMA Netw Open, 2019, 2(12): e1918254. DOI: 10.1001/jamanetworkopen.2019.18254.

[29] MOLINE M, ZAMMIT G, CHENG J Y, et al. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder [J]. J Clin Sleep Med, 2021, 17(6): 1167-1174. DOI: 10.5664/jcsm.9150.

[30] MCELROY H, O'LEARY B, ADENA M, et al. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis [J]. J Manag Care Spec Pharm, 2021, 27(9): 1296-1308. DOI: 10.18553/jmcp.2021.21011.

[31] YUE J L, CHANG X W, ZHENG J W, et al. Efficacy and tolerability of pharmacological treatments for insomnia in adults: a systematic review and network meta-analysis [J]. Sleep Med Rev, 2023, 68: 101746. DOI: 10.1016/j.smrv.2023.101746.

[32] MIYATA S, IWAMOTO K, OKADA I, et al. Assessing the real-world, long-term impact of lemborexant on sleep quality in a home-based clinical study [J]. Nat Sci Sleep, 2024, 16: 291-303. DOI: 10.2147/NSS.S448871.

[33] TERAUCHI M, CHENG J Y, YARDLEY J, et al. Efficacy and safety of lemborexant in midlife women with insomnia disorder [J]. Menopause, 2023, 30(8): 839-848. DOI: 10.1097/GME.0000000000002209.

[34] INOUE Y, WATANABE T, TAKASHIMA S, et al. Efficacy and safety of lemborexant in adults with insomnia: comparing Japanese and non-Japanese subgroups from the global, phase 3, randomized, double-blind, placebo-controlled SUNRISE 2 study [J]. J Clin Sleep Med, 2021, 17(5): 1067-1074. DOI: 10.5664/jcsm.9148.

[35] ARNOLD V, ANCOLI-ISRAEL S, DANG-VU T T, et al. Efficacy of lemborexant in adults $ $65 years of age with insomnia disorder [J]. Neurol Ther, 2024, 13(4): 1081-1098. DOI: 10.1007/s40120-024-00622-9.

[36] KÄRPPÄ M, YARDLEY J, PINNER K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2 [J]. Sleep, 2020, 43(9): zsaa123. DOI: 10.1093/sleep/zsaa123.

[37] KRYSTAL A, BLIER P, CULPEPPER L, et al. Efficacy and safety of lemborexant in subjects with insomnia disorder receiving medications for depression or anxiety symptoms [J]. Neuropsychopharmacol Rep, 2025, 45(1): e12509. DOI: 10.1002/npr2.12509.

[38] MURAYAMA T, ITO Y, NARITA K, et al. The effect of lemborexant on insomnia in patients with psychiatric disorders: Detailed evaluation using the Athens Insomnia Scale [J]. PCN Rep, 2024, 3(1): e165. DOI: 10.1002/pcn5.165.

[39] KATSUTA N, TAKAHASHI K, KUROSAWA Y, et al. Safety and real-world efficacy of lemborexant in the treatment of comorbid insomnia [J]. Sleep Med X, 2023, 5: 100070. DOI: 10.1016/j.sleepx.2023.100070.

[40] HORIKOSHI S, MIURA I, SUZUKI Y, et al. Switching to lemborexant for the management of insomnia in mental disorders: the SLIM study [J]. J Clin Sleep Med, 2023, 19(10): 1753-1758. DOI: 10.5664/jcsm.10668.

[41] JIAN W Y, FENG M Y, ZHAO Y F, et al. Efficacy and safety of Lemborexant in treating adult patients with insomnia in China: a single-center, retrospective observational study [J]. Front Neurol, 2025, 16: 1495965. DOI: 10.3389/fneur.2025.1495965.

[42] KISHI T, KOEBIS M, SUGAWARA M, et al. Orexin receptor antagonists

in the treatment of insomnia associated with psychiatric disorders: a systematic review [J]. Transl Psychiatry, 2024, 14(1): 374. DOI: 10.1038/s41398-024-03087-4.

[43] UEMATSU T, TOMITA T, OBARA R, et al. Reducing the use of psychotropics in a convalescent rehabilitation ward [J]. Neuropsychopharmacol Rep, 2024, 44(1): 227-233. DOI: 10.1002/npr2.12388.

[44] LIGUORI C, NUCCETELLI M, IZZI F, et al. Rapid eye movement sleep disruption and sleep fragmentation are associated with increased orexin-a cerebrospinal-fluid levels in mild cognitive impairment due to Alzheimer' s disease [J]. Neurobiol Aging, 2016, 40: 120-126. DOI: 10.1016/j.neurobiolaging.2016.01.007.

[45] LIGUORI C, ROMIGI A, NUCCETELLI M, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease [J]. JAMA Neurol, 2014, 71(12): 1498-1505. DOI: 10.1001/jamaneurol.2014.2510.

[46] MUSIEK E S, XIONG D D, HOLTZMAN D M. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease [J]. Exp Mol Med, 2015, 47(3): e148. DOI: 10.1038/emm.2015.121.

[47] DUNCAN M J, FARLOW H, TIRUMALARAJU C, et al. Effects of the dual orexin receptor antagonist DORA-22 on sleep in 5XFAD mice [J]. Alzheimers Dement, 2019, 5: 70-80. DOI: 10.1016/j.trci.2019.01.003.

[48] MOLINE M, THEIN S, BSHARAT M, et al. Safety and efficacy of lemborexant in patients with irregular sleep-wake rhythm disorder and Alzheimer' s disease dementia: results from a phase 2 randomized clinical trial [J]. J Prev Alzheimers Dis, 2021, 8(1): 7-18. DOI: 10.14283/jpad.2020.69.

[49] BAYLAN S, GRIFFITHS S, GRANT N, et al. Incidence and prevalence of post-stroke insomnia: a systematic review and meta-analysis [J]. Sleep Med Rev, 2020, 49: 101222. DOI: 10.1016/j.smrv.2019.101222.

[50] WINROW C J, RENGER J J. Discovery and development of orexin receptor antagonists as therapeutics for insomnia [J]. Br J Pharmacol, 2014, 171(2): 283-293. DOI: 10.1111/bph.12261.

[51] WINROW C J, GOTTER A L, COX C D, et al. Promotion of sleep by suvorexant-a novel dual orexin receptor antagonist [J]. J Neurochem, 2011, 119(5): 1095-1104. DOI: 10.1111/j.1471-4159.2011.07450.x.

[52] KAWADA K, OHTA T, TANAKA K, et al. Addition of suvorexant to ramelteon therapy for improved sleep quality with reduced delirium risk in acute stroke patients [J]. J Stroke Cerebrovasc Dis, 2019, 28(1): 142-148. DOI: 10.1016/j.jstrokecerebrovasdis.2018.09.024.

[53] OZONE M, HIROTA S, ARIYOSHI Y, et al. Efficacy and safety of transitioning to lemborexant from Z-drug, suvorexant, and ramelteon in Japanese

insomnia patients: an open-label, multicenter study [J]. Adv Ther, 2024, 41(4): 1728-1745. DOI: 10.1007/s12325-024-02811-2.

[54] DE CRESCENZO F, D' ALÒ G L, OSTINELLI E G, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis [J]. Lancet, 2022, 400(10347): 170-184. DOI: 10.1016/S0140-6736(22)00878-9.

[55] TERADA T, HIRAYAMA T, SADAHIRO R, et al. Pilot study of lemborexant for insomnia in cancer patients with delirium [J]. J Palliat Med, 2022, 25(5): 797-801. DOI: 10.1089/jpm.2021.0509.

[56] OGURA T, UENO S, OKUDA A, et al. Can lemborexant for insomnia prevent delirium in high-risk patients with pancreatobiliary disease after endoscopic procedures under deep sedation? [J]. J Clin Med, 2022, 12(1): 297. DOI: 10.3390/jcm12010297.

[57] CHENG J Y, FILIPPOV G, MOLINE M, et al. Respiratory safety of lemborexant in healthy adult and elderly subjects with mild obstructive sleep apnea: a randomized, double-blind, placebo-controlled, crossover study [J]. J Sleep Res, 2020, 29(4): e13021. DOI: 10.1111/jsr.13021.

[58] CHENG J Y, LORCH D, LOWE A D, et al. A randomized, double-blind, placebo-controlled, crossover study of respiratory safety of lemborexant in moderate to severe obstructive sleep apnea [J]. J Clin Sleep Med, 2024, 20(1): 57-65. DOI: 10.5664/jcsm.10788.

[59] CHENG J Y, MOLINE M, ZAMMIT G K, et al. Respiratory safety of lemborexant in healthy subjects: a single-dose, randomized, double-blind, placebo-controlled, crossover study [J]. Clin Drug Investig, 2021, 41(5): 449-457. DOI: 10.1007/s40261-021-01018-5.

[60] KUSHIDA C A, ZAMMIT G K, CHENG J Y, et al. Effect of lemborexant on sleep architecture in participants with insomnia disorder and mild obstructive sleep apnea [J]. Sleep Med, 2025, 127: 170-177. DOI: 10.1016/j.sleep.2024.12.023.

[61] CHENG J Y, LORCH D, HALL N, et al. Respiratory safety of lemborexant in adult and elderly subjects with moderate-to-severe chronic obstructive pulmonary disease [J]. J Sleep Res, 2025, 34(2): e14334. DOI: 10.1111/jsr.14334.

[62] TOGO Y, KAIZUKA Y, NAGASAWA S, et al. Efficacy and safety of lemborexant for insomnia patients with nocturia-a prospective study [J]. Low Urin Tract Symptoms, 2024, 16(6): e12534. DOI: 10.1111/luts.12534.

[63] PRESKORN S H. Comparative pharmacology of the 3 marketed dual orexin antagonists-daridorexant, lemborexant, and suvorexant: part 1: pharmacokinetic profiles [J]. J Psychiatr Pract, 2022, 28(6): 478-480. DOI: 10.1097/PRA.0000000000000672.

[64] MURPHY P, MOLINE M, MAYLEBEN D, et al. Lemborexant, A dual

orexin receptor antagonist (DORA) for the treatment of insomnia disorder: results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study [J]. J Clin Sleep Med, 2017, 13(11): 1289-1299. DOI: 10.5664/jcsm.6800.

[65] HABIBA U, WASEEM R, SHAIKH T G, et al. Comparative efficacy and safety of lemborexant 5 Mg versus 10 Mg for the treatment of insomnia: a systematic review [J]. Neurol Sci, 2023, 44(5): 1533-1541. DOI: 10.1007/s10072-023-06601-8.

[66] LANDRY I, ALURI J, NAKAI K Y, et al. Evaluation of the CYP3A and CYP2B6 drug-drug interaction potential of lemborexant [J]. Clin Pharmacol Drug Dev, 2021, 10(6): 681-690. DOI: 10.1002/cpdd.915.

[67] UENO T, MIYAJIMA Y, LANDRY I, et al. Physiologically-based pharmacokinetic modeling to predict drug interactions of lemborexant with CYP3A inhibitors [J]. CPT Pharmacometrics Syst Pharmacol, 2021, 10(5): 455-466. DOI: 10.1002/psp4.12606.

[68] WATANABE K, MISAKA S, KANNO-NOZAKI K, et al. Effect of lemborexant on pharmacokinetics of clozapine: a potential drug-drug interaction mediated by time-dependent inhibition of CYP3A4 [J]. Br J Clin Pharmacol, 2024, 90(1): 354-359. DOI: 10.1111/bcp.15889.

[69] LANDRY I, ALURI J, HALL N, et al. Effect of gastric acid-reducing agents on the pharmacokinetics and efficacy of lemborexant [J]. Pharmacol Res Perspect, 2020, 8(6): e00678. DOI: 10.1002/prp2.678.

[70] LANDRY I, ALURI J, HALL N, et al. Effects of lemborexant on the pharmacokinetics of oral contraceptives: results from a phase 1 drug-drug interaction study in healthy females [J]. Clin Pharmacol Drug Dev, 2021, 10(9): 1089-1098. DOI: 10.1002/cpdd.953.

[71] OKINO K, SUZUKI H, TOMIOKA H, et al. Efficacy and safety of lemborexant as an alternative drug for patients with insomnia taking gamma-aminobutyric acid-benzodiazepine receptor agonists or suvorexant [J]. Hum Psychopharmacol, 2023, 38(3): e2868. DOI: 10.1002/hup.2868.

[72] TAKAESU Y, SAKURAI H, AOKI Y, et al. Treatment strategy for insomnia disorder: Japanese expert consensus [J]. Front Psychiatry, 2023, 14: 1168100. DOI: 10.3389/fpsyt.2023.1168100.

[73] TACHIBANA M, KANAHARA N, ODA Y, et al. A retrospective clinical practice study comparing the usefulness of dual-orexin receptor antagonists and a melatonin receptor agonist in patients switching from long-term benzodiazepine receptor agonists [J]. J Clin Sleep Med, 2024, 20(4): 603-613. DOI: 10.5664/jcsm.10946.

[74] PALAGINI L, BRUGNOLI R, DELL' OSSO B M, et al. Clinical practice guidelines for switching or deprescribing hypnotic medications for chronic insomnia: Results of European neuropsychopharmacology and sleep expert' s consensus group [J]. Sleep Med, 2025, 128: 117-126. DOI: 10.1016/j.sleep.2025.01.033.

[75] HINTZE J P, EDINGER J D. Hypnotic discontinuation in chronic insomnia [J]. Sleep Med Clin, 2020, 15(2): 147-154. DOI: 10.1016/j.jsmc.2020.02.003.

[76] AHMAD M, KELLY J, MONTANO C B, et al. Transitioning insomnia patients from zolpidem to lemborexant: a multicenter, open-label study evaluating a next-dose transition approach to insomnia pharmacotherapy [J]. Sleep Med X, 2024, 7: 100098. DOI: 10.1016/j.sleepx.2023.100098.

[77] TANAKA-MIZUNO S, FUJIMOTO K, MISHIMA K, et al. Evaluation of prescribing patterns of switching to and add-on lemborexant in patients treated with hypnotic medication: a nationwide claims database study in Japan [J]. Expert Opin Pharmacother, 2024, 25(12): 1707-1716. DOI: 10.1080/14656566.2024.2392018.

[78] SUZUKI H, HIBINO H. Characteristics of patients who were able to switch from benzodiazepine hypnotics to lemborexant [J]. SAGE Open Med, 2021, 9: 20503121211037903. DOI: 10.1177/20503121211037903.

[79] WATSON N F, BENCA R M, KRYSTAL A D, et al. Alliance for sleep clinical practice guideline on switching or deprescribing hypnotic medications for insomnia [J]. J Clin Med, 2023, 12(7): 2493. DOI: 10.3390/jcm12072493.

[80] TAKAESU Y, SUZUKI M, MOLINE M, et al. Effect of discontinuation of lemborexant following long-term treatment of insomnia disorder: Secondary analysis of a randomized clinical trial [J]. Clin Transl Sci, 2023, 16(4): 581-592. DOI: 10.1111/cts.13470.

[81] MAYLEBEN D, ROSENBERG R, PINNER K, et al. Assessment of morning sleep propensity with lemborexant in adults with insomnia disorder in a randomized, placebo-controlled crossover study [J]. Sleep Adv, 2021, 2(1): zpab011. DOI: 10.1093/sleepadvances/zpab011.

[82] MURPHY P, KUMAR D, ZAMMIT G, et al. Safety of lemborexant versus placebo and zolpidem: effects on auditory awakening threshold, postural stability, and cognitive performance in healthy older participants in the middle of the night and upon morning awakening [J]. J Clin Sleep Med, 2020, 16(5): 765-773. DOI: 10.5664/jcsm.8294.

[83] VERMEEREN A, JONGEN S, MURPHY P, et al. On-the-road driving performance the morning after bedtime administration of lemborexant in healthy adult and elderly volunteers [J]. Sleep, 2019, 42(4): zsy260. DOI: 10.1093/sleep/zsy260.

[84] VERMEEREN A, VUURMAN E F P M, LEUFKENS T R M, et al. Residual effects of low-dose sublingual zolpidem on highway driving performance the morning after middle-of-the-night use [J]. Sleep, 2014, 37(3): 489-496. DOI: 10.5665/sleep.3482.

[85] FORNARO M, CAIAZZA C, ROSSANO F, et al. Residual effects of medications for sleep disorders on driving performance: a systematic review and network meta-analysis of randomized controlled trials: NMA

driving and hypnotics [J]. Eur Neuropsychopharmacol, 2024, 81: 53-63. DOI: 10.1016/j.euroneuro.2024.01.011.

[86] GOTTER A L, WINROW C J, BRUNNER J, et al. The duration of sleep promoting efficacy by dual orexin receptor antagonists is dependent upon receptor occupancy threshold [J]. BMC Neurosci, 2013, 14: 90. DOI: 10.1186/1471-2202-14-90.

[87] NA H J, JEON N, STAATZ C E, et al. Clinical safety and narcolepsy-like symptoms of dual orexin receptor antagonists in patients with insomnia: a systematic review and meta-analysis [J]. Sleep, 2024, 47(2): zsad293. DOI: 10.1093/sleep/zsad293.

[88] MCINTYRE R S, WONG S, KWAN A T H, et al. Association between dual orexin receptor antagonists (DORAs) and suicidality: reports to the United States Food and Drug Administration Adverse Event Reporting System (FAERS) [J]. Expert Opin Drug Saf, 2025, 24(6): 753-757. DOI: 10.1080/14740338.2024.2361300.

[89] ASAKURA S, SHIOTANI M, GAUVIN D V, et al. Nonclinical evaluation of abuse liability of the dual orexin receptor antagonist lemborexant [J]. Regul Toxicol Pharmacol, 2021, 127: 105053. DOI: 10.1016/j.yrtph.2021.105053.

[90] MOLINE M, ASAKURA S, BEUCKMAN C, et al. The abuse potential of lemborexant, a dual orexin receptor antagonist, according to the 8 factors of the Controlled Substances Act [J]. Psychopharmacology, 2023, 240(4): 699-711. DOI: 10.1007/s00213-023-06320-y.

[91] MISHIMA K, FUJIMOTO K, ENDO A, et al. Safety and efficacy of lemborexant in insomnia patients: results of a postmarketing observational study of dayvigo® tablets [J]. Drugs R D, 2024, 24(2): 211-226. DOI: 10.1007/s40268-024-00462-w.

[92] DAYAL S, ALURI J, HALL N, et al. Effect of hepatic impairment on pharmacokinetics, safety, and tolerability of lemborexant [J]. Pharmacol Res Perspect, 2021, 9(2): e00758. DOI: 10.1002/prp2.758.

[93] LANDRY I, ALURI J, HALL N, et al. Effect of severe renal impairment on pharmacokinetics, safety, and tolerability of lemborexant [J]. Pharmacol Res Perspect, 2021, 9(2): e00734. DOI: 10.1002/prp2.734.

[94] SAITO J, ISHII M, SANDAIJI N, et al. Lemborexant levels in maternal serum, cord blood, and breast milk during pregnancy and lactation: a case report [J]. PCN Rep, 2023, 2(1): e62. DOI: 10.1002/pcn5.62.

[95] RAWAL S, BRIMHALL D, ALURI J, et al. Lemborexant levels in breast milk after single doses in healthy, lactating women [J]. Br J Clin Pharmacol, 2024, 90(1): 158-163. DOI: 10.1111/bcp.15880.

[96] GOTFRIED M H, AUERBACH S H, DANG-VU T T, et al. Efficacy and safety of insomnia treatment with lemborexant in older adults: analyses from

three clinical trials [J]. Drugs Aging, 2024, 41(9): 741-752. DOI: 10.1007/s40266-024-01135-8.

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