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Comparative Efficacy and Safety of Dual Orexin Receptor Antagonists (DORAs) Versus Z-Drugs for Insomnia in Older Adults : A Systematic Review

Background: Insomnia affects up to 48% of adults ≥55 globally, often treated with Z-drugs which may increase incidence of cognitive impairment and adverse events such as falls. Dual Orexin Receptor Antagonists (DORAs) offer a targeted alternative by specifically suppressing wakefulness-promoting pathways to minimize these adverse effects. Therefore, this study aims to compare the effectiveness and safety profile of DORAs and Z-Drugs.

Objective: This systematic review aims to compare the efficacy and safety of Dual Orexin Receptor Antagonists (DORAs) against Z-drugs as an alternative therapy for diagnosed insomnia present in older adults.

Methods: The PRISMA 2020 standards were followed in conducting this systematic review. RCTs were searched through Online databases including PubMed, ScienceDirect, ProQuest and Sage Journals. The review included studies on adults aged ≥55 years with diagnosed insomnia with DORAs and Z-Drugs as the interventions. The studies recovered were then assessed by the Cochrane RoB 2 risk of bias tool. Adverse events were assessed as the primary outcome; SOL, WASO and overall sleep quality improvement as the secondary outcome.

Results: Seven studies consisting of RCT, Crossover and SUNRISE-1 Cohort were evaluated. DORAs demonstrated significantly superior efficacy over Z-drugs, with Least Squares Mean differences of -6.7 and -8.0 minutes for 5 mg and 10 mg doses, respectively. Furthermore, safety analyses revealed DORAs had a significantly lower relative incidence of residual effects and cognitive impairment (<5%) compared to Z-drugs (>15%).

Conclusion: Although DORAs and Z-Drugs are used to manage insomnia, DORAs appeared to have lower side effects and lower levels of falls during the intervention. However further quantitative analysis is needed to confirm its efficacy and heterogeneity in the studies limits confidence levels in current findings.

Keywords: Insomnia, Dual Orexin Receptor Antagonists, Z-Drugs, Accidental Falls, Older Adults

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Introduction

Insomnia is one of the most common sleep disorders suffered by the elderly population and these situations are affecting growing public health concern worldwide. Physiological changes such as pattern in circadian rhythm, reduced sleep efficiency, and shorter sleep duration, making adults aged over ≥55 years particularly vulnerable to insomnia. Studies estimated that approximately 30-48% of older adults worldwide are experiencing symptoms of insomnia, whereas specifically 12-20% of the elderly individual meet the criteria.[1,2] Prolonged insomnia that occurs in the elderly population is associated with impaired daily daytime functional performance, reduced quality of life, depression, and decline in their cognitive performance.[3] Moreover, insomnia significantly increases the risk of falls, fracture, and accidents which are the major contributors to morbidity and mortality among the geriatric populations.[4]

In Indonesia, reports from several national and regional studies show that insomnia symptoms are affecting 30.3% of the Indonesia adults population, particularly among individuals aged ≥55 years.[5] The prevalence tends to increase with age and is associated with chronic disease suffered among the older adults. Despite its high prevalence, insomnia remains undertreated in Indonesia due to low awareness and low exposure of sleep health education.[5] Consequently, pharmacological therapies are often utilised as the primary treatment for symptoms among older patients.

Historically, non-benzodiazepine hypnotics commonly referred to as Z-drugs (such as zolpidem and zopiclone) have been widely used for the pharmacological treatment of insomnia.[6] While effective in initiating and maintaining sleep by enhancing GABAergic inhibition, their use in the older adults is frequently complicated by adverse effects, including cognitive impairment, psychomotor depression, and a significantly increased risk of falls.[7]

Dual Orexin Receptor Antagonists (DORAs) has recently gained popularity emerging as a novel therapeutic class.[8] Unlike Z-drugs, which broadly depress the central nervous system, DORAs (such as lemborexant and suvorexant) target the orexin neuropeptide system to specifically block wakefulness-promoting pathways. This targeted mechanism presents a potentially safer side-effect profile for older adults, mitigating many of the classical hypnotic risks and still effectively reducing insomnia for older adults. When selecting hypnotic therapy it is important to consider fall-related safety in the context of insomnia and sleep disturbance.[9] Recent evidence suggests that orexin receptor antagonists do not significantly increase the risk of falls or fractures in patients treated for insomnia, although available data for DORAs remain limited. In addition, lemborexant has been shown to improve sleep variables in older adults without impairing cognitive function, risk of falls or fractures compared with placebo. These findings demonstrate that DORAs may offer a safer therapeutic profile than traditional non-benzodiazepine hypnotics for older adults with insomnia and sleep disturbance.[9,13,17] However, direct comparative evidence between DORAs and Z-drugs in adults aged ≥55 years remains limited, especially regarding important safety outcomes such as risk of falls, morning somnolence, and cognitive or psychomotor impairment. Therefore, this review aims to evaluate the safety and efficacy of DORAs compared with Z-drugs in adults aged ≥55 years with primary or comorbid insomnia.

Method

PICO

This systematic review was conducted using the PICO approach (Population, Intervention, Comparison and Outcome).[10] In this study, the population included were older adults aged ≥55 years with formally diagnosed insomnia. The main interventions used were Dual Orexin Receptor Antagonists (DORAs), while Z-drugs and placebo were used as a comparison. The primary outcome assessed were the incidence of adverse events. The Secondary outcomes were Sleep onset latency (SOL), wake after sleep onset (WASO), and overall sleep quality improvement.

Search Strategy

A comprehensive literature search was systematically conducted across four electronic databases: PubMed, ScienceDirect, ProQuest, and Sage Journals, from May 12, 2026, to May 28, 2026. The search process used a combination of keywords that are relevant to this review. Identified studies are then screened using Rayyan.ai as a tool for selecting studies based on the inclusion and exclusion criteria. To ensure rigorous methodology in accordance with PRISMA guidelines[11], the study selection and data extraction processes were independently conducted by two reviewers (J.C.T. & F.K.H.). Any disagreements regarding study eligibility during the screening process were resolved through a

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Table 1. PICO Framework

Population	Intervention	Comparison	Comparison
Older adult patients (aged ≥50 years) formally diagnosed with primary insomnia or insomnia comorbid with other conditions.	Dual Orexin Receptor Antagonists (Lemborexant, Daridorexant and Suvorexant)	Traditional non-benzodiazepine hypnotics (Z-drugs), including agents such as Zolpidem, Zopiclone	• Primary: Incidence of adverse events (specifically focusing on falls, morning hangover/ somnolence, and next-morning cognitive/ psychomotor impairment). • Secondary: Sleep onset latency (SOL), wake after sleep onset (WASO), and overall sleep quality improvement

joint full-text re-evaluation to reach a mutual consensus. A third reviewer from the research team was available for final arbitration if a consensus could not be achieved. The search strategy was developed using five core keywords: Insomnia, Dual Orexin Receptor Antagonists, Z-Drugs, Accidental Falls, Older Adults

The inclusion criteria for this manuscript were visualized using the PRISMA guideline.[11] Eligible study designs included studies of Randomized Controlled Trials (RCT) and high quality observational studies such as prospective or retrospective cohort studies. The studies involved older adults aged ≥ 55 years which have a higher risk of insomnia due to decreased quality and quantity of sleep as the brain ages, DORAs such as Lemborexant, Suvorexant and Daridorexant used as primary therapy to treat insomnia were included in the selection process. Studies were also required to assess the incidence of adverse events such as falls, somnolence and psychomotor impairments as the primary outcomes. Alongside Sleep Onset Latency (SOL), Wake After Sleep Onset (WASO) and the overall quality of sleep as the secondary assessed outcome.

Exclusion criteria were also developed using the PRISMA guideline.[11] Studies were excluded if they met one of these criteria. Systematic reviews, meta-analyses, narrative reviews, in vitro or animal studies, insomnia present in adults <50 years of age, other diagnosed sleep disorders, studies that don't use DORAs as a primary intervention, studies without a relevant comparison group such as Zolpidem or Zopiclone and studies that do not assess the overall safety and efficacy of the sleep-related outcomes.

Risk of Bias Assessment

The included studies were then assessed for risk of bias using tools tailored based on their study design. The

Table 2. Search Strategy

Database	Search Strategy	Search Results
PubMed	("Sleep Initiation and Maintenance Disorders"[Mesh] OR "insomnia"[tiab] OR "sleep disorder*"[tiab]) AND ("lemborexant"[tiab] OR "daridorexant"[tiab] OR "Dayvigo"[tiab] OR "Quviviq"[tiab]) AND ("zolpidem"[Mesh] OR "zolpidem"[tiab] OR "zopiclone"[tiab] OR "Ambien"[tiab] OR "Imovane"[tiab])	27
ScienceDirect	(insomnia OR "sleep disorder") AND (lemborexant OR daridorexant OR suvorexant) AND (zolpidem OR zopiclone)	53
Proquest	Box 1: insomnia OR "sleep disorder" OR "sleep disorders" Box 2 (AND): lemborexant OR daridorexant OR Dayvigo OR Quviviq Box 3 (AND): zolpidem OR zopiclone OR Ambien OR Imovane	140
Sage Journal	(insomnia OR "sleep disorder" OR "sleep disorders") AND (lemborexant OR daridorexant OR Dayvigo OR Quviviq) AND (zolpidem OR zopiclone OR Ambien OR Imovane)	15

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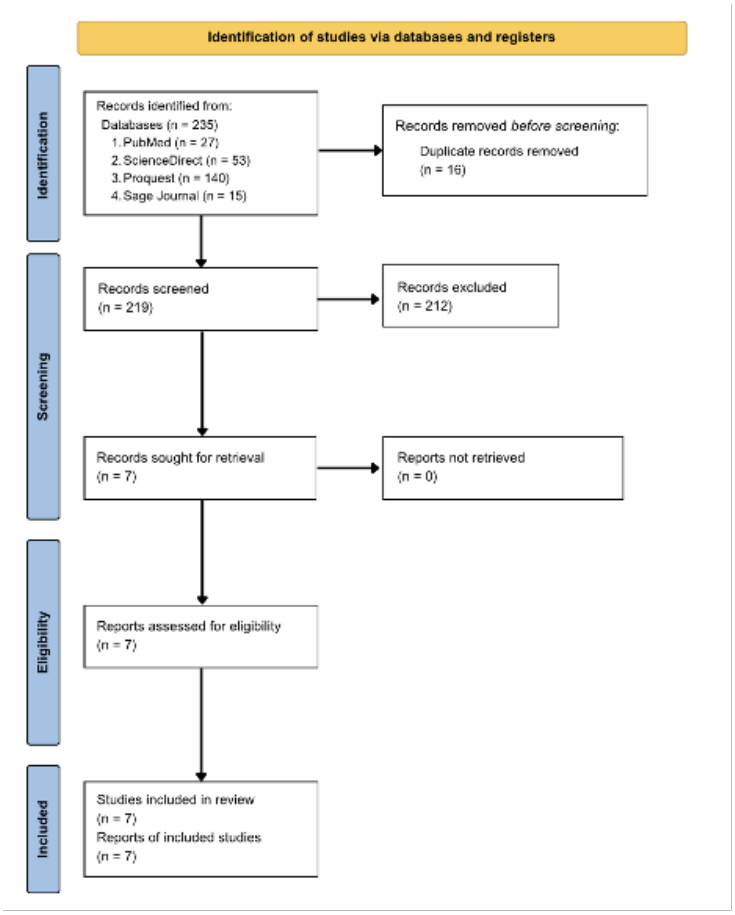

Figure 1: PRISMA Flowchart

risk of bias for Randomized Controlled Trials, SunRISe-1 trials and Crossover trials were assessed using the Cochrane Risk of Bias 2 (ROB 2.0) tool, which assesses the study based on five domains to determine the overall methodological quality.[12]

Result

A total of seven studies consisting of five parallel randomized controlled trials and two randomized crossover trials were evaluated in this review (Table 3). Due to the high clinical and methodological heterogeneity across the included studies, particularly the variations in study design and the diverse measurement tools used for primary and secondary outcomes, a quantitative meta-analysis was not feasible. Consequently, a narrative synthesis approach was employed to compare the findings across the studies.

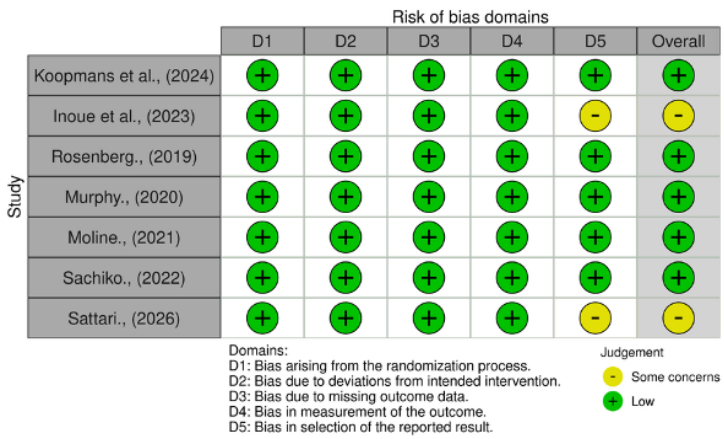

Figure 2: Risk of Bias Traffic Plot

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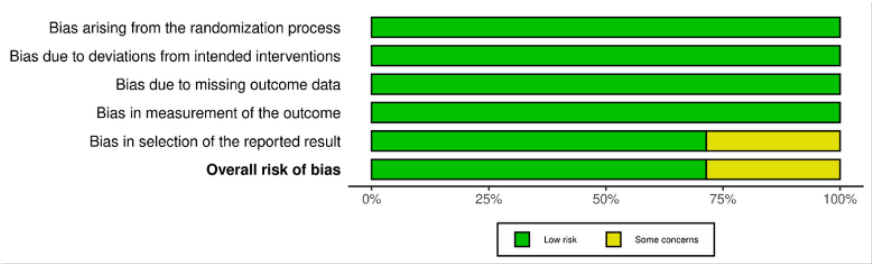

Figure 3: Risk of Bias Conclusion

Study quality appraisal conducted using the Cochrane ROB 2.0 tool across five domains: bias arising from the randomization process (D1), bias due to deviations from intended intervention (D2), bias due to missing outcome data (D3), bias in measurement of the outcome (D4), and bias in selection of the reported result (D5). The overall quality of the studies was generally at a low risk of bias, indicating an adequate randomization process, correct interventions used, and complete outcome data across the studies. Nevertheless, the main area of concern was observed in domain five (D5) with 2 studies observed to have some concerns (n=2). Although the trials were pre-registered, the nature of the post hoc analysis showed a risk of selective reporting in the trials.

Discussion

Safety Findings (Primary Outcome)

Based on our narrative synthesis, the analysis of safety parameters illustrates distinct differences in residual effect profiles that are vital for the older adult population.[13] Quantitatively, the use of a Z-drug (zolpidem) is associated with significantly higher levels of postural instability and morning cognitive impairment, with a relative incidence of >15%. In contrast, the DORA class maintains lower incidence metrics closer to baseline or placebo levels (<5%).[14,15] These safety findings confirm that the DORA class successfully minimizes the risk of falls during the night and the following morning, directly addressing a major historical challenge in the pharmacotherapy of geriatric insomnia.

Efficacy Findings

With respect to sleep maintenance efficacy, 5 mg and 10 mg doses of lemborexant were significantly superior to 6.25 mg of zolpidem in reducing Wake After Sleep Onset in the second half of the night (WASO-2H).[16] The Least Squares Mean (LSM) differences were -6.7 minutes (95% CI: -11.2 to -2.2) for the 5 mg dose and -8.0 minutes (95% CI: -12.5 to -3.5) for the 10 mg dose.[14] In a broader clinical context, this reduction in WASO addresses a fundamental characteristic of geriatric insomnia: older adults frequently experience fragmented sleep and frequent nocturnal awakenings. While Z-drugs may aid initial sleep onset, they often fail to sustain sleep through the second half of the night.[17] In contrast, the sustained, targeted action of DORAs supports a more prolonged and uninterrupted sleep cycle, translating to more restorative sleep essential for daytime functioning and quality of life in the elderly population.[3]

Mechanistic Explanations

Following the evaluation of safety, the secondary outcomes regarding sleep maintenance efficacy highlight a clear clinical advantage for Dual Orexin Receptor Antagonists (DORAs) over conventional Z-drugs in managing geriatric insomnia. Rather than suppressing global neural activity through GABAergic hyperactivation as Zolpidem does. DORAs does inhibit the wake-promoting orexin pathway, resulting in a much more natural and physiological sleep state. The focused target mechanisms also improve sleep architecture. EEG and polysomnography data confirm that lemborexant preserves natural sleep microarchitecture over time, supported by data showing an increasing Rapid Eye Movement (REM) sleep proportion and shortening REM latency.[18] The data also suggests that a one-size-fits-all aspect is outdated. Lemborexant demonstrates more consistent objective and subjective benefits specifically for older adults with a short sleep duration (<6 hours), which proved highly effective for those struggling with maintenance insomnia.[19]

Clinical Implications

The findings of this review have substantial clinical applicability for the current landscape of geriatric care. A part of shifting away from GABAergic agents in favour towards DORAs marks a much more necessary evolution in geriatric, in whom reliable sleep maintenance must be balanced against the risk of cognitive impairment

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Table 3. Study Characterisation

First Author, year	Design	Population (N,Stage Age)	Intervention (I)	Comparator (C)	Protocol (Dose/ Freq)	Outcomes
Koopmans , 2024	RCT	N: 18, Stage: Healthy elderly, Age: 66 - 88 (mean: 71.9)	Suvorexant	Zolpidem and placebo	Dose: 10 mg suvorexant, 5 mg zolpidem, or placebo. Frequency: Single dose administered in the morning following a 2-hour fast	Interactive Walk Way (IWW) Body Sway Adaptive tracking (%) Timed Up and Go
Inoue , 2023	RCT	N: 1006 Stage: Participants met the DSM-5 criteria for insomnia disorder Age: ≥ 55 years	Lemborexant	Zolpidem and placebo	Single daily oral dose (5 mg or 10 mg lemborexant, 6.25 mg zolpidem ER, or placebo) for 30 nights, taken within 5 minutes of the time they intended to sleep	SOL WASO TST
Rosenberg , 2019	RCT	N: 1006 Stage: Participants met the DSM-5 criteria for insomnia disorder Age: 63.9 (Mean)	Lemborexant	Zolpidem and placebo	5 mg of lemborexant, 10 mg of lemborexant 6.25 mg of zolpidem, or placebo in a 5:5:5:4 ratio.	Latency to persistent sleep WASO Sleep efficiency (%) AEs
Murphy , 2020	CrossOver	Healthy Older Adults Women ≥ 55 y.o., Men ≥ 65 y.o. (Crossover design)	Lemborexant 5 mg and 10 mg (Single-dose, 4-period crossover)	Placebo Zolpidem ER (6.25 mg)	Dose: 5 mg or 10 mg lemborexant, 6.25 mg zolpidem ER, or placebo. Single dose at bedtime in a 4-period crossover design.	5 mg and 10 mg showed no significant impairment in MOTN postural stability or AAT compared to placebo.
Moline , 2021	SUNRISE-1 Cohort	Older Adults with Insomnia ≥ 55 y.o. (SUNRISE-1 Cohort)	Lemborexant 5 mg and 10 mg (1 month)	Placebo Zolpidem ER (6.25 mg)	Dose: 5 mg or 10 mg lemborexant, 6.25 mg zolpidem ER, or placebo. Single daily oral dose at bedtime for 1 month.	LEM significantly increased TST and REM sleep, and decreased latency to REM compared to both placebo and Zolpidem.

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First Author, year	Design	Population (N,Stage Age)	Intervention (I)	Comparator (C)	Protocol (Dose/ Freq)	Outcomes
Sachiko, 2022	CrossOver	Healthy Elderly Subjects Older adults (Evaluated via crossover)	Suvorexant (Low dose) Ramelteon	Placebo Zolpidem	Dose: Suvorexant (low dose), ramelteon, zolpidem, or placebo. Single dose at bedtime in a crossover design	Low-dose Suvorexant and Ramelteon demonstrated significantly fewer next-morning residual effects compared to Zolpidem.
Sattori , 2026	RCT	Older Adults with Insomnia ≥ 55 y.o. (RCT)	Lemborexant (Acute and chronic use)	Zolpidem	Dose: Lemborexant or zolpidem. Acute and chronic administration at bedtime	ZOL & LEM different effects LEM better maintains physiological sleep microarchitecture

and nocturnal falls. In routine geriatric practice, DORAs may be particularly favorable for frail older patients, those with a history of falls, and those receiving concurrent polypharmacy, given their comparatively lower psychomotor and cognitive burden relative to Z-drugs. Nonetheless, clinical adoption should remain proportionate to the current strength of evidence, which still remains limited by heterogeneity across the available studies.

Strengths

This review itself benefits from a systematic type of plan , PRISMA-guided search strategy across four databases, independent dual-reviewer screening, and structured risk-of-bias appraisal using the Cochrane RoB 2 tool which provides a transparent and better synthesis of the current evidence. By intentionally including both randomized and high-quality non-randomized designs, this review captures a broader range of controlled and real-world evidence than a review restricted to RCTs alone, offering a better comprehensive view of patient care that connects controlled polysomnographic efficacy with real-world functional safety outcomes.

Limitations and Future Research

Despite the promising findings, this review is constrained by limitations within the current evidence base. Specifically, the clinical and methodological heterogeneity observed across the current literature prevents a formal meta-analysis and restricts the statistical data power. However, it still provides a necessary and comprehensive view of patient care that really connects the gap between controlled polysomnography efficacy and real-world functional safety. To address these evidence gaps, there is a critical need for more standardized study designs. Future research should prioritize long-term, randomized controlled trials (RCTs) that specifically stratify geriatric patients based on their frailty status and varying degrees of polypharmacy.[20] Additionally, evaluating the efficacy of DORAs in older adults with comorbid neurocognitive disorders, such as early-stage dementia or Alzheimer's disease, remains an underexplored area that is essential for translating these polysomnographic benefits into broader, real-world clinical guidelines.[21]

Conclusion

In conclusion, Dual Orexin Receptor Antagonists (DORAs), particularly lemborexant and suvorexant demonstrate superior safety profiles and favorable efficacy compared with conventional Z-drugs on managing insomnia among older adults. DORAs significantly improve sleep maintenance parameters especially Wake After Sleep Onset (WASO), while preserving REM sleep quality. In contrast with zolpidem, DORAs were proven with lower rates of next-morning

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residual effects, cognitive impairment, postural instability, and fall risk, which are major concerns in geriatric populations.

The therapeutic advantages of DORAs are linked to their selective inhibition of orexin-mediated wakefulness pathways, giving more natural sleep induction without excessive global central nervous system suppression seen in GABAergic hypnotics. However, given the substantial clinical and methodological heterogeneity and the relatively small evidence base identified in this review, these findings should be regarded as preliminary rather than conclusive. DORAs represent a promising and physiologically rational pharmacological option for older adults with insomnia, but confirmation through standardized, adequately powered trials is required before firm clinical recommendations can be made.

Acknowledgement

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Conflict of Interest

The authors report no commercial associations, financial ties, or personal relationships that might pose a conflict of interest in connection with this manuscript.

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Supplementary Files

Comparative Efficacy and Safety of Dual Orexin Receptor Antagonists (DORAs) Versus Z-Drugs for Insomnia in Older Adults : A Systematic Review

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Appendix 1. PICO Framework

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Older adult patients (aged ≥50 years) formally diagnosed with primary insomnia or insomnia comorbid with other conditions.	Dual Orexin Receptor Antagonists (Lemborexant, Daridorexant and Suvorexant)	Traditional non-benzodiazepine hypnotics (Z-drugs), including agents such as Zolpidem, Zopiclone	• Primary: Incidence of adverse events (specifically focusing on falls, morning hangover/ somnolence, and next-morning cognitive/ psychomotor impairment). • Secondary: Sleep onset latency (SOL), wake after sleep onset (WASO), and overall sleep quality improvement

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Sage Journal	(insomnia OR "sleep disorder" OR "sleep disorders") AND (lemborexant OR daridorexant OR Dayvigo OR Quviviq) AND (zolpidem OR zopiclone OR Ambien OR Imovane)	15

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Appendix 3. PRISMA result

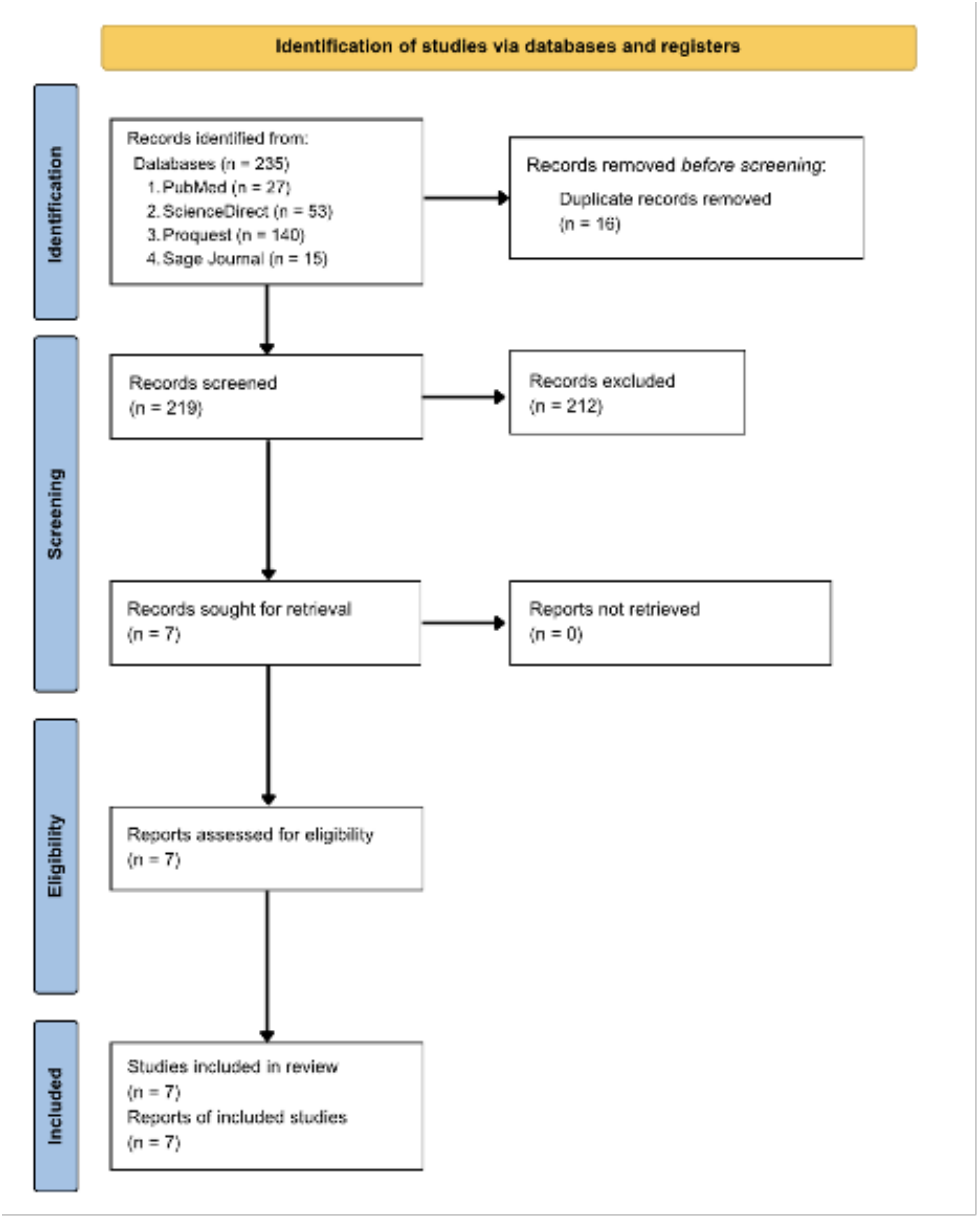

Figure 1: PRISMA Flowchart

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Appendix 4. Study Characterisation

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Inoue , 2023	RCT	N: 1006 Stage: Participants met the DSM-5 criteria for insomnia disorder Age: ≥ 55 years	Lemborexant	Zolpidem and placebo	Single daily oral dose (5 mg or 10 mg lemborexant, 6.25 mg zolpidem ER, or placebo) for 30 nights, taken within 5 minutes of the time they intended to sleep	SOL WASO TST
Rosenberg , 2019	RCT	N: 1006 Stage: Participants met the DSM-5 criteria for insomnia disorder Age: 63.9 (Mean)	Lemborexant	Zolpidem and placebo	5 mg of lemborexant, 10 mg of lemborexant 6.25 mg of zolpidem, or placebo in a 5:5:5:4 ratio.	Latency to persistent sleep WASO Sleep efficiency (%) AEs
Murphy , 2020	CrossOver	Healthy Older Adults Women ≥ 55 y.o., Men ≥ 65 y.o. (Crossover design)	Lemborexant 5 mg and 10 mg (Single-dose, 4-period crossover)	Placebo Zolpidem ER (6.25 mg)	Dose: 5 mg or 10 mg lemborexant, 6.25 mg zolpidem ER, or placebo. Single dose at bedtime in a 4-period crossover design.	5 mg and 10 mg showed no significant impairment in MOTN postural stability or AAT compared to placebo.
Moline , 2021	SUNRISE-1 Cohort	Older Adults with Insomnia ≥ 55 y.o. (SUNRISE-1 Cohort)	Lemborexant 5 mg and 10 mg (1 month)	Placebo Zolpidem ER (6.25 mg)	Dose: 5 mg or 10 mg lemborexant, 6.25 mg zolpidem ER, or placebo. Single daily oral dose at bedtime for 1 month.	LEM significantly increased TST and REM sleep, and decreased latency to REM compared to both placebo and Zolpidem.

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First Author, year	Design	Population (N,Stage Age)	Intervention (I)	Comparator (C)	Protocol (Dose/ Freq)	Outcomes
Sachiko, 2022	CrossOver	Healthy Elderly Subjects Older adults (Evaluated via crossover)	Suvorexant (Low dose) Ramelteon	Placebo Zolpidem	Dose: Suvorexant (low dose), ramelteon, zolpidem, or placebo. Single dose at bedtime in a crossover design	Low-dose Suvorexant and Ramelteon demonstrated significantly fewer next-morning residual effects compared to Zolpidem.
Sattori , 2026	RCT	Older Adults with Insomnia ≥ 55 y.o. (RCT)	Lemborexant (Acute and chronic use)	Zolpidem	Dose: Lemborexant or zolpidem. Acute and chronic administration at bedtime	ZOL & LEM different effects LEM better maintains physiological sleep microarchitec-ture

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Appendix 5. Risk of Bias Assessment

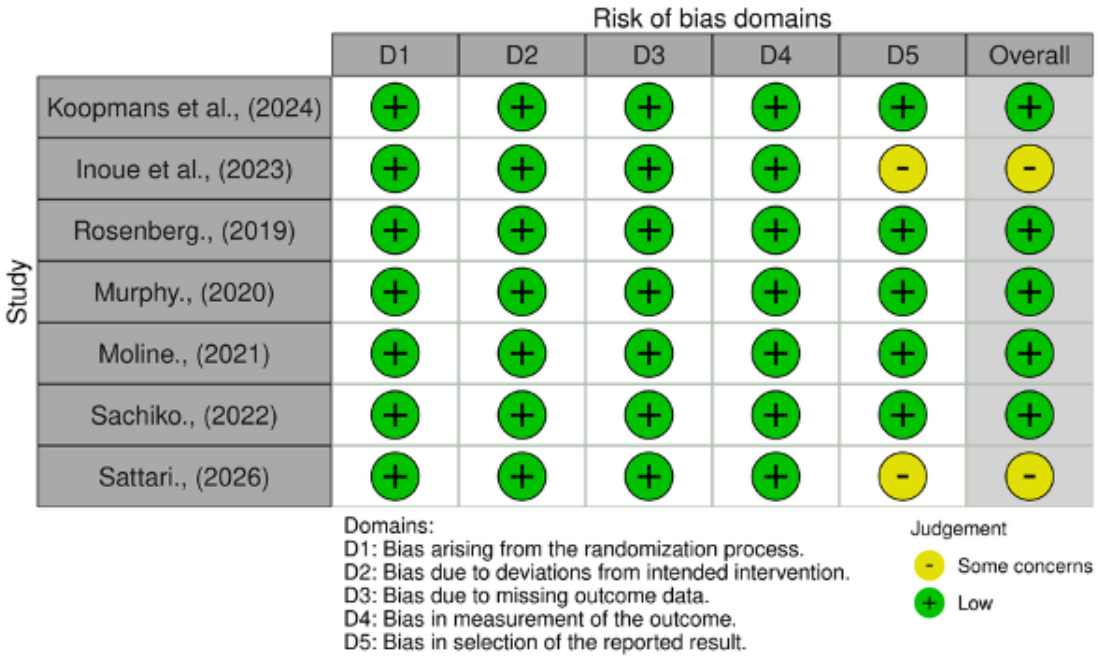

Figure 2: Risk of Bias Traffic Plot

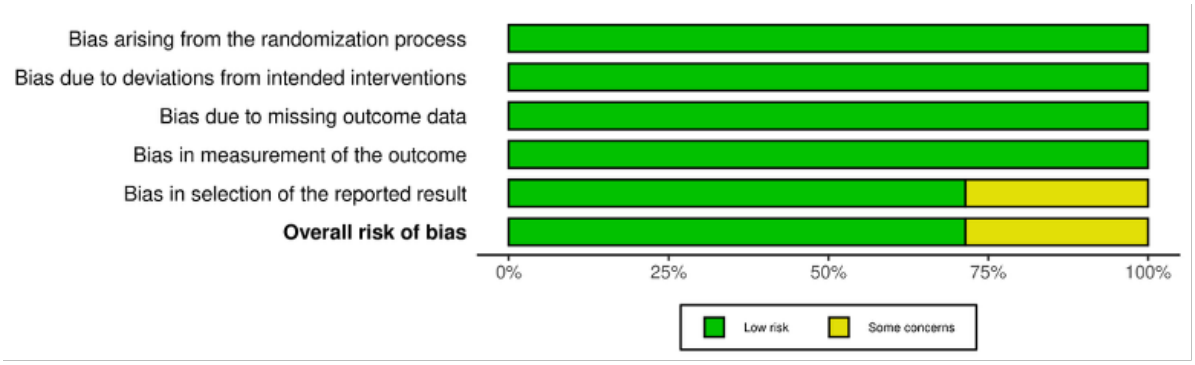

Figure 3: Risk of Bias Conclusion

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Appendix 6. Author's Contributions

Credit Role	Author(s)
Conceptualization	Jason Conrad Tanely
Methodology	Frederick Karel Himawan & Jason Conrad Tanely
Investigation / Literature Search	Frederick Karel Himawan & Jason Conrad Tanely
Data Curation / Screening	Jason Conrad Tanely , Frederick Karel Himawan , Given Anugraha Wijaya
Formal Analysis	Given Anugraha Wijaya
Writing – Original Draft	Jason Conrad Tanely , Frederick Karel Himawan , Given Anugraha Wijaya
Writing – Review & Editing	Jason Conrad Tanely , Frederick Karel Himawan , Given Anugraha Wijaya
Project Administration	Given Anugraha Wijaya