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Article

The Role of Dual Orexin Receptor Antagonists (DORAs) in Preventing Delirium: A Meta-Analysis and Systematic Review

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Abstract

Introduction: Delirium is defined as a neurological incapacity that is acute in nature and usually subside after some time. It is one of the most serious metabolic disorders that is usually attributed to a wide range of complications. Delirium has been linked to dual orexin receptor antagonists (DORAs); medications commonly prescribed to treat insomnia. The objective of this study is to evaluate the efficacy of DORA drugs, Suvorexant and Lemborexant in delirium prevention. Methods: We conducted a literature search on PUBMED, EMBASE, and Cochrane Library electronic databases among others from inception to September 1, 2024. Published papers on dual orexin receptor antagonists (DORA) in delirium prevention that have met the eligibility criteria were included for data extraction and quality assessment. Results: From the evaluated studies with 930 patients of who 132 were on Suvorexant and 58 on Lemborexant. We pooled this evidence and identified that the incidence of delirium is significantly low in patients treated with Dora medications as compared to non-users. Conclusions: Dual orexin receptor antagonists were effective in preventing delirium in critically ill patients. Prospective studies are needed for confirmation of these results and evaluation of the effect of the drugs on the death rates in the hospital, their effect on the duration of stays in the ICU and the days that the patients are under mechanical ventilation.

Keywords: Dual Orexin receptor antagonist; Suvorexant and Lemborexant; prevention of delirium

Introduction

Delirium is a clinical syndrome marked by acute cerebral dysfunction, which is defined by three key features: fluctuating mental status, inattention, and an altered level of consciousness or disorganized thinking. It arises in response to changes in environmental and physical conditions, and its prevalence among hospitalized patients ranges from 3% to 56%.1,2 Delirium is associated with increased length of hospital stay, higher healthcare costs, and increased risk of long-term cognitive impairment and mortality.3,4

Despite its significant impact on patient outcomes, the prevention of delirium remains a challenging task. Current prevention strategies, such as non-pharmacological interventions and early mobilization, have shown promise but have limitations in their effectiveness.5 As a result, there is a growing interest in the use of pharmacological agents to prevent delirium. Two such agents, suvorexant and Lemborexant, have recently gained attention for their potential role in delirium prevention.

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Suvorexant, a dual orexin receptor antagonist, has been shown to reduce the incidence of delirium in critically ill patients. Tamura et al. found that the incidence of delirium in patients undergoing elective coronary artery bypass grafting was significantly lower in the suvorexant treatment group compared to the control group (2.8% vs. 21.2%; P = .008).6Similarly, Hatta et al. reported that delirium was less common among acute care patients receiving suvorexant than in those who did not receive it (0% vs. 17%; P = .025).7

Similarly, Lemborexant, another orexin receptor antagonist, Terada et al. reported that it is effective in addressing sleep disturbances in cancer patients experiencing delirium.8

This meta-analysis and systematic review aim to critically evaluate the current evidence on the use of suvorexant and Lemborexant in the prevention of delirium, with a focus on their efficacy, safety, and potential clinical applications

Materials and method

This meta-analysis followed the PRISMA guidelines. there was no need for either ethical approval or patient consent because this study used secondary data obtained from already published articles.

Table 1. PICOS criteria (Population, Intervention, Comparison, Outcome; Study design)

Component	Description
Population	Critically ill adult patients requiring mechanical ventilation; setting advanced emergency center
Intervention	Dual Orexin Receptor Antagonist (DORA); Focus on its preventive effect against delirium
Comparison	Standard of care
Outcome	The primary outcome measured was the incidence of delirium
Study Design	Single center, retrospective, observation study

Data Sources and searches

The databases of PUBMED, EMBASE and the Cochrane library were all searched up to 01 September 2024, with the use of search strategy: Dual orexin receptor antagonist (“Suvorexant”) (“Lemborexant”) AND (“delirium”). These were additional studies that were sought from the reference list of the studies already included.

Study selection and data extraction

Studies involving adult human patients receiving dual orexin receptor antagonist for delirium prevention, published in English language and has sufficient data for statistical analysis were included.

Duplicated publications, case series and reports, reviews or non-human studies were excluded in the analysis. Publications meeting the inclusion criteria were obtained as full articles and reassessed for eligibility.

The reviewers independently gathered the predefined data items using a designated data extraction form. This data encompassed information about the study design, methods, and characteristics of the included patients, interventions, and outcomes. For binary data, the reviewers obtained the proportion or count of specific events, as well as the total number of individuals assigned to each group and the overall number analyzed. For continuous data, they collected the total number of participants randomized per group, the number of patients analyzed, the distribution of participants across the compared groups, along with the mean values and standard deviations for certain outcomes. To address any missing information or uncertainties, they contacted the authors of the trials. In instances of discrepancies or uncertainties, a third party facilitated discussions to reach a resolution.

Included studies

Table 2. Studies included

Authors	Country	Year	Journal	Total Participants	Treatment	DORA	Control	Outcomes
Matsuoka et al.	Japan	2022	Journal of Clinical Psychiatry	633	DORAs	123	510	28 developed delirium (DORA), 208 (control)
Matsuoka et al.	Japan	2023	General Hospital Psychiatry	297	DORAs	67	230	15 developed delirium (DORA), 163 (control)

Assessment of risk bias

The quality of each study was evaluated according to the Cochrane Handbook for Systematic Reviews of Interventions. Each item was rated as having a low risk, unclear risk, or high risk.

Measurement of treatment effect

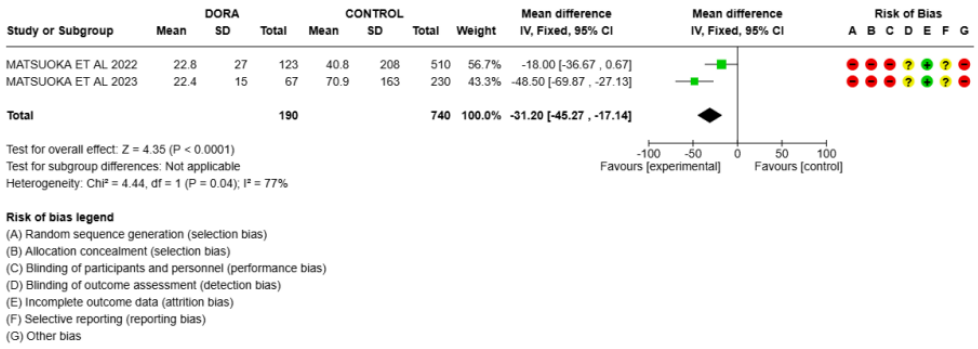

Figure 1. Dora at the end point and risk bias

Results

Published trials obtained from a specific database search yielded a total of nine articles. One study was excluded due to redundancy, and five were eliminated following the screening of titles and abstracts. One additional study was excluded because it did not correlate with both the control group and the DORA group. Consequently, two studies were included, comprising a total of 930 patients: 132 patients received Suvorexant, 58 received Lemborexant, and 740 served as controls.

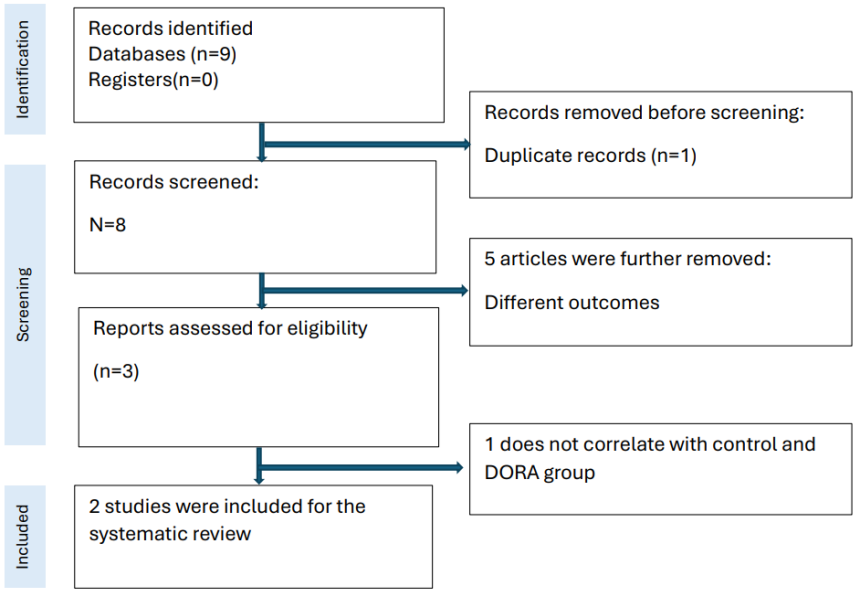

Figure 2. Flow diagram of selection process of the studies

The study by Matsuoka et al. (2022) was performed in an advanced emergency and critical care center. Patients who were treated with DORA after admission were defined as the DORA group, while patients who did not receive DORA or were treated with DORA after the onset of delirium were defined as the control group.

The study by Matsuoka et al. (2023) focused on patients undergoing oral intubation and ventilator management. Those who received either Suvorexant or Lemborexant were classified as the DORA group, while the control group consisted of patients who did not receive DORA.

Participants

The study by Matsuoka et al. (2022) was a single-center retrospective study including patients aged 18 years and above admitted to the emergency center. Kaplan–Meier curves were plotted, and log-rank tests were performed to compare outcomes between patients with and without DORA treatment.

The study by Matsuoka et al. (2023) was also a single-center retrospective study including patients aged greater than 18 years who were admitted to the emergency room and received ventilator support. The hazard ratio (HR) with 95% confidence interval (CI) for delirium development in patients receiving DORA was estimated using a Cox proportional hazards model.

Setting

The two studies included in this review were conducted in an advanced emergency and critical care center at Saga University in Japan.

Outcomes

The primary outcome evaluated in the study by Matsuoka et al 2023 involving critically ill adult patients requiring ventilatory support with tracheal intubation showed that 15 patients in the DORA group developed delirium, compared to 163 in the control group. In another aspect of Matsuoka et al 2022 research on delirium prevention in critically ill adults,

the primary endpoint indicated that 28 patients in the DORA group developed delirium, while 208 patients in the control group did.

Risk of bias in included studies

The assessment of risk bias by the reviewers in summarized in Figure 2.

Publication bias

The included studies exhibited substantial risk of bias across several domains, including random sequence generation, allocation concealment, and blinding, as evidenced by standard risk-of-bias assessment because both studies were retrospective studies. However, the funnel plot displayed was less likely in the included studies.

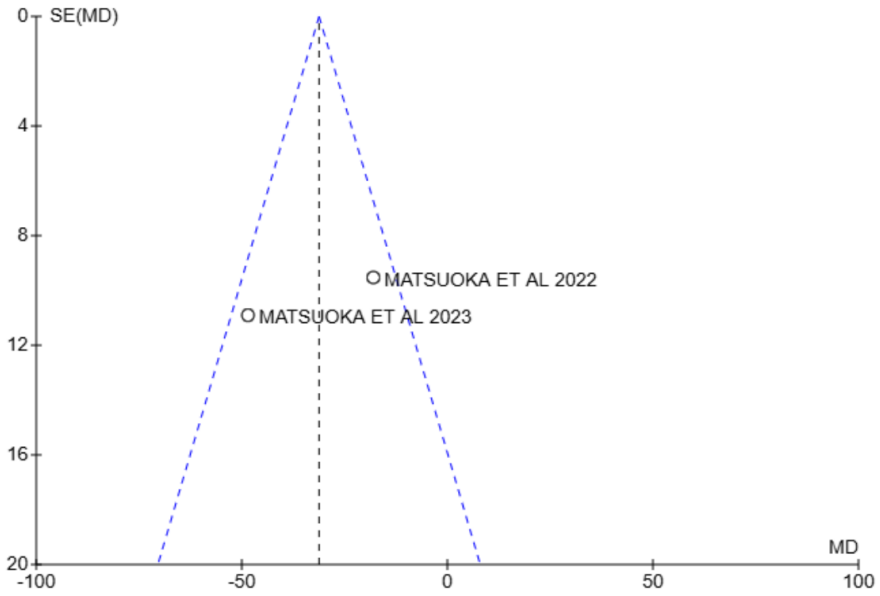

Figure 3. Dora at the end point and risk bias

Effect of interventions

For the comparison of DORA group vs Placebo in the study of Matsuoka et al 2022 and Matsuoka et al 2023. Nine hundred thirty patients were pooled from 2 studies indicated that the incidence of delirium could be reduced, the forest plot showed that Dora could reduce the incidence of delirium (95% CI, P<.0001). The Chi square suggests a strong association or effect, indicating that the observed data significantly differ from what would be expected under the null hypothesis.

Discussion

Suvorexant and Lemborexant decrease the incidence of delirium in critically ill patients) with a 95% confidence interval and a p-value of less than 0.0001). Our findings are consistent with a meta-analysis conducted by Shu Xu et al in 2020 which evaluated the efficacy and safety of suvorexant in preventing delirium in high-risk populations Their study showed that suvorexant can enhance sleep quality and reduce delirium incidence in at-risk populations. To my knowledge this is the first meta-analysis which included Lemborexant in the analysis.

Implications

Based on the findings, suvorexant and Lemborexant show potential in mitigating the risk of delirium by enhancing sleep and cognitive function. However, additional research is necessary to better understand their effectiveness and role in this context. Their application should be part of a broader strategy for delirium prevention that incorporates environmental and behavioral interventions.

AUTHORS' CONCLUSION

This systematic review aims to investigate the use of agents like suvorexant and Lemborexant in hospitalized patients to prevent delirium. It emphasizes the need for a more detailed examination of each medication individually, as the study did not distinguish between their effects. Furthermore, comparisons between dual orexin receptor antagonists (DORAs) and other non-dominant agents, such as benzodiazepines and antipsychotics, were not conducted, which could have clarified therapeutic recommendations. There is a significant need for newly designed prospective randomized controlled trials to confirm these findings. Additionally, further validation of adverse effects is required, particularly regarding hospital outcomes like patient length of stay in both intensive care and general wards, as well as the duration of mechanical ventilation. This should be accomplished through rigorously designed prospective RCTs.

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Declaration of Competing interest

NONE

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