Current Neuropharmacology, 2022, *20,* 1956-1968

SYSTEMATIC REVIEW ARTICLE

Melatonin Receptor Agonists for the Prevention of Delirium: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: ***Background***: Although a previous review illustrated the efficacy of melatonin receptor agonists (MRAs) in preventing delirium, some recent randomized controlled trials (RCTs) did not confirm these effects.

***Objectives*:** This study systematically reviewed the efficacy, acceptability, and tolerability of MRAs for delirium prevention.

***Materials and Methods*:** We searched electronic databases, including Scopus, PubMed, CINAHL, and Controlled Trials Register, from their inception to February 20, 2022. The primary efficacy outcome was delirium incidence rate after MRA administration; relative risks (RRs), overall discontinuation, and discontinuation due to adverse events are also presented.

***Results*:** The overall pooled incidence rates of delirium in MRA-treated and placebo-treated groups were significantly different with RR (95% CI)=0.66(0.52, 0.84,), I^2=59%. Similarly, the incidence rate was significantly lower in the melatonin-treated group than in the placebo-treated group [RR (95% CI) =0.65 (0.49, 0.88), I^2=65%]. Unfortunately, incidence rates were not significantly different between ramelteon-treated and placebo-treated groups [RR (95% CI) =0.67 (0.42, 1.08), I^2=50%]. The pooled incidence rate of delirium in either melatonin or ramelteon-treated groups was not significantly different from the placebo-treated group in elderly patients. The pooled incidence rate of delirium was significantly lower in the melatonin-treated group than in the benzodiazepine-treated group.

***Conclusion*:** Based on this review, melatonin could prevent delirium with a small effect size. However, ramelteon did not show efficacy in preventing delirium. Additionally, neither melatonin nor ramelteon individually showed effectiveness in preventing delirium in elderly patients. Therefore, using MRAs to prevent delirium in clinical practice should be cautious. However, future well-defined and large sample size studies could verify these findings.

ARTICLE HISTORY

Received: July 26, 2021
Revised: February 10, 2022
Accepted: April 19, 2022

DOI:
10.2174/1570159X20666220507024219

Keywords: Melatonin receptor agonist, melatonin, ramelteon, delirium, prevention, incidence.

1. INTRODUCTION

Delirium is common among hospitalized patients [1]. A previous review of medical inpatients has illustrated that prevalent and incident rates of delirium range from 10 to 31 and 3 to 29%, respectively [2]. Previous evidence has promised numerous causes of delirium, particularly in medical conditions [3-5]. Delirium has also been associated with higher morbidity rates, including accidental falls, postoperative complications, increased length of hospitalization, functional decline [6-8] and mortality [8]. Additionally, the disturbing behaviors related to delirium such as agitation [9], psychotic symptoms [10], and sleep-wake cycle reversal [11] are often found in those patients. As a result, clinical attention and rapid intervention are necessary for these patients.

The optimal intervention is the removal of its causes. Unfortunately, the numerous causes of delirium are not usually determined, or some are identified after hospitalization for several days. Although some causes of delirium could be removed in some patients, the symptoms gradually disappear over a week. Although antipsychotics effectively treat delirium symptoms, patients may encounter adverse events from these medications [4, 12]. Prevention of delirium may decrease morbidity and mortality in high-risk patients.

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1875-6190/22 $65.00+.00

Several methods have been proposed to prevent delirious occurrences in hospitalized patients. Based on non-pharmacological approaches, the multicomponent approach removes any risk factors in each patient. It has shown some efficacy, such as anesthesia protocols, assessment of bowel/bladder functions, early mobilization, improved nutrition and hydration, medication review, pain management, sleep enhancement, oxygen supplement, cognitive orientation, and vision /hearing aids [13]. However, since some risk factors cannot be removed, an alternative method could benefit. Previous studies have attempted to use certain antipsychotics to prevent delirium in some settings. Although these medications can reduce symptoms of delirium, patients may risk side effects from such antipsychotics. Therefore, an effective pharmacological agent with a low risk of adverse events would benefit these patients.

Exogenous melatonin agonists such as melatonin and ramelteon are commonly used to treat insomnia. Their mechanism involves melatonin receptors, including melatonin 1 and 2 receptors [14]. Several randomized controlled trials (RCTs) of melatonin receptor agonists (MRAs) have recently shown efficacy in preventing delirious occurrences [15-30]. Unfortunately, the outcomes have varied across studies. Although a previous review displayed the effectiveness of melatonin agonists for preventing delirium [31], the review did not include some studies [16, 20-23, 26] . Additionally, several recent studies have been published [27-29]. For this reason, an updated systematic review and meta-analysis should be conducted.

This study purposefully carried out a systematic review and meta-analysis to determine the efficacy, tolerability, and acceptability of exogenous MRAs to prevent delirium in hospitalized patients. Therefore, this review included only RCTs evaluating exogenous MRAs compared to placebo or other drugs.

2. MATERIALS AND METHODS

2.1. Protocol and Registration

The researchers registered the protocol of this systematic review at the Open Science Foundation (OFS). The present review was organized based on the PRISMA 2009 Checklist, and two reviewers separately accomplished each review task.

2.2. Eligibility Criteria

Each eligible RCT met the following inclusion criteria: i) conducted with hospitalized patients; ii) administered an exogenous MRA for the prevention of delirium occurrence; iii) compared to placebo or other medications, and iv) reported the incidence of delirium or dropout rates after receiving those medications or placebo.

2.3. Information Sources

We searched the Scopus, PubMed, CINAHL, and Cochrane Library databases from their inception to February 20, 2022. No language limitation was applied, and we also searched the reference lists of relevant studies and systematic reviews.

2.4. Searches

This study applied the search terms [(melatonin) OR (ramelteon) OR (tasimelteon) OR (agomelatine) OR (TIK 301) OR (melatonin receptor agonist)] AND (delirium) in all databases. However, the specific strategic search for each database was as follows.

CINAHL: [(melatonin) OR (ramelteon) OR (tasimelteon) OR (agomelatine) OR (TIK 301) OR (melatonin receptor agonist)] AND (delirium) Filters: Randomized Controlled Trials.

Cochrane Library: [(melatonin) OR (ramelteon) OR (tasimelteon) OR (agomelatine) OR (TIK 301) OR (melatonin receptor agonist)] AND (delirium) Filters: Trials.

PubMed: [(melatonin) OR (ramelteon) OR (tasimelteon) OR (agomelatine) OR (TIK 301) OR (melatonin receptor agonist)] AND (delirium) Filters: Randomized Controlled Trial.

Scopus: [(melatonin) OR (ramelteon) OR (tasimelteon) OR (agomelatine) OR (TIK 301) OR (melatonin receptor agonist)] AND (delirium) Filters: Randomized Controlled Trial.

2.5. Study Selection

After the duplicated records were removed, the acquired titles and abstracts individually collected from the electronic database searches were evaluated by two reviewers (NM and BM). When the full-text versions of the relevant studies were collected, the two reviewers independently examined the study for eligibility. If disputes between reviewers occurred, a consensus was used for decision-making.

2.6. Data Collection Process

NM and BM individually extracted the data by using a data record form. When disagreements occurred, a conclusion was reached by consensus of the two reviewers.

2.7. Data Items

The collected data included i) the data related to the eligibility criteria, ii) first author and year of publication; iii) trial duration; iv) participant characteristics in each treatment arm, including the number of participants and mean age (SD); iv) exogenous MRA and the dose of each drug; v) a placebo and other comparators with their doses; vi) incidence rate of delirium for each treatment arm; and vii) overall dropout rates in each treatment arm.

2.8. Risk of Bias Within Individual Trials

NM and BM independently evaluated the risk of bias based on the Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias assessment consisted of evaluating sequence generation (randomization), allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting, and other biases [32].

2.9. Summary Measures and Methods of Analysis

Efficacy, acceptability, and tolerability were the interesting results. The incidence rate of delirium measured the efficacy. According to the previous meta-analysis, this review estimated acceptability based on the overall discontinuation rate [33], and tolerability was calculated by discontinuation rate due to adverse events [34]. We calculated relative risks (RRs) to compare incidence and dropout rates across

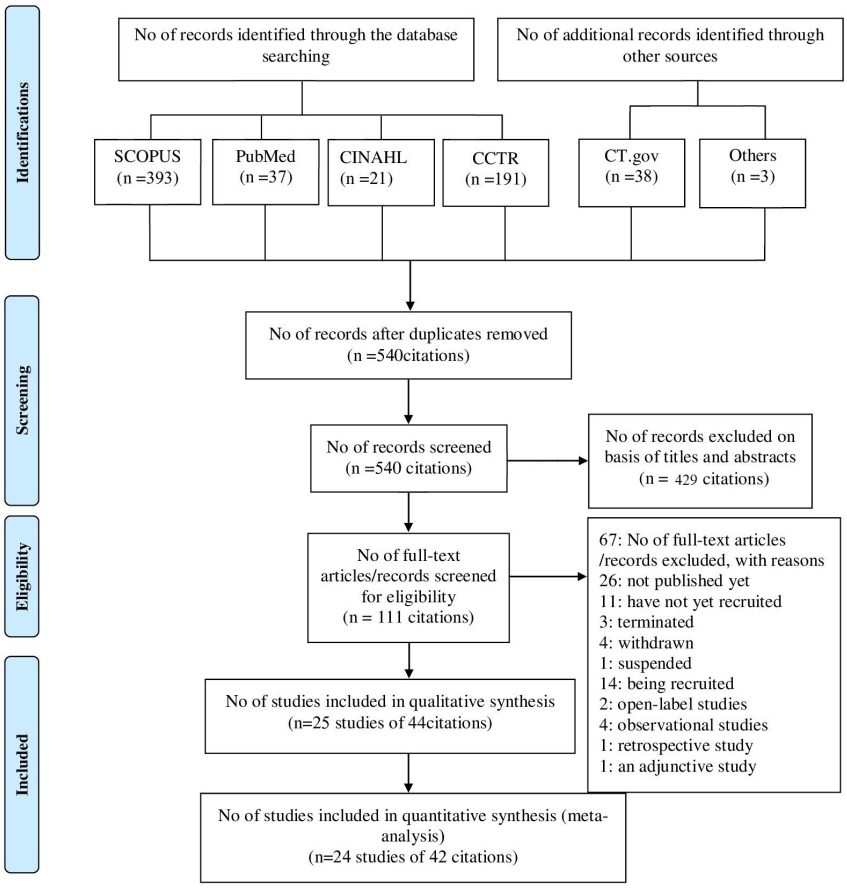

Fig. (1). Flow diagram of the study. **Abbreviations:** CCTR, Cochrane Controlled Trials Register; CT, Clinical Trials.

melatonin-treated and placebo-treated groups. Relative risk (RR) is the probability of an event occurring in the exposed group versus the event occurring in the non-exposed group. For example, the relative risk of developing an incident of delirium (event) in the MRA group (exposed group) versus Placebo group (non-exposed group) would be the probability of developing an incident of delirium for the MRA group divided by the probability of developing delirium for the placebo group. The relative risk does not provide any information about the absolute risk of the event occurring, but rather the higher or lower likelihood of the event in the exposure versus the non-exposure group. The RR that was more than 1 suggested a higher incidence rate of delirium with exogenous MRA than with placebo. The RR that was less than 1 suggested a lower incidence rate of delirium with exogenous MRA than with placebo. Similarly, the RR of dropout rates of more than 1 indicated more significant dropouts following exogenous MRA than placebo administration.

2.10 Statistical Analysis and Synthesis of Results

All dichotomous data were synthesized thoroughly using RRs with 95% confidence intervals (95% CI). If the RR is precisely one, it illustrates that the outcome does not differ between the treatment and the control groups. When RR is more or less than one, it indicates that the treatment, respectively, possibly increases or decreases the risk of the outcomes. All pooled RRs with 95% CIs were calculated using the Mantel–Haenszel method [32]. A summary of effects for all outcomes in this review was applied using either fixed or random effect models based on homogeneity across the included studies. Heterogeneity was estimated using I^2 statistics [35], and a funnel plot was applied. A random-effect model was applied when heterogeneity was 50% or more. Synthesis of all outcomes was accomplished using RevMan 5.4.1.

2.11. Risk of Bias Across Studies

We assessed the risks of bias across studies using the Cochrane Risks of Bias scale and Begg's funnel plots test for publication bias [32, 36]. A simple scatter plot of the intervention effect was estimated from each study against a measure of individual study size based on a funnel plot. If the plot resembled a symmetrical inverted funnel, this bias was possibly absent [37].

3. RESULTS

3.1. Study Selection

Six hundred and eighty-three citations were collected from electronic searches of the following databases: SCOPUS=393, PubMed=37, CINAHL=21, Cochrane Controlled Trials Register=191. An additional 41 citations were derived from other sources (ClinicalTrials.gov identifiers=38, reference list of a relevant study=1, [15] hand search=2 [38, 39] (Fig. **1**). After 143 duplicates were removed, 540 citations were chosen based on the title and abstract assessment. Then, 111 citations were retrieved for the full-text evaluation. The

Table 1. The basic characteristics of randomized, controlled trials of melatonin agonists vs. placebo in prevention of delirium.

Study (Author, Year)	Number of Randomized Patients	Age of Subjects (Years)	Study Duration (Days)	Drug/Dose	Diagnostic Criteria	Outcome Measures	Settings	Note
Sultan 2010	203	≥ 65	3	- Melatonin / 5 mg, 2 doses[a,b] - Midazolam / 7.5 mg, 2 doses[a,b] - Clonidine / 100 µg, 2 doses[a,b] - Placebo	AMT score of < 8	- AMT	Surgical ward	- Medications administered at sleep time and 90 min before operation time
Al-Aama 2011	145	≥ 65	Up to 14	- Melatonin / 0.5 mg / night, ≤14 days[c] - Placebo	CAM	- CAM - MDAS	Internal medical ward	- Acute medical care settings
NCT01505465 2012	50	18-90	6	- Melatonin / 0.5 mg / night, 6 days[c] - Placebo	Clinical Assessment	- Clinical Assessment	Surgical ward	- Medications administered at 3 night prior and 3 night post operation of total knee replacement
de Jonghe 2014	452	≥ 65	Up to 8	- Melatonin / 3 mg / night, 5 days - Placebo	DSM-IV-TR	- DSM-IV-TR - DOSS - MMSE	Surgical ward	- Emergent surgical treatment of a hip fracture
Hatta 2014	67	65-89	Up to 7	- Ramelteon / 8 mg / night, 7 days[b] - Placebo	DRS-R-98	- DRS-R-98	ICU or regular acute wards	- Serious medical problems
Yamaguchi 2014	45	≥ 70	4	- Ramelteon / 8 mg /night - Placebo	ICDSC	- ICDSC	N/A	- Total knee arthroplasty
Dianatkhah 2015	137	-	≥ 3	- Melatonin / 3 mg / night ≥ 3 days (until discharge)[b] - Oxazepam / 10 mg / night ≥ 3 days (until discharge)[b]	Clinical observations	- Clinical observations	Surgical ward	- Postoperative condition
Agar 2016	30	≥ 18	Until death or discharge	- Melatonin PR / 2 mg / night, during in inpatient admission[a] - Placebo	DRS-R-98	- DRS-R-98	Acute/subacute inpatient palliative care or oncology facility	- Advanced cancer
NCT(02654314) 2016	277	≥ 65	Up to14	- Melatonin / 5 mg / night , ≤ 14 days - Placebo	Short CAM	- Short CAM	General internal medical ward	- Admission to a general internal medicine service
Vijayakumar 2016	56	18-50	Duration of ICU stay	- Melatonin / 3 mg / night, during in ICU admission - Placebo	CAM-ICU	- CAM-ICU - RASS	N/A	- Organophosphorus compound poisoning
Abbasi 2018	172	> 18	5-8	- Melatonin / 3 mg / night, 6 doses - Placebo	CAM-ICU (Persian version)	- CAM-ICU (Persian version)	ICU	- Critically Ill Patients
Jaiswal 2018	87	65-99	Up to 14	- Melatonin / 3 mg / night, ≤ 14 days[a] - Placebo	CAM	- CAM	Internal medical ward (non-ICU)	-

(Table 1) contd….

Study (Author, Year)	Number of Randomized Patients	Age of Subjects (Years)	Study Duration (Days)	Drug/Dose	Diagnostic Criteria	Outcome Measures	Settings	Note
Kasnavieh 2019	140	40-70	3	- Melatonin / 3 mg /day - Placebo	CAM-ICU	- CAM-ICU	N/A	- Coronary artery bypass grafting
Nishikimi 2018	92	≥ 20	Until discharged from ICU	- Ramelteon / 8 mg / night, during in ICU admission - Placebo	CAM-ICU	- CAM-ICU - RASS	Emergency and medical ICU	- Critical care treatment
Gupta 2019	100	> 65	3	- Ramelteon / 8 mg / 12 hours and 1 hour before surgery - Placebo	CAM	- CAM	Surgical ward	- Undergoing surgery
Jaiswal 2019	120	≥ 18	Up to 7	- Ramelteon / 8 mg / night, ≤ 7 days - Placebo	CAM-ICU	- CAM-ICU - RASS	PTE ward	- Elective PTE surgery
Ford 2020	210	≥ 50	Up to 7	- Melatonin / 3 mg / night, 7 days - Placebo	CAM	- CAM - MDAS	Surgical ward	- Coronary artery bypass grafting and/or valve replacement
Gandolfi 2020	206	> 18	Up to 7	- Melatonin / 10 mg / day at 8 PM - Placebo at 8 PM	ICDSC≥ 4	- ICDSC - RCSQ	ICU	-
Hussein 2020	180	60-85	9	- Melatonin Sleep Patch (7 mg) / 5 doses[c] - Rivastigmine patch (4.6 mg) / 5 doses[c]	CAM	- CAM - RASS	Orthopaedic surgical ward	- Medications administered at 24 hours preoperation, the morning of operation and 3 successive days of postoperation - Postoperative condition
Komazaki 2020	50	18-119 months	45–60 min before induction	- Remelteon / 0.1mg / kg - Placebo	PAED	- PAED	Inpatients	- Tonsillectomy under general anesthesia
Lawlor 2020	60	≥ 18	Up to 28	- Ramelteon / 3 mg / night, ≤ 28 days[d] - Placebo	CAM	- CAM - CGR - MDAS - Nu-DESC - SOMCT	Palliative care unit	- Advanced cancer
Oh 2021	80	≥ 65	3	- Ramelteon / 8 mg / night, 3 days - Placebo	CAM	- CAM - DRS-R-98	Surgical ward	- Joint replacement
Shi 2021	297	> 60	Up to 7	- Melatonin / 3 mg / day - Placebo	CAM	- CAM - CAM-ICU	ICU	- PCI
Singla 2021	135	3-8	30 minutes	- Melatonin 0.3 mg / kg - Midazolam 0.3 mg / kg - Placebo	Watcha scale ≥3	- Watcha scale	PACU	- Emergence of delirium after medicating with melatonin, midazolam, and a placebo
Zadeh 2021	60	≥ 30	3	- Melatonin PR / 3 mg / day in evening[e] - Placebo	CAM-ICU	- CAM-ICU - MDAS	N/A	- Coronary artery bypass grafting

Abbreviations: AMT, Abbreviated Mental Test; CAM, Confusion Assessment Method; CGR, Clinician Global Rating of delirium severity; DOSS, Delirium Observation Screening Scale; DRS-R-98, Delirium Rating Scale-Revised 98; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICDSC, Intensive Care Delirium Screening Checklist; ICU, Intensive care units; MDAS, Memorial Delirium Assessment Scale; MMSE, Mini-Mental State Examination; N/A, Not available; NCT, National Clinical Trial; Nu-DESC, Nursing Delirium Screening Scale; PACU, postanaesthesia care unit; PAED, Paediatric Anaesthesia Emergence Delirium; PR, Prolonged-release; PCI, percutaneous transluminal coronary intervention; PTE, Pulmonary thromboendarterectomy; RASS, Richmond Agitation-Sedation Scale; RCSQ, Richards Campbell Sleep Questionnaire; SOMCT, Short Orientation Memory Concentration Test.

[a]Administered at sleep time, [b]90 minutes before operative time in 1 day, [c]administered Rivastigmine and Melatonin patches to the patient 24 hours preoperatively, on the morning of the operation, and then every day postoperatively for the following 3 successive days, [d] administered sublingually or *via* a gastrostomy tube, [e]administered 3 mg of melatonin in the evening before operation and on the morning of surgery and continued 3 mg/day until the second postoperative day.

67 citations were eliminated from this review since twenty-six were not published, [40-65] eleven did not recruit subjects [66-76] three were terminated [77-79], four were withdrawn [80-83] one was suspended [84] fourteen were recruiting [85-98] two studies were open-label trials, [99, 100] four were observational studies, [101-104] one study was a retrospective study [105], and one study evaluated dexmedetomidine plus melatonin [106]. As a result, 44 citations of 25 studies were included for qualitative synthesis in this review [15-20, 30, 41, 107-119]. However, only 24 studies could be included for quantitative synthesis [15-30, 113, 120-124].

3.2. Study Characteristics

The treatment duration in most of the included studies varied from 3 to 28 days or until the patients were discharged or had died. However, one study was carried out in the first 30 minutes of post-anesthesia care unit [121]. The MRAs in the included trials included melatonin and ramelteon. Delirium in eligible studies was evaluated by standardized delirium rating scales, except for one study in which clinical observations of trained nurses [19] assessed delirium. However, the diagnostic criteria for delirium were various due to the different treatment settings (for example, medical-surgical wards and ICUs). We included 3451 patients and compiled the basic characteristics of eligible RCTs, as shown in Table **1**.

3.3. Risk of Bias Within Studies

Fig. (**2**) displays the risk of bias summary. Most included studies had various risks of bias. However, four studies had a low risk of selection, performance, detection, reporting, and other biases [17, 24, 26, 27]. However, intention-to-treat analysis was described in nine studies [17, 24-27, 29, 120, 123, 124].

3.4. Synthesis of Results

3.4.1. Efficacy

3.4.1.1. Melatonin Receptor Agonists versus Placebo

Significant heterogeneity in the MRA-treated versus placebo-treated group comparisons was noted regarding the pooled incidence rate of delirium. The overall pooled incidence rate of delirium in the MRA-treated group was significantly lower than that in the placebo-treated group, with an RR (95% CI) of 0.66 (0.52, 0.84) (I^2=59%). Similarly, the incidence rate in the melatonin-treated group was significantly less than that in the placebo-treated group [RR (95% CI)=0.65 (0.49, 0.88), I^2=65%]. Unfortunately, the incidence in the ramelteon-treated group was not significantly different from that in the placebo-treated group [RR (95% CI)=0.67 (0.42, 1.08), I^2=50%] (Fig. **3**). In the elderly population, although the delirium incidence rate of the MRA-treated groups was significantly less than placebo-treated groups, [RR (95% CI) of 0.53 (0.28, 0.99) (I^2=67%)], the incidence rates in melatonin and ramelteon-treated groups individually were not significantly different from the placebo-treated group (Fig. **4**).

3.4.1.2. Melatonin Receptor Agonists versus Benzodiazepines

Three previous studies comparing the efficacy of melatonin preventing non-withdrawal delirium with benzodiazepines (midazolam [15, 121] and oxazepam [19] were identified. Significant heterogeneity in the melatonin-treated versus benzodiazepine-treated group comparison was not found regarding the pooled incidence rate of delirium. The overall pooled incidence rate of delirium in the melatonin-treated group was significantly lower than that in the benzodiazepine-treated group, with an RR (95% CI) of 0.39 (0.24, 0.63) (I^2=22%) (Fig. **5**)

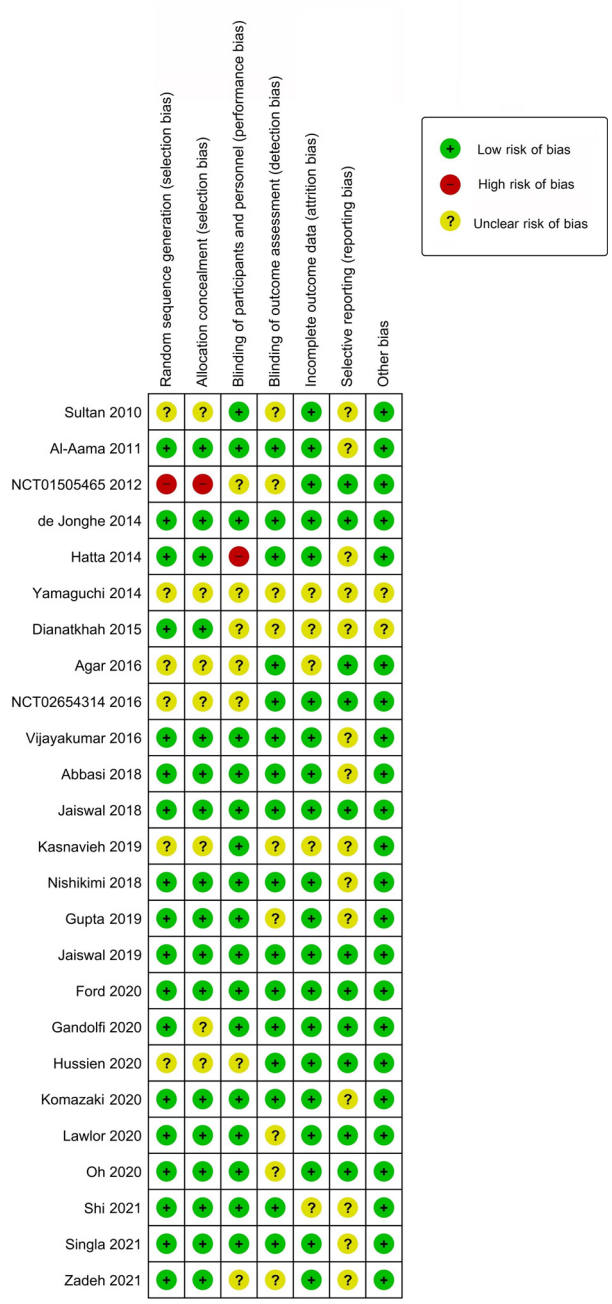

Fig. (2). Summary of risk of bias in randomized, controlled trials of melatonin receptor agonists.

3.4.1.3. Melatonin Receptor Agonists versus Other Medications

Based on two studies with elderly patients, one study compared the efficacy of melatonin and clonidine [15], and

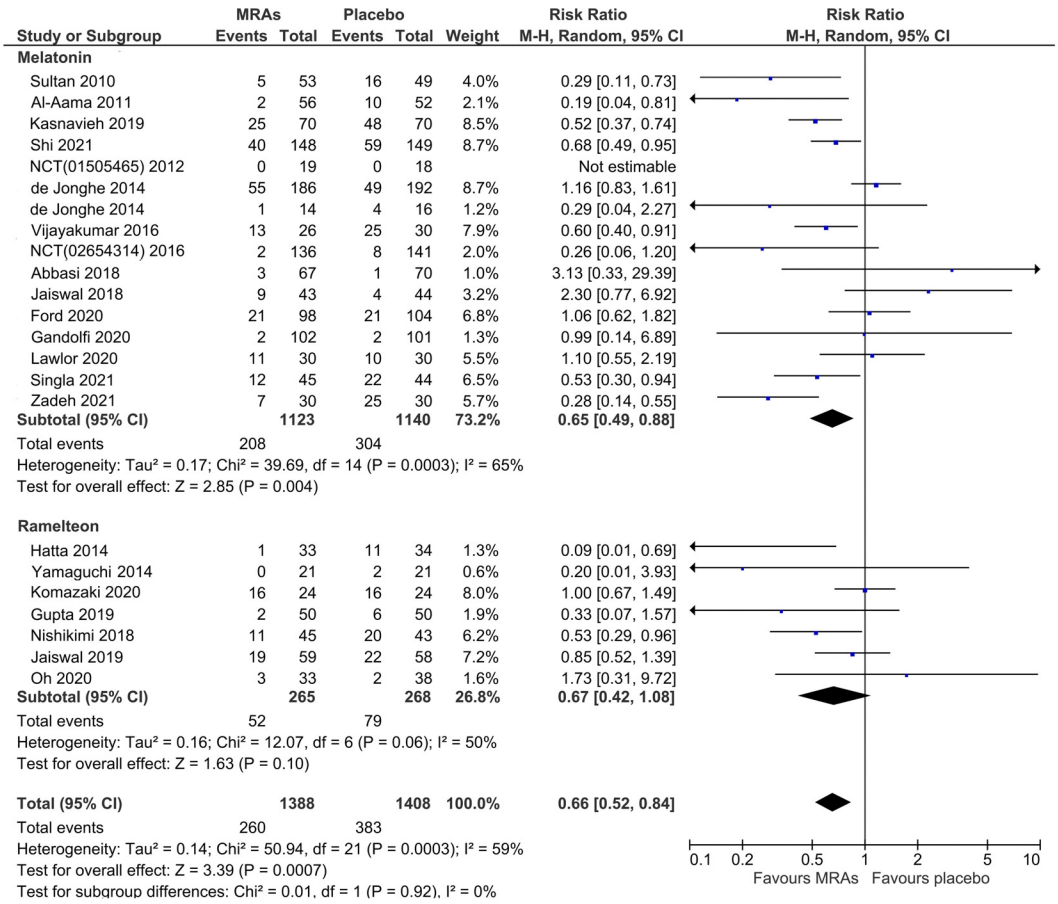

Fig. (3). The forest plot of comparison of the incidence of delirium (95% confidence interval) of melatonin receptor agonists *vs*. the placebo.

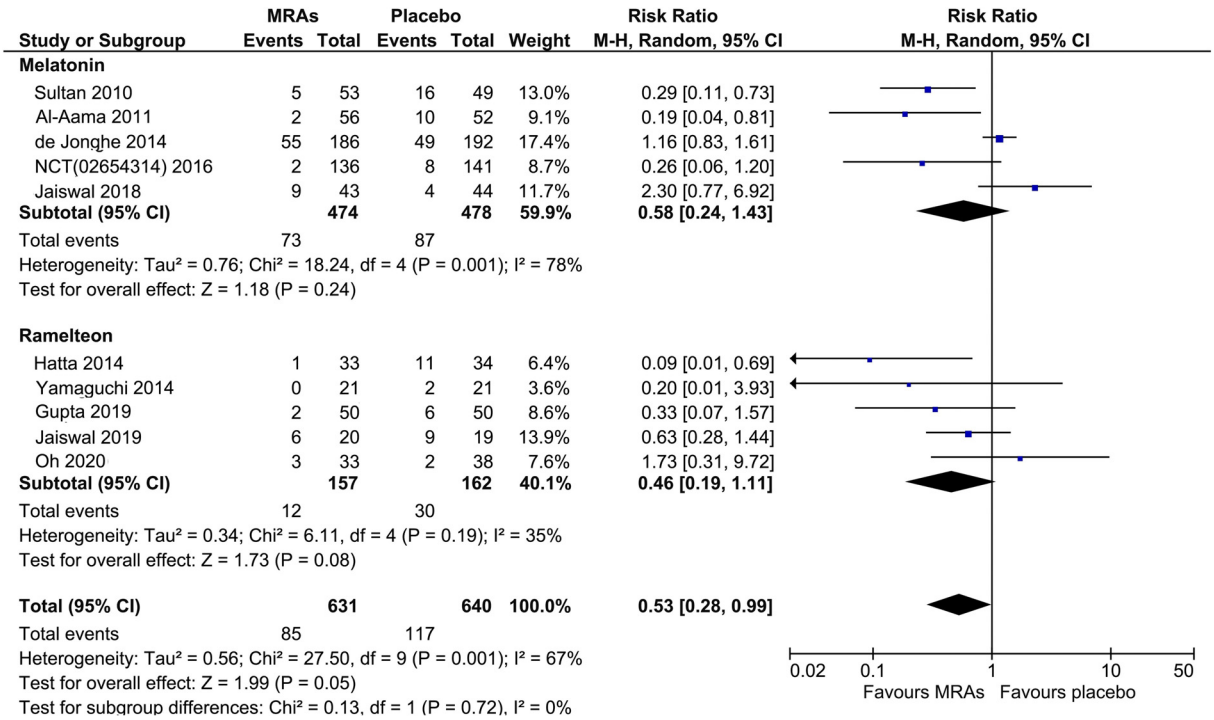

Fig. (4). The forest plot of comparison of the incidence of delirium (95% confidence interval) of melatonin receptor agonists *vs*. the placebo in elderly patients.

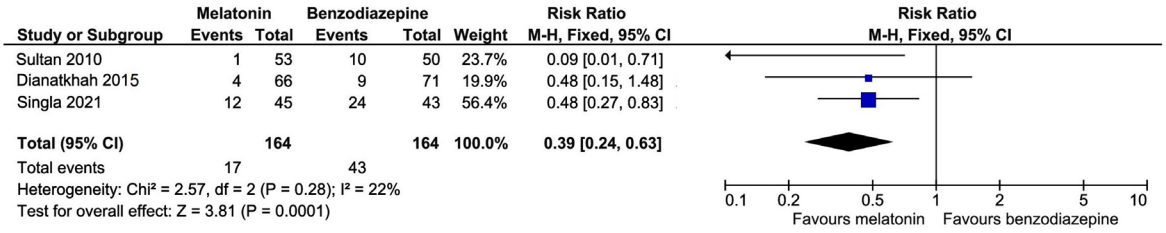

Fig. (5). The forest plot of comparison of the incidence of delirium (95% confidence interval) of melatonin agonists *vs*. benzodiazepines.

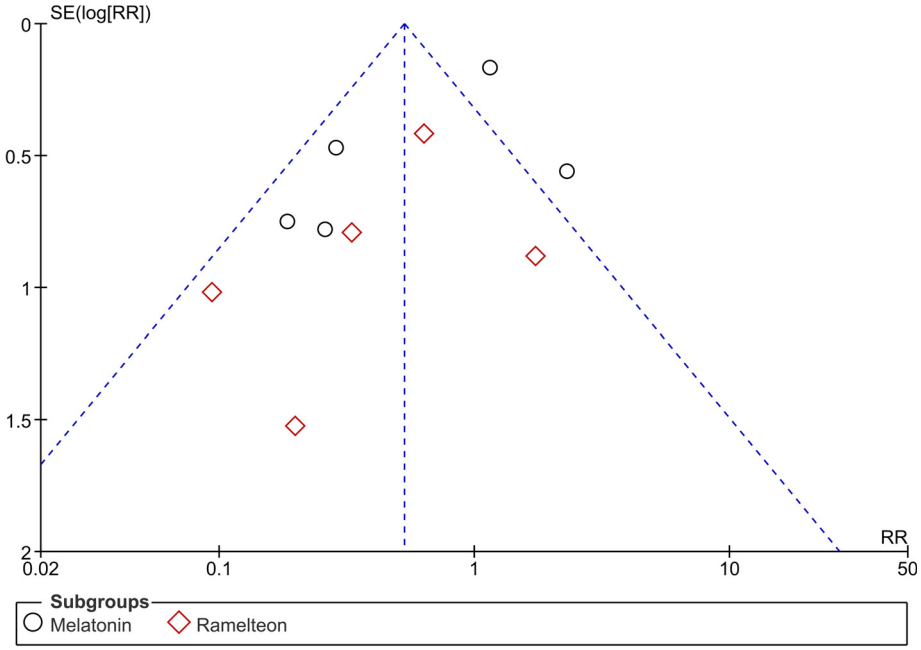

Fig. (6). The funnel plot of risk difference in delirium occurrence between melatonin receptor agonists and the placebo.

another compared the efficacy of melatonin sleep patches (7 mg) and rivastigmine patches (4.6 mg) [38]. One study suggested that the melatonin-treated group had a significantly lower incidence of delirium than the clonidine-treated group [15]. However, another study displayed a significantly greater incidence of delirium in the melatonin sleep patch group than in the rivastigmine patch group [38].

3.4.2. Discontinuation Rates

3.4.2.1. Overall Discontinuation Rate (Acceptability)

Based on the MRAs *versus* placebo comparisons for delirium prevention, the heterogeneity was insignificant regarding the overall discontinuation rate. Thus, the pooled overall discontinuation rates between MRA-treated and placebo-treated groups were comparable [RR (95% CI) of 1.07 (0.73, 1.56), I^2=33%].

3.4.2.2. Discontinuation Rates Due to Adverse Events (Tolerability)

Discontinuation from the study due to adverse events was not described in any of the included trials.

3.4.3. Risk of Bias across Studies

Based on the symmetry of a funnel plot for the overall incidence rate of delirium noted, publication bias was less likely to have occurred (Fig. **6**).

4. DISCUSSION

Based on the present review, MRAs could prevent the occurrence of delirium. Considering each MRA, melatonin (but not ramelteon) displayed the effect of preventing delirium compared to the placebo. Unfortunately, neither melatonin nor ramelteon illustrated their effects for preventing delirium in elderly populations. Based on little evidence, melatonin had more efficacy than clonidine and benzodiazepine but less efficacy than rivastigmine in preventing delirium. The discontinuation rates, acceptability, and tolerability of MRAs were comparable to the placebo.

Previous systematic reviews have illustrated the benefit of melatonin in preventing delirium compared with the placebo [31, 125]. Although the overall effect of melatonin on the prevention of delirium was consistent with previous studies, their effect sizes were small in the present review [31, 125]. Unfortunately, Ramelteon did not display this effect. Therefore, only melatonin can be used to prevent delirium in clinical practice. However, further studies could clarify the present results. Additionally, non-pharmacological interventions such as multimodal approaches emphasizing the removal of delirium risk factors may be alternative or adjunctive methods for preventing delirium [126].

The effect of MRAs on the prevention of delirium also varied compared to the effects of other agents. The findings

possibly suggest that benzodiazepines may not effectively prevent delirium, which is concordant with a previous study with benzodiazepines that did not illustrate its efficacy in treating non-withdrawal delirium [127]. Additionally, benzodiazepine may deteriorate the symptoms of delirium since it could interfere with the patients' cognition [127]. The present review suggested that melatonin appears to be more efficacious than clonidine in preventing delirium. Similarly, previous evidence illustrated that clonidine had no efficacy in treating delirium [128]. The outcomes imply that the pathophysiology of delirium related to autonomic nervous system activity alterations is still controversial. Based on one study, the present review found that rivastigmine appeared to be more efficacious in prevention than melatonin, which is compatible with a previous epidemiological study of rivastigmine in delirious patients [129]. Since few studies were included in the present review, these outcomes may be inconsistent. Therefore, further studies could clarify these findings.

In elderly patients, a previous review illustrated the efficacy of melatonin for preventing delirium [130]. The positive outcome reported in the last review may have resulted from the inclusion of two observational nonrandomized studies [131, 132]. Unfortunately, the updated outcome in the present review, which included only RCTs, did not illustrate the efficacy of either melatonin or ramelteon as superior to that of placebo. Hence, the use of melatonin to prevent delirium in the elderly population should be considered in the context of risks and benefits. While waiting for further large sample studies for delirium prevention in elderly patients, a non-pharmacological approach such as a multimodal method may be favorable.

Previous studies have suggested that MRAs are tolerable in the treatment for delirium prevention, which is compatible with the present review. However, their acceptability was not better than the placebo. Consequently, using MRAs in patients should be closely monitored for adherence.

Some limitations were found in the present review. Since the initial measurement of delirium used in each eligible study varied, the outcomes across individual studies may have varied. Finally, a limited number of eligible studies compared melatonin agonists and other agents.

CONCLUSION

Based on the present review, melatonin could prevent delirium with a small effect size. However, ramelteon did not show efficacy in preventing delirium. Additionally, neither melatonin nor ramelteon individually showed effectiveness in preventing delirium in elderly patients. Although the acceptability was not superior to the placebo, patients tolerated melatonin well. Therefore, the use of melatonin in clinical practice should be cautious. However, further well-defined and large sample size studies should be conducted to verify these findings.

AUTHORS' CONTRIBUTION

All the authors conceptualized the idea, developed the review protocol, prepared the manuscript for publication, and affirmed its current form. NM and BM searched for articles from the databases, extracted the data, and analysed the data. BM and SK are joint first authors who contributed equally to this paper.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines were followed for the study.

FUNDING

This study was partially supported by a grant from Chiang Mai University in Chiang Mai, Thailand (grant number 15/2565). However, the funding source was not involved in the study design, data collection, data analysis, data interpretation, manuscript preparation, and the decision to submit this article for publication.

CONFLICT OF INTEREST

BM has received speaker's honoraria from *SERVIER* (*Thailand*) Limited and *Pfizer* (*Thailand*) Limited. MS has received speaker's honoraria from Lundbeck A/G, Janssen (Thailand), and Sumitomo Dainippon Pharmaceuticals in the last three years.

ACKNOWLEDGEMENTS

AJE edited this article. The authors would like to thank the Faculty of Medicine at Chiang Mai University in Thailand for their immense support and help during this project. The authors would like to thank Ms. Prapinpatch Maneeton for drawing the graphical abstract.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available on the publisher's website along with the published article.

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