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Comparative efficacy and acceptability of pharmacological interventions for the treatment and prevention of delirium: A systematic review and network meta-analysis

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ABSTRACT

We performed a network meta-analysis to build clear hierarchies of efficacy and tolerability of pharmacological interventions for the treatment and prevention of delirium. Electronic databases including PubMed, Google Scholar, Embase, Cochrane Central Register of Controlled Trials, PsycINFO, and MEDLINE were searched published up to February 22, 2019. A total of 108 randomized controlled trials (RCTs) investigating pharmacotherapy on delirium were included for analysis, and the strength of evidence (SoE) was evaluated for critical outcomes. In terms of treatment, quetiapine (low SoE), morphine (low SoE), and dexmedetomidine (moderate SoE) were effective in the intensive care unit (ICU) patients. In terms of prevention, dexmedetomidine (high SoE) and risperidone (high SoE) significantly reduced the incidence of delirium in ICU surgical patients, while ramelteon (high SoE) reduced the incidence of delirium in ICU medical patients. Despite the efficacy, dexmedetomidine and risperidone demonstrated higher drop-out rate (moderate to high SoE). Haloperidol and other antipsychotics, except for quetiapine and risperidone, showed no benefit. None of the agents showed benefit in non-ICU patients. In conclusion, dexmedetomidine may be a drug of choice for both treating and preventing delirium of the ICU and postsurgical patients. However, it may be less tolerable, and side-effects should be adequately managed. Current evidence does not support the routine use of antipsychotics. For medical patients, oral ramelteon might be useful for prevention.

1. Introduction

Delirium is an acute decline in attention and cognition, which can develop over a short period of time and fluctuate during the course of the day (Inouye, 2006). The risk of developing delirium can be up to 30 percent in older medical patients (Inouye et al., 1998) and 30–50 percent in surgical and intensive care unit (ICU) patients (McNicoll et al., 2003; Salluh et al., 2015). Delirium may result in adverse clinical outcomes such as increased mortality, increased length of hospital stays, iatrogenic complications, readmission, and dementia (Jackson et al., 2016). Even after adjusting for confounding factors, delirium itself can be an independent marker for mortality (Robinson et al., 2009; Salluh et al., 2015).

Numerous randomized head-to-head trials tried to find optimal treatment and prevention medication for delirium. To date, over 27 medical agents and combinations were studied, and this quantity of interventions now far exceeds the capacity of a clinical trial, which normally can compare up to 2 to 4 arms simultaneously. Network meta-analysis (NMA) is especially feasible to identify efficacy and safety hierarchy of such numerous interventions. Recent NMA by Wu et al.

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(2019) concluded that haloperidol plus lorazepam might be the best treatment and ramelteon the best preventive medicine for delirium (Wu et al., 2019). Although they carried out a thorough analysis, the study was challenged for its potentially misleading conclusion and its overlook of multifactorial etiologies and the impact of different clinical settings of delirium (Neerland et al., 2019). Therefore, we conducted a new and updated NMA of 108 RCTs to consider different clinical settings and etiologies of delirium and incorporate a large number of new RCTs. Furthermore, when discussing safety issues, we included tolerability (all-cause discontinuation) and specific drug-related side effects to discuss each intervention more in-depth.

2. Methods

2.1. Data sources and searches

We searched PubMed, Google scholar, Embase, Cochrane Central Register of Controlled Trials, PsycINFO, and MEDLINE for randomized controlled trials (RCTs) published up to February 22, 2019 that evaluated the prevention and treatment effects of pharmacotherapy on delirium. We also screened an abstract database of international conferences to acquire the latest data, with a preference for English and other languages that could be translated to English. The identified review articles' reference lists were also reviewed to search for additional articles that may not have been indexed.

2.2. Study selection

A diverse spectrum of pharmacotherapy interventions which have been applied for either the prevention or treatment of delirium was included in the present NMA, including antipsychotics, anesthetics, and sedatives. Studies which were not randomized or quasi-randomized, focused on adolescence (< 18 years old), were related to delirium from alcohol withdrawal, or involved patients with cognitive impairment or dementia were excluded.

2.3. Data extraction and quality assessment

The study search and data extraction were independently conducted by 2 authors (MS Kim and HC Rhim). The main article and supplementary materials were reviewed to extract relevant information that we specified previously. Any discrepancy encountered during this process was resolved by consensus or by the intervention of a third party, including a corresponding author (C Han). Cochrane PICO (Patient, Population or Problem; Intervention; Comparison; and Outcome) components (Higgins and Green, 2011) were identified with consensus among the authors and reviewed literature adhering to the PICO consensus. To avoid duplication, we extracted data only from the latest follow-up research if they were published with an identical or overlapping pool. The risk of bias of individual study was assessed by three researchers using the Cochrane guidance tool (Higgins and Green, 2011), and the strength of evidence (SoE) of critical outcomes were estimated using the AHRQ framework (Berkman et al., 2013) as done in previous systematic reviews (Vemulapalli et al., 2015; Drucker et al., 2018; Balk et al., 2019). We defined critical outcome as those with the greatest relevance to decision making about the use of active drugs for treating or preventing delirium. Strength of evidence (SoE) evaluates potential biases of outcomes including small sample size effect, unrealistically large or small odds ratio with extended 95% confidential interval, high risk of bias of individuals studies composing each outcome, inconsistency between direct and indirect evidence, and several other reporting biases. Each result is graded into insufficient, low, moderate, and high SoE after considering potential evidence deficiencies (Berkman et al., 2013). A comparison-adjusted funnel plot was constructed to assess publication bias (Chaimani et al., 2013).

2.4. Data synthesis and analysis

For treatment analysis, we considered the response rate, defined as the resolution of delirium symptoms, as a primary outcome. Studies from ICU, PCU (palliative care unit), and non-ICU (general ward/medical inpatient) settings were analyzed separately in the treatment analysis. However, as most of the studies investigated treatment agents on mixed patient pools (surgical and medical), separate treatment analysis for surgical versus medical patients was not feasible. On the other hand, we extracted the incidence of delirium as the primary outcome for prevention analysis. Prevention analysis was also conducted for ICU versus non-ICU (general ward/medical inpatient) settings. Since most studies investigated prevention agents on individual surgical or medical patients, we further provided separate prevention analysis for surgical versus medical patients. Diagnosis of delirium was done by Confusion Assessment Method (CAM), Intensive Care Delirium Screening Checklist (ICDSC), Diagnostic and Statistical Manual of Mental Disorders (DSM), Delirium Rating Scale (DRS), and their modifications by the study investigators.

The secondary outcomes included tolerability (all-cause discontinuation or drop-out rate), in-hospital mortality (median 30 days), after-discharge mortality (three months to five years), length of ICU stay (days), duration of delirium (hours), and safety profile of individual drug-related side-effects. We evaluated tolerability of active drugs with all-cause discontinuation or drop-out rate since loss of follow-up and withdrawal from medication reflect both severe adverse events and lack of efficacy (Cipriani et al., 2018; Slee et al., 2019). The definitions of individual drug-related side effects were adhered to each author's classification, and they are presented in the Appendix.

We initially conducted pairwise meta-analysis using a random-effect model. The effect estimation was the standardized mean difference (SMD) for continuous variables and odds ratios (OR) for dichotomous variables, both with 95% confidential intervals (CI). Statistical heterogeneity was estimated using Higgins I^2 statistics and the Cochran Q test (Higgins and Thompson, 2002). A two-sided p-value of less than 0.05 was regarded as statistically significant.

We conducted random-effects NMA within a frequentist framework using the STATA (Stata Corp, College Station, TX, US, version 15.0) and R (version 3.5.1) software (Xu et al., 2018). We duplicated the results by analyzing an identical data set independently in the two different software packages and cross-checked whether the results are comparable to minimize error. Indirect and mixed comparison were accomplished through the mvmeta command and self-programmed routines of STATA (Chaimani et al., 2013; Shim et al., 2017), and the netmeta package of R (Neupane et al., 2014). The pooled estimation of the effect size for network meta-analysis was presented in SMD for continuous outcomes and OR for dichotomous outcomes with a 95% CI. When a continuous variable is presented in the median (interquartile range), it was converted to a mean (standard deviation) by calculation (Hozo et al., 2005; Wan et al., 2014). We used the restricted maximum likelihood method to evaluate heterogeneity, assuming a common heterogeneity variable for all comparisons (the tau value)(Lumley, 2002), and computed I^2 and its 95% CI. Global inconsistencies between direct and indirect comparisons were evaluated using a design-by-treatment model (Caldwell and Ades, 2010; Higgins et al., 2012). Local inconsistencies were assessed by a loop-specific approach for every closed triangular or quadratic loop and by a node-splitting method (Caldwell and Ades, 2010; Shim et al., 2017; Xu et al., 2018). The net heat plot was constructed using the netmeta package of R (version 3.5.1) to visualize the inconsistency matrix and detect specific comparisons which contribute to large inconsistencies (Krahn et al., 2013). The rank of effect estimation for each treatment was investigated using the surface under the cumulative rank curve (SUCRA) of STATA (Salanti et al., 2011) and P rank score of R (Rücker and Schwarzer, 2015).

Prespecified subgroup and sensitivity analyses were performed to determine whether the results were affected by the patient

characteristics. The primary outcomes were sub-grouped into different patient pools (medical versus surgical patients), different clinical settings (ICU, PCU, and non-ICU), and administration routes (intravenous route injection versus oral administration) since these factors can substantially affect the outcome. A sensitivity analysis was also conducted by restricting the analyses to studies with post-cardiac surgery and anesthetic interventions to evaluate the effects of potential factors.

This study is registered with PROSPERO, number CRD42019123811.

3. Results

Overall, 3,691 citations were identified and further screened by prespecified inclusion and exclusion criteria. Among this list, 1,116 article abstracts were reviewed and 149 studies were eligible for full-text review. With the exclusion of 41 studies, 108 RCTs, published up to February 2019, were finally included in our NMA. Out of the 108 RCTs, 24 (1,846 patients) investigated the treatment of delirium, while 84 RCTs (28,089 patients) investigated the prevention of delirium, with one study presenting both treatment and prevention data. All reference list of included studies is presented in supplementary appendix. The mean study sample size was 83 participants (ranging from 15 to 376 patients) for treatment analysis and 322 participants (ranging between 18 and 7,507 patients) for prevention analysis. The median duration of follow-up for delirium incidence or resolution was seven days (ranged from 8 h to 30 days). The median duration of follow up for in-hospital mortality was 30 days (ranged from 21 days to 45 days), and the after-discharge mortality was six months (ranged from three months to five years). These data are included in the background table in Appendix (pp.10–53). The risk of bias for studies involved in primary outcomes was generally low (Appendix pp.156–241).

For both pairwise meta-analysis and NMA, the primary outcomes of treatment and prevention efficacy presented no evidence for heterogeneity (I^2) in general. For secondary outcomes in NMA, continuous variables, including the length of ICU stay and duration of delirium, were highly heterogeneous perhaps due to different follow-up periods and discharge protocols of each study. Inconsistency, which represents disagreement between direct and indirect comparisons, was also assessed for primary and secondary outcomes. No evidence of global inconsistency was observed for all outcomes. Local inconsistency estimation by the loop-specific approach and node-splitting method detected one loop inconsistency in the duration of delirium.

Fig. 1 shows PRISMA flow of the search process, and Fig. 2 presents the network of eligible comparisons for the treatment and prevention of delirium. Network map in the main body encompasses all agents, and detailed network map for each outcome is presented in the Appendix. Data for the pairwise meta-analysis are shown in the upper right portion of league tables in the Appendix for each outcome. Primary outcome results derived from NMA are presented as forest plots in Figs. 3 and 4 while secondary NMA outcomes are presented in Figs. 5 and 6. The strength of evidence (SoE) varies from low to high as summarized in Table 1.

3.1. Treatment outcomes (response rate)

Quetiapine (OR 8.00, 95% CI 1.41–45.41, low SoE), morphine (OR 3.88, 95% CI 1.18–12.80, low SoE), and dexmedetomidine (OR 2.66, 95% CI 1.05–6.77, moderate SoE) were significantly effective while haloperidol (OR 1.01, 95% CI 0.72–1.44, moderate SoE) and ziprasidone (OR 1.23, 95% CI 0.82–1.84, moderate SoE) were not effective compared to placebo for treating delirium in ICU patients. Lorazepam plus haloperidol significantly resolved the symptoms of delirium in advanced cancer patients in PCU (OR 5.73, 95% CI 1.53–21.51, low SoE). In non-ICU medical inpatient setting, there was no significantly effective drug (Fig. 3).

3.2. Prevention outcomes (incidence of delirium)

Acetaminophen plus dexmedetomidine demonstrated the least incidence of delirium (OR 0.09, 95% CI 0.02–0.55, low SoE), followed by DFP (diazepam plus flunitrazepam plus pethidine)(OR 0.10, 95% CI 0.01–0.96, low SoE), risperidone (OR 0.29, 95% CI 0.13–0.64, high SoE), and dexmedetomidine alone (OR 0.46, 95% CI 0.32–0.66, high SoE) with statistical significance for ICU postoperative patients. Ramelteon (OR 0.28, 95% CI 0.11–0.67, high SoE) was only effective agent for ICU medical patients. There was no effective drug in preventing delirium for non-ICU medical inpatients (Fig. 4).

3.3. Tolerability and mortality

To evaluate the safety profile of each drug, tolerability and mortality were explored. Suvorexant (OR 0.18, 95% CI 0.04–0.89, moderate SoE) demonstrated significantly fewer drop-out rate while risperidone (OR 2.01, 95% CI 1.26–3.20, moderate SoE), dexmedetomidine (OR 1.52, 95% CI 1.00–2.32, high SoE), and ziprasidone (OR 1.45, 95% CI 1.07–1.95, moderate SoE) resulted in higher drop-out rate than that of placebo (Fig. 5). Tolerability of haloperidol was comparable to that of placebo with high SoE. All experimental groups with active drugs showed no difference in in-hospital mortality and after-discharge mortality compared to those of the control group except for risperidone (OR 1.94, 95% CI 1.05–3.56, moderate SoE), which showed no survival benefit at all (Fig. 5).

3.4. Duration of delirium

Dexmedetomidine and acetaminophen plus propofol significantly reduced duration of delirium (hours, SMD -0.56, 95% CI -1.07 to −0.05, moderate SoE and SMD -1.44, 95% CI -2.79 to −0.09, low SoE, respectively), while haloperidol showed no effect with moderate SoE.

3.5. Length of ICU stay

Dexmedetomidine and acetaminophen plus dexmedetomidine shortened the length of ICU stay (days, SMD -0.22, 95% CI -0.41 to −0.04, low SoE and SMD -0.96, 95% CI -1.63 to −0.28, insufficient SoE, respectively) while all other agents including haloperidol (moderate SoE), midazolam (low SoE), and propofol (low SoE) did not alter the length of ICU stay.

3.6. Specific drug-related side effects

When evaluating for cardiac and neurological effects of each drug in depth (Fig. 6), the incidence of bradycardia and hypotension were significantly high in dexmedetomidine group (OR 1.84, 95% CI 1.14–2.96 and OR 1.50, 95% CI 1.15–1.94, respectively, both high SoE). Regarding the adverse events of antipsychotics, QTc-prolongation was significantly more prominent with ziprasidone (OR 1.83, 95% CI 1.04–3.23, low SoE) while extrapyramidal symptoms significantly occurred less with olanzapine (OR 0.19, 95% CI 0.06–0.60, low SoE). Haloperidol did not induce QTc-prolongation and extrapyramidal symptoms with low to moderate SoE.

The results of our overall, subgroup, and sensitivity analysis are reported in the Appendix (pp.146–155). Comparison-adjusted funnel plots for the primary outcomes demonstrated a low probability of publication bias.

4. Discussion

The current consensus is that a one-size-fits-all pharmacologic treatment is unlikely to be of much use as delirium involves multiple underlying mechanisms (Neerland et al., 2019). Discrete treatment and prevention strategies on different clinical setting may reduce a negative

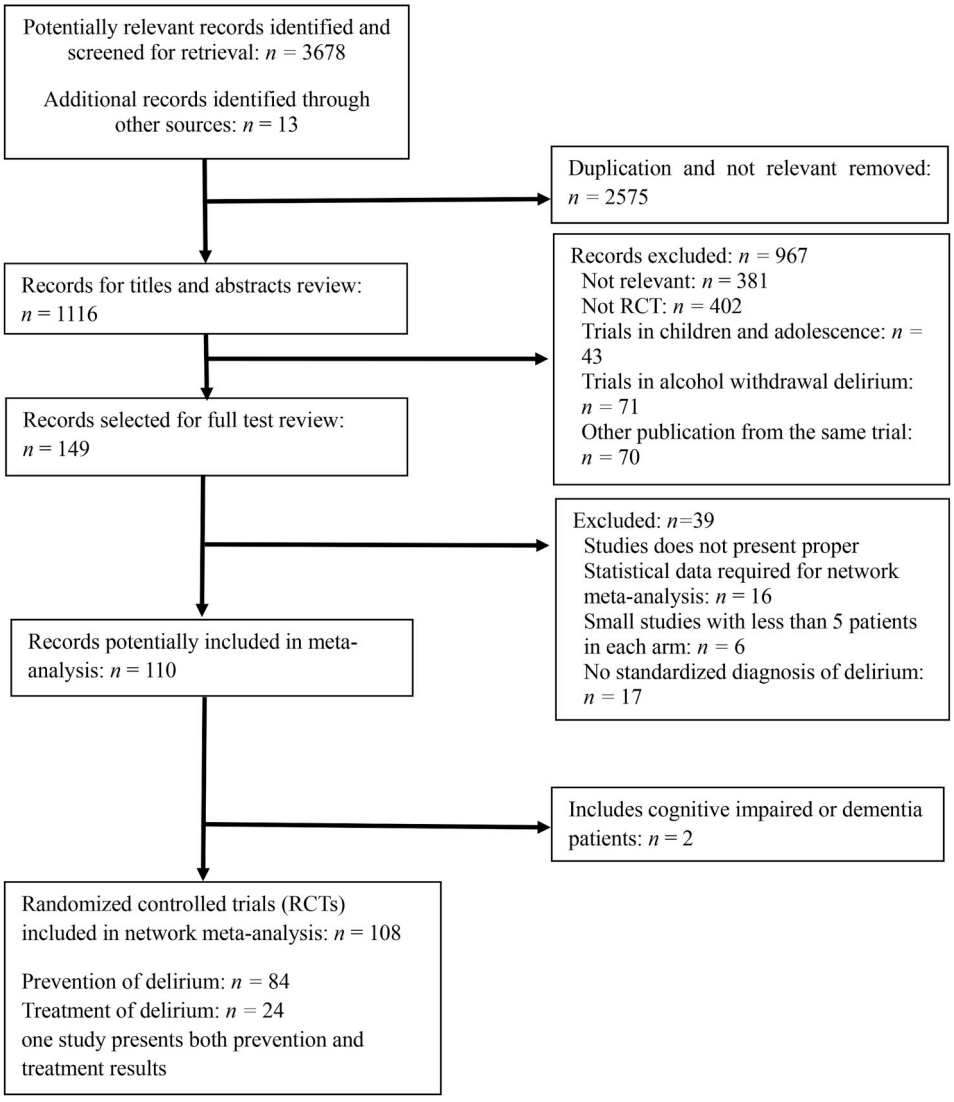


Fig. 1. PRISMA diagram showing selection of articles for pairwise and network meta-analysis.

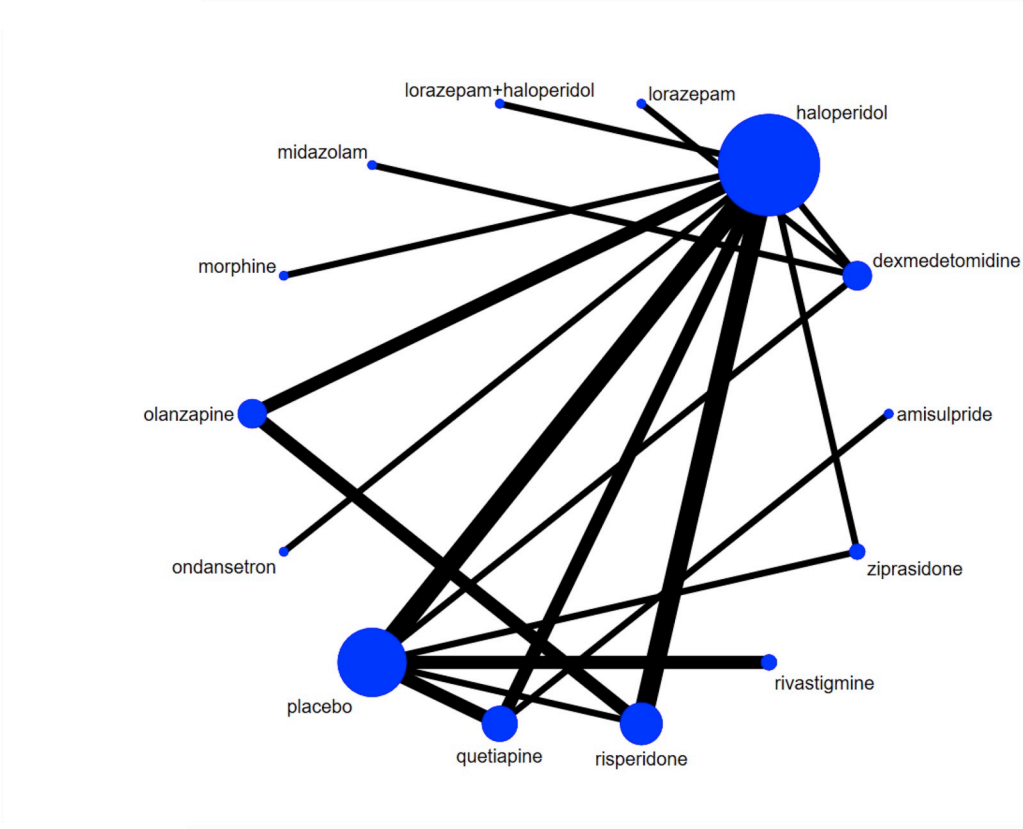
course of delirium, but currently collective evidence for clinical setting-based strategies is absent. To meet this need, we evaluated efficacy and safety profile of pharmacological interventions in each clinical population, and this novel approach justifies our early update of previous NMA by Wu et al.

The present NMA represents the most comprehensive quantitative synthesis for currently available pharmacological interventions for managing delirium as it is the largest up-to-date with 108 RCTs. This is the first NMA to identify potential agents that can be used in preventing and treating delirium for individual clinical setting and to explore drug tolerability, cardiac and neurologic harms, duration of delirium, length of ICU stay, and provide strength of evidence for individual outcomes. Our study revealed that dexmedetomidine is an agent to consider for both treatment and prevention of delirium in ICU and postsurgical patients with moderate to high strength of evidence (SoE). Furthermore, dexmedetomidine significantly reduced the duration of delirium (moderate SoE) and the length of ICU stay (low SoE)(Fig. 5). Despite its efficacy, dexmedetomidine significantly induced hemodynamic instabilities such as bradycardia and hypotension, and these adverse events may explain high drop-out rate of the dexmedetomidine group. In terms of antipsychotics, only second-generation agents, quetiapine and risperidone, showed benefits in treating and preventing delirium, respectively. However, commonly used haloperidol did not show any benefit or harm in both treating and preventing delirium in ICU patients. All antipsychotics did not help to reduce mortality rate, duration of delirium, and the length of ICU stay. For medical patients, oral ramelteon can be convenient and safe alternative over antipsychotics in preventing delirium.

The recent NMA on delirium by Wu et al. (2019) concluded that haloperidol plus lorazepam might be the best treatment and ramelteon the best preventive agent for delirium (Wu et al., 2019). The conclusion was challenged by clinicians as collective evidence suggests ineffectiveness of haloperidol on delirium (Atalan et al., 2013; Girard et al., 2018; Nikooie et al., 2019; Oh et al., 2019), and lorazepam has been shown to be an independent risk factor for delirium (Pandharipande et al., 2006, 2008; Pisani et al., 2009). It is hard to generalize that the pairing of an inefficacious drug and a deliriogenic one would help to treat delirium. Limited biological plausibility and lack of empirical or theoretical support for the combination further resulted in controversy. It is also noteworthy that the beneficial effect of lorazepam plus haloperidol in previous NMA was deduced from a single study with advanced cancer patients in a palliative care unit (PCU) (Hui et al., 2017). While the treatment option for the PCU patients is worthwhile identifying, a specialized patient pool makes it difficult to generalize the result and extrapolate it to diverse clinical settings such as ICU or general wards.

Furthermore, a substantial number of RCTs were published during and after the analysis of Wu et al. For prevention analysis, our NMA

Treatment



Prevention

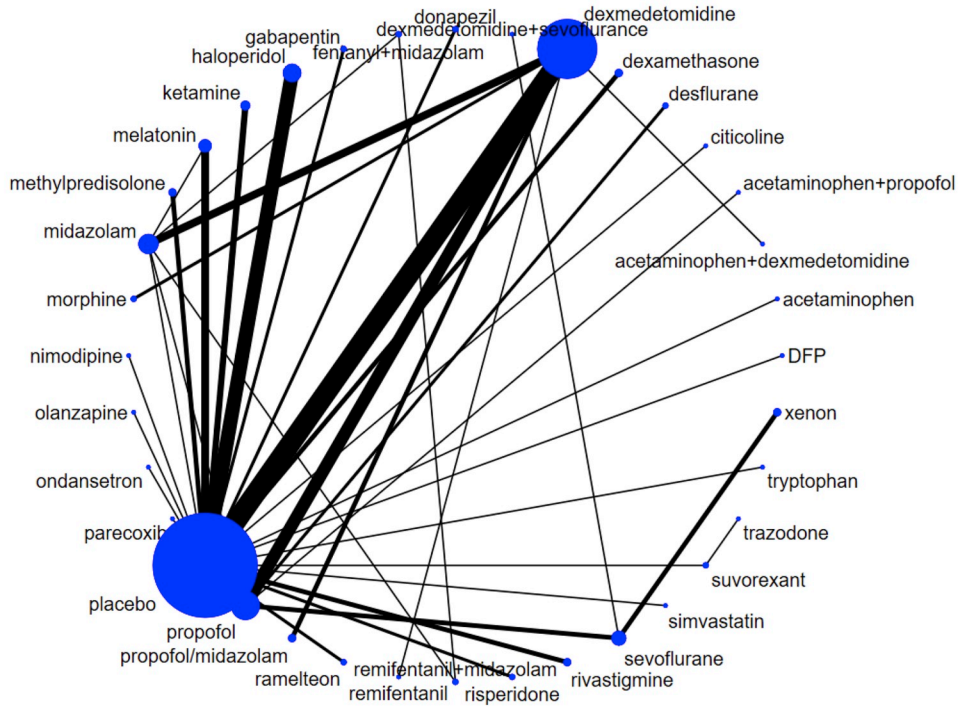


Fig. 2. Network of eligible comparisons for treatment and prevention of delirium Line indicates direct comparison of agents, and the thickness of line corresponds to the number of trials in the comparison. Size of node corresponds to the number of studies that involve the intervention. DFP = diazepam plus flunitrazepam plus pethidine.

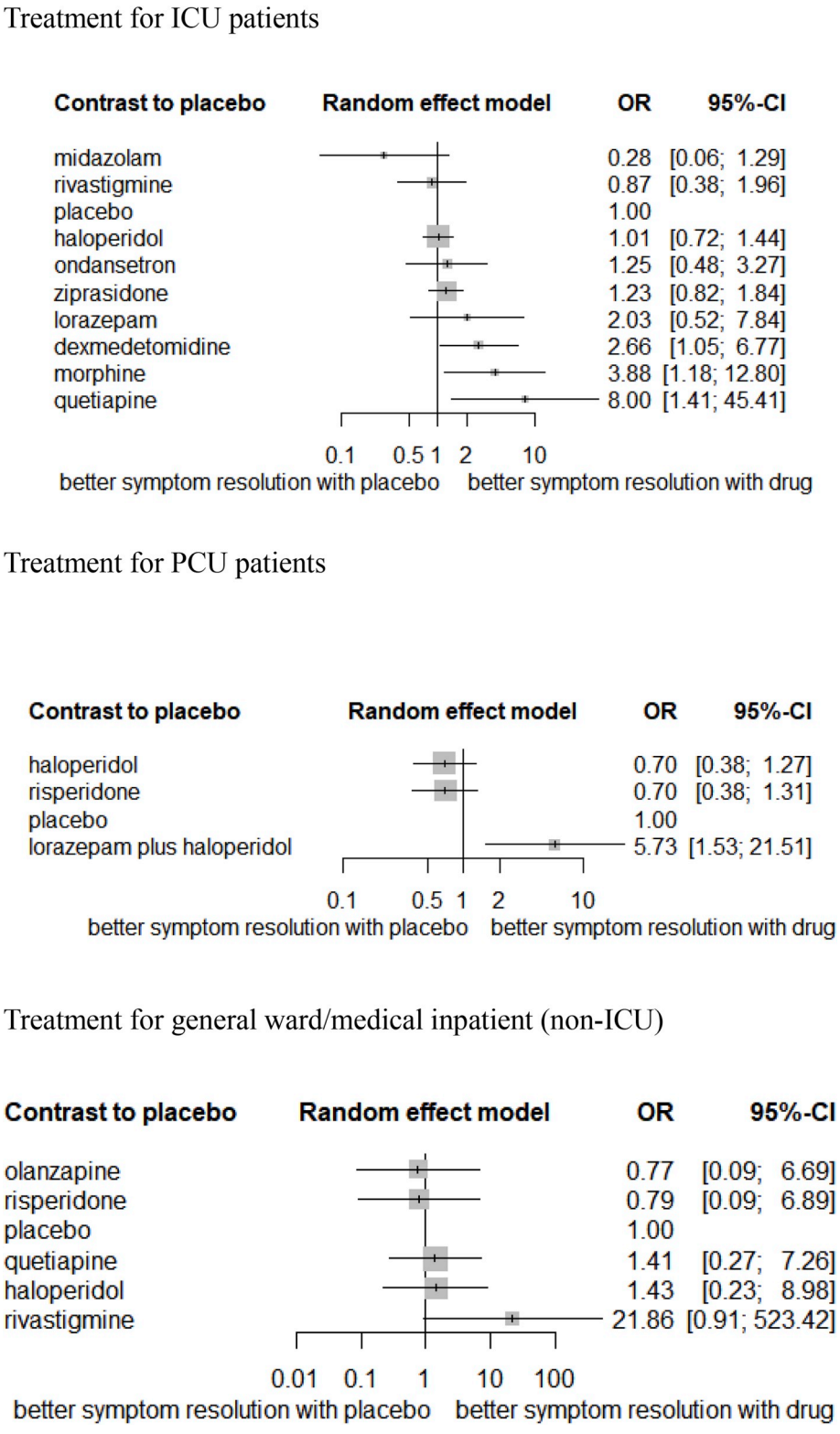
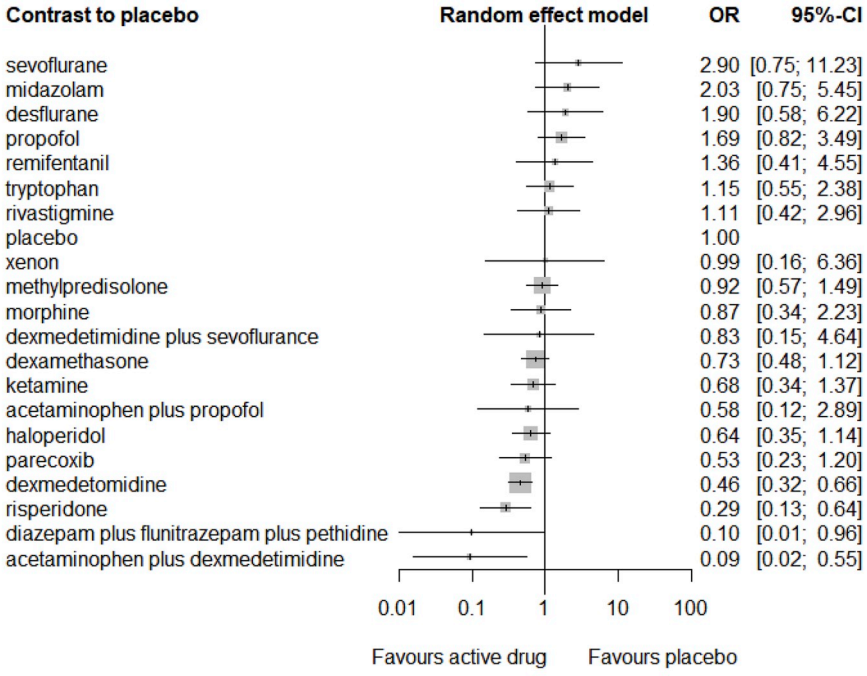


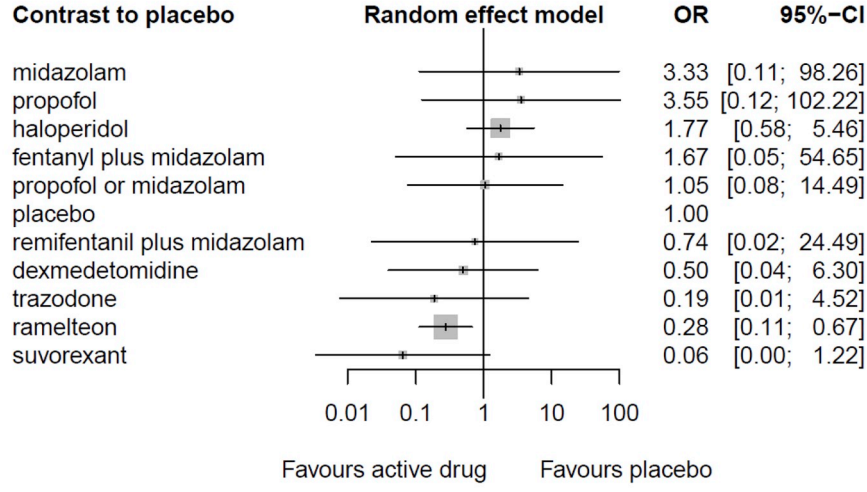
Fig. 3. Network meta-analysis of pharmacological interventions compared with placebo for treatment outcomes (response rate) Effect estimation is presented in odds ratio (OR) with 95% CI. Pharmacological agents are ranked by surface under the cumulative ranking curve (SUCRA) value. ICU = intensive care unit. PCU = palliative care unit.

included 84 RCTs, which doubled the number of studies included in the prevention analysis by Wu et al. These large additional RCTs allowed us to introduce novel results and analyze the efficacy hierarchy of preventive drugs in diverse clinical settings. In terms of treatment analysis, only 4 RCTs were additionally included in our study, and therefore the treatment hierarchy in the overall population demonstrates similar results (Appendix p. 148) to that of Wu et al. with haloperidol plus lorazepam being the primary treatment of choice. To avoid generalized inference derived from the clustering of populations with diverse etiologies and comorbidities, we sub-divided our treatment analysis

Prevention for ICU surgical patients



Prevention for ICU medical patients



Prevention for general ward/medical inpatient (non-ICU)

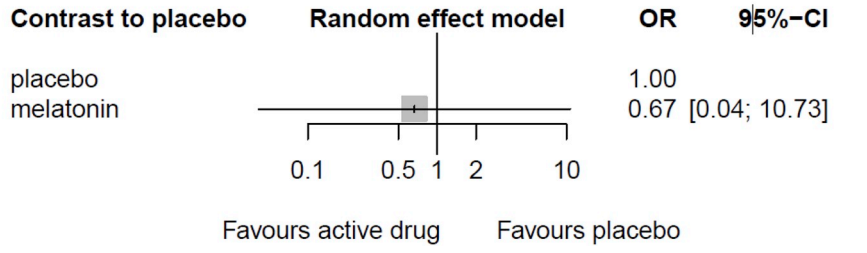
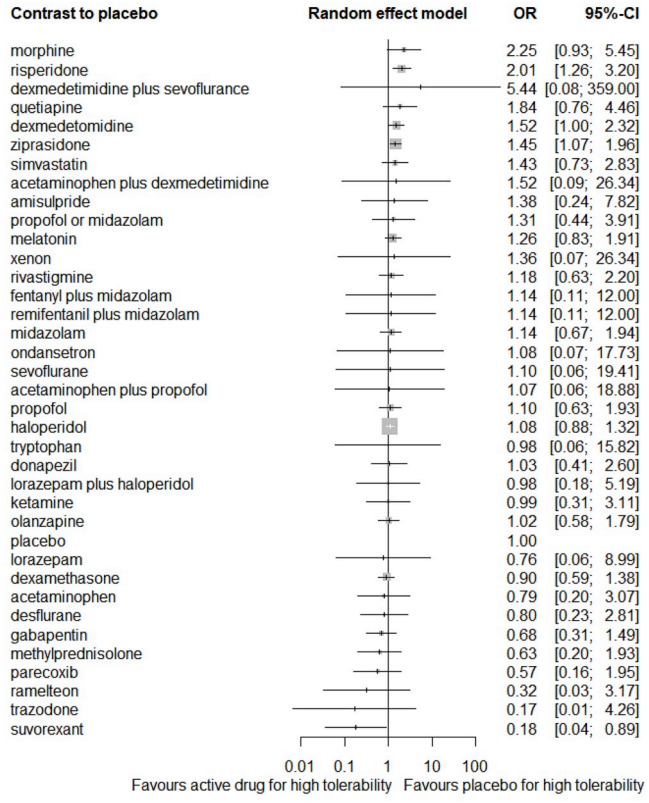
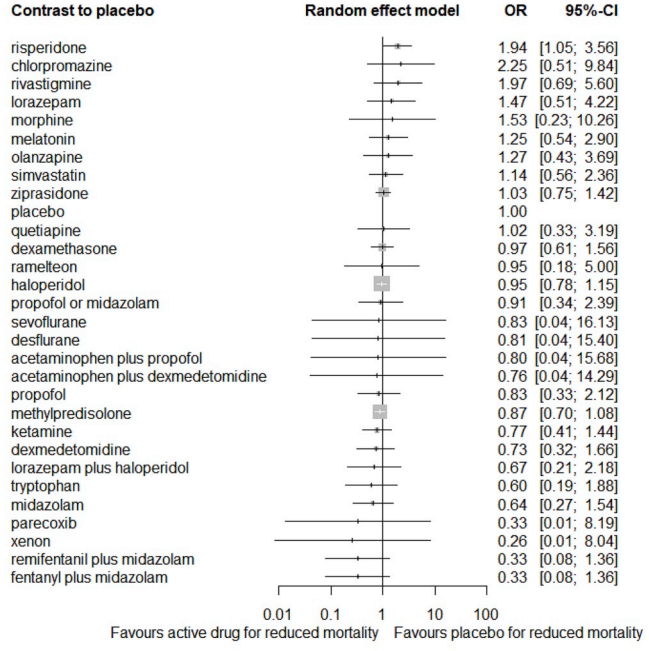


Fig. 4. Network meta-analysis of pharmacological interventions compared with placebo for prevention outcomes (incidence of delirium) Effect estimation is presented in odds ratio (OR) with 95% CI. Pharmacological agents are ranked by surface under the cumulative ranking curve (SUCRA) value. ICU = intensive care unit.

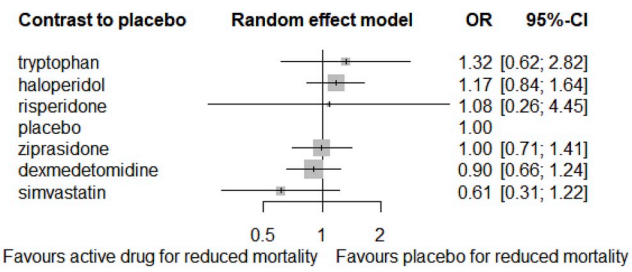
Tolerability (all-cause discontinuation)



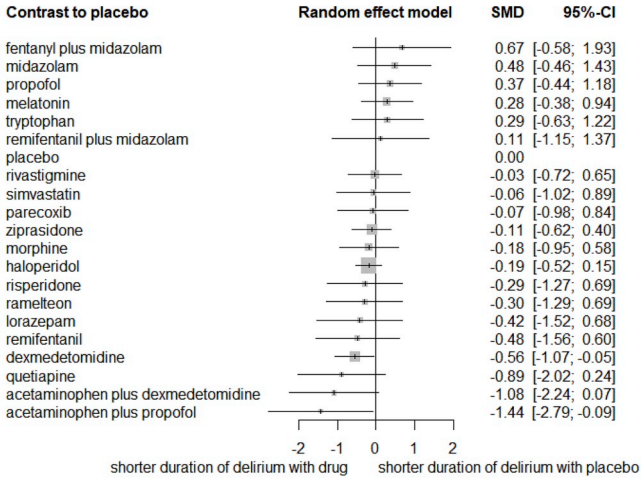
In-hospital mortality (<45 days)



After-discharge mortality (up to 5 years follow up)



Duration of delirium (hours)



Length of ICU stay (days)

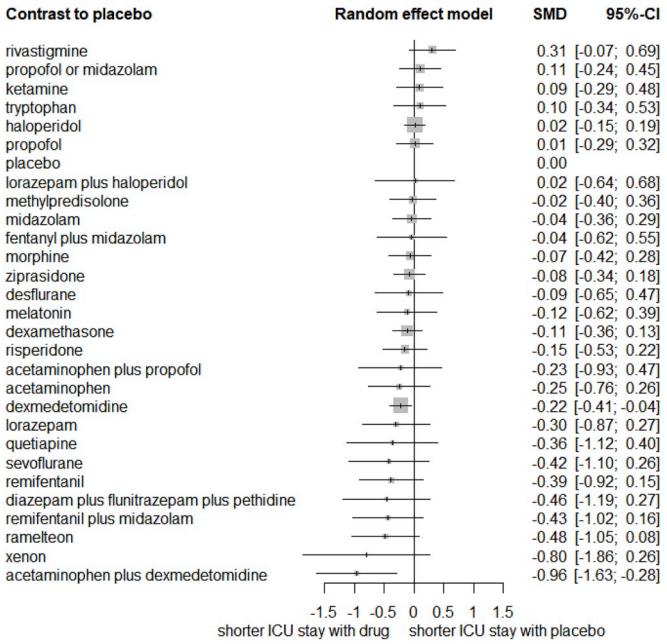


Fig. 5. (*continued*)

Fig. 5. Network meta-analysis of pharmacological interventions compared with placebo for secondary outcomes Effect estimation is presented in odds ratio (OR) or standardized mean difference (SMD) with 95% CI. Pharmacological agents are ranked by surface under the cumulative ranking curve (SUCRA) value.

into the individual clinical setting, as shown in Fig. 3. Since the incidence of delirium differs among patient pools (surgical and medical patients) and clinical settings (ICU, PCU, and general ward or medical inpatients), we postulated that the severity and etiology of delirium may be different among these groups and as is the drug response. Clinical setting-based analysis, in turn, may potentially increase clinical relevance and differentiate our analysis from the previous NMA by Wu et al.

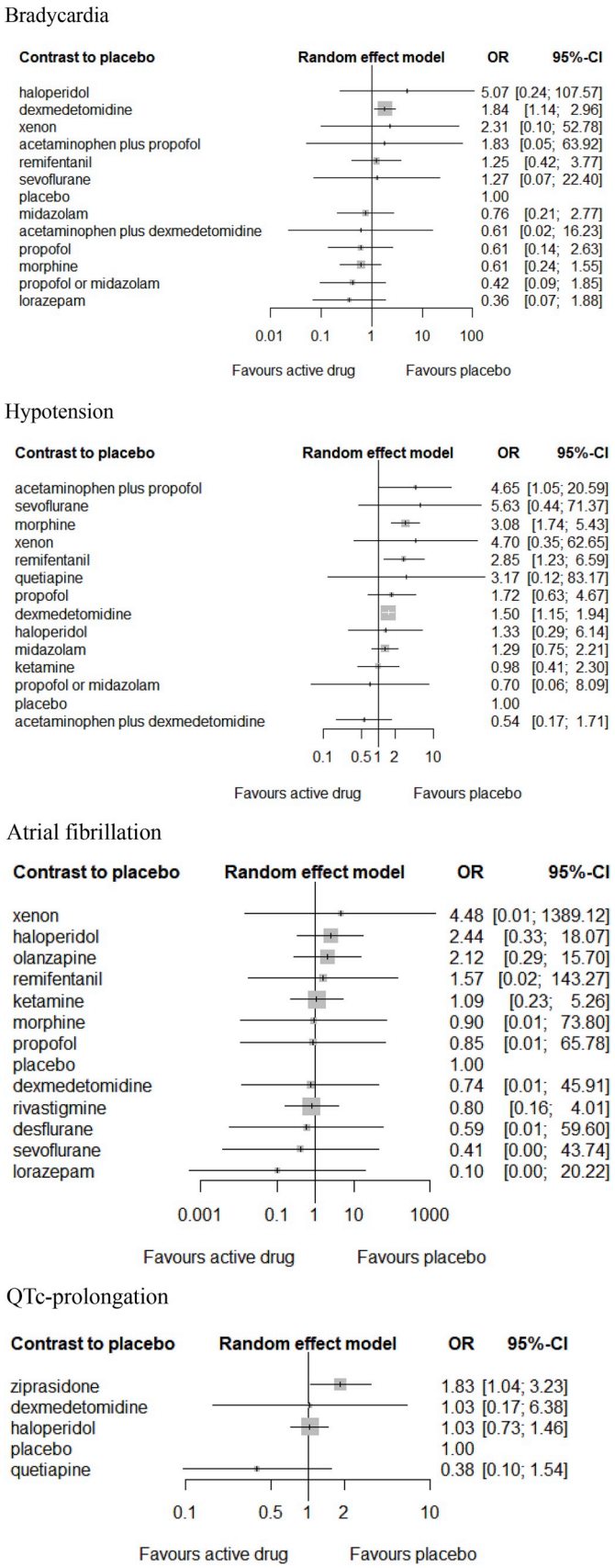


Fig. 6. Network meta-analysis of pharmacological interventions compared with placebo for specific drug-related side effects Effect estimation is presented in odds ratio (OR) with 95% CI. Pharmacological agents are ranked by surface under the cumulative ranking curve (SUCRA) value.

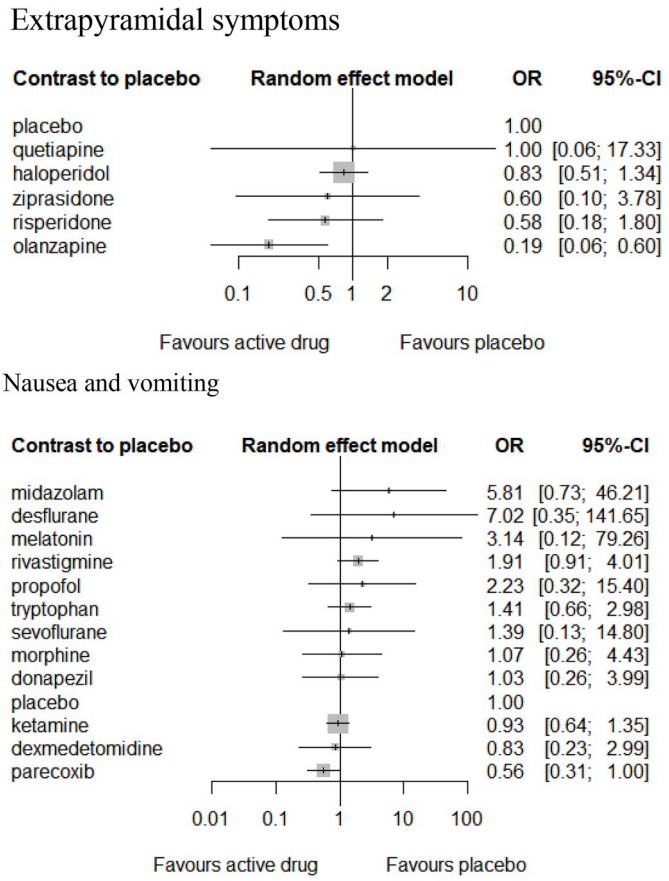


Fig. 6. (*continued*)

Since the incidence of delirium differs among patient pools (surgical and medical patients) and clinical settings (ICU, PCU, and general ward or medical inpatients), we postulated that the severity and etiology of delirium may be different among these groups and as is the drug response. To consider multifactorial etiologies of delirium and draw clinically relevant conclusion, the present NMA provided analyses for each clinical setting (ICU versus non-ICU) and etiology (surgical versus medical patients) as prespecified in the protocol, and this is a critical difference with the previous NMA. Furthermore, this study is first NMA to explore drug tolerability, cardiac and neurologic harms, duration of delirium, length of ICU stay, and provide strength of evidence for individual outcomes.

In terms of treatment, our results suggested that quetiapine (low SoE), morphine (low SoE), and dexmedetomidine (moderate SoE) help to resolve delirium in ICU patients while none was effective for the non-ICU patients. This result differs from that of previous NMA by Wu et al. as they found dexmedetomidine and quetiapine not to be effective in managing delirium. Such discordance of the results may be attributed to the increased number of included studies for dexmedetomidine and the split of clinical settings, leaving one significant study on quetiapine in the ICU population. It is important to note that conventional antipsychotics, including haloperidol, do not have clear evidence for benefit in ICU-related delirium, and our result is in line with the current guideline (Devlin et al., 2018) and previous studies (Girard et al., 2018; Nikooie et al., 2019). Although quetiapine showed a positive effect, the strength of evidence was low since the result was deduced from a single study and had large 95% CI. While the outcome of dexmedetomidine is supported by several studies and has fewer evidence deficiencies (moderate SoE), conflicting results between direct and indirect evidence limit its evidence strength, and further studies are required to confirm the findings.

In terms of prevention, the present study revealed that

dexmedetomidine regimens and risperidone are beneficial for reducing postoperative delirium in ICU surgical patients while ramelteon was effective in ICU medical patients. Preventive effect of risperidone in ICU surgical patients was consistent with the finding of recent study by Oh et al. (2019), but high rate in drop-out and in-hospital mortality were observed (Fig. 5) with risperidone in our study. Several pairwise meta-analyses have demonstrated the efficacy of dexmedetomidine in reducing the length of ICU stays (Tan and Ho, 2010), postoperative pain, postoperative opioid consumption (Schnabel et al., 2013), risk of delirium, and agitation (Pasin et al., 2014), but its role in reducing postoperative delirium has yielded contradictory results (Dasta et al., 2006; Djaiani et al., 2016; Deiner et al., 2017; Li et al., 2017). Our comprehensive NMA concluded that dexmedetomidine is effective in reducing postoperative delirium with high strength of evidence.

While dexmedetomidine seems to be an optimal choice for both preventing and treating delirium in ICU setting, low tolerability (high drop-out rate) and high incidence of bradycardia and hypotension were observed in our results (Figs. 5 and 6). It may be important to recognize such hemodynamic instabilities as physiological responses anticipated with using dexmedetomidine and attempt to attenuate these responses by pretreatment such as atropine (Mahmoud and Mason, 2015; Ahn et al., 2016). Since these cardiovascular responses appear in a dose-dependent manner (Penttila et al., 2004), adequate control of bolus loading, rate of drug infusion, volume repletion, and patient selection are expected to reduce the risk of hemodynamic disturbance induced by dexmedetomidine (Ickeringill et al., 2004). Therefore, the importance of peri-injection management should not be neglected in order to maximize the beneficial effect of dexmedetomidine while maintaining a tolerable safety margin.

For antipsychotics, both first- and second-generation agents demonstrated relatively safe drug profile. However, QT interval prolongation occurred more frequently with ziprasidone compare to haloperidol, and this finding is consistent with recent study by Nikooie et al. which found harmful cardiac effects, particularly prolongation of the QT interval, more frequently with second-generation antipsychotics compared to placebo or haloperidol (Nikooie et al., 2019). Also, risperidone was found to have higher dropout rate and increase in in-hospital mortality in the present study. Given that atypical antipsychotics were shown to have relative lower extrapyramidal symptoms (Rivière et al., 2019) and better safe profile than haloperidol (Kishi et al., 2016), our result may have been affected by one trial composed of critically ill patients in palliative care which reported high drop-out rate in the risperidone group (Agar et al., 2017).

Oral ramelteon, a melatonin receptor agonist, was well tolerated by critically ill patients (Hatta et al., 2014) and has been shown to lack abuse liability and adverse sedative effects compared to benzodiazepines (Johnson et al., 2006). In this respect, ramelteon may be considered in general ward or medical patients but further studies are needed.

Despite our effort to distinguish different clinical settings, it is important to recognize that delirium involves multiple mechanisms and "one-size-fits-all pharmacologic treatment" may be clinically infeasible as Neerland et al. noted (Neerland et al., 2019). Therefore, we still recommend combining multi-component, nonpharmacological approaches (Davis et al., 2019) in addition to evidence-based pharmacological managements. As interdisciplinary approach is important in preventing and treating delirium, further RCTs are needed to search for non-pharmacological approach that would elicit the most synergistic effect with pharmacological treatments.

Our study has several limitations. First, our treatment analysis represents delirium symptom resolving intervention rather than therapeutic agents. Therefore, the result of our NMA does not necessarily

Table 1
Summary of effect estimation and strength of evidence (AHRQ grading system) of significant outcomes.

Comparisons (vs. Placebo)	Effect size (95% CI)	Direction of effect	Study limitation	Directness	Consistency	Precision	Reporting bias	SoE Grade
Treatment of delirium for ICU patients (response rate)								
Dexmedetomidine	OR 2.66 (1.05, 6.77)	+	Low	Direct	Inconsistent	Precise	Unsuspected	Moderate
Morphine	OR 3.88 (1.18, 12.80)	+	Low	Indirect	Unknown*	Precise	Unsuspected	Low
Quetiapine	OR 8.00 (1.41, 45.41)	+	Low	Direct	Unknown*	Imprecise †	Unsuspected	Low
Haloperidol	OR 1.01 (0.72, 1.44)	NS	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate
Ziprasidone	OR 1.23 (0.82, 1.84)	NS	Low	Direct	Inconsistent	Precise	Unsuspected	Moderate
Treatment of delirium for PCU patients								
Lorazepam plus haloperidol	OR 5.73 (1.53, 21.51)	+	Low	Indirect	Unknown*	Imprecise †	Unsuspected	Low
Treatment of delirium for non-ICU patients								
Quetiapine	OR 1.41 (0.27, 7.26)	NS	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate
Haloperidol	OR 1.43 (0.23, 8.98)	NS	Low	Indirect	Inconsistent	Imprecise	Unsuspected	Low
Prevention of delirium for ICU surgical patients (incidence of delirium)								
Dexmedetomidine	OR 0.46 (0.32, 0.66)	+	Low	Direct	Consistent	Precise	Unsuspected	High
Risperidone	OR 0.29 (0.13, 0.64)	+	Low	Direct	Consistent	Precise	Unsuspected	High
DFP	OR 0.10 (0.01, 0.96)	+	High	Direct	Unknown*	Imprecise ‡	Unsuspected	Low
Acetaminophen plus dexmedetomidine	OR 0.09 (0.02, 0.55)	+	Low	Indirect	Unknown*	Imprecise †	Unsuspected	Low
Haloperidol	OR 0.64 (0.35, 1.14)	NS	Low	Direct	Consistent	Precise	Unsuspected	High
Propofol	OR 1.64 (0.82, 3.49)	NS	Low	Indirect	Consistent	Precise	Unsuspected	Moderate
Prevention of delirium for ICU medical patients								
Ramelteon	OR 0.28 (0.11, 0.67)	+	Low	Direct	Consistent	Precise	Unsuspected	High
Haloperidol	OR 1.77 (0.58, 5.46)	NS	Low	Direct	Unknown*	Imprecise	Unsuspected	Low
Dexmedetomidine	OR 0.50 (0.04, 6.30)	NS	Low	Direct	Consistent	Imprecise[c]	Unsuspected	Moderate
Tolerability (all-cause discontinuation)								
Risperidone	OR 2.01 (1.26, 3.20)	-, higher drop-out rate	Medium	Direct	Consistent	Precise	Unsuspected	Moderate
Dexmedetomidine	OR 1.52 (1.00, 2.32)	-	Low	Direct	Consistent	Precise, but borderline significance	Unsuspected	High
Ziprasidone	OR 1.45 (1.07, 1.95)	-	Low	Direct	Inconsistent	Precise	Unsuspected	Moderate
Suvorexant	OR 0.18 (0.04, 0.89)	+	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate
Haloperidol	OR 1.08 (0.88, 1.32)	NS	Low	Direct	Consistent	Precise	Unsuspected	High
In-hospital mortality								
risperidone	OR 1.94 (1.05, 3.56)	-, higher mortality rate	Low	Direct	Inconsistent	Precise	Unsuspected	Moderate
Haloperidol	OR 0.95 (0.78, 1.15)	NS	Low	Direct	Consistent	Precise	Unsuspected	High
Dexmedetomidine	OR 0.73 (0.32, 1.66)	NS	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate

(*continued on next page*)

Table 1 (*continued*)

Duration of delirium (hours)								
Dexmedetomidine	SMD -0.56 (-1.07, -0.05)	+	Low	Direct	Inconsistent	Precise	Unsuspected	Moderate
Acetaminophen plus propofol	SMD -1.44 (-2.79, -0.09)	+	Low	Indirect	Unknown*	Imprecise †	Unsuspected	Low
Haloperidol	SMD -0.19 (-0.52, 0.15)	NS	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate
Length of ICU stay (days)								
Dexmedetomidine	SMD -0.22 (-0.41, -0.04)	+	Low	Direct	Inconsistent	Precise	Suspected	Low
Acetaminophen plus dexmedetomidine	SMD -0.96 (-1.63, -0.28)	+	Low	Indirect	Unknown*	Precise	Suspected	Insufficient
Haloperidol	SMD 0.02 (-0.15, 0.19)	NS	Low	Direct	Consistent	Precise	Suspected	Moderate
Midazolam	SMD	NS	Low	Indirect	Consistent	Imprecise	Unsuspected	Low
Propofol	SMD 0.01 (-0.29, 0.32)	NS	Low	Indirect	Consistent	Imprecise	Unsuspected	Low
Bradycardia								
Dexmedetomidine	OR 1.84 (1.14, 2.96)	-	Low	Direct	Consistent	Precise	Unsuspected	High
Hypotension								
Acetaminophen plus propofol	OR 4.65 (1.05, 20.59)	-	Low	Indirect	Unknown*	Precise	Unsuspected	Low
Morphine	OR 3.08 (1.74, 5.43)	-	Low	Indirect	Unknown*	Precise	Unsuspected	Low
Remifentanil	OR 2.85 (1.23, 6.59)	-	Unclear	Indirect	Unknown*	Precise	Unsuspected	Insufficient
Dexmedetomidine	OR 1.50 (1.15, 1.94)	-	Low	Direct	Consistent	Precise	Unsuspected	High
Atrial fibrillation								
Dexmedetomidine	OR 0.74 (0.01, 45.91)	NS	Low	Indirect	Consistent	Imprecise †	Suspected	Low
Haloperidol	OR 2.44 (0.33, 18.07)	NS	Moderate	Direct	Consistent	Imprecise	Suspected	Low
Olanzapine	OR 2.12 (0.29, 15.70)	NS	Low	Direct	Unknown*	Imprecise	Suspected	Low
QTc-prolongation								
Ziprasidone	OR 1.83 (1.04, 3.23)	-	Low	Direct	Unknown*	Precise	Unsuspected	Moderate
Haloperidol	OR 1.03 (0.73, 1.46)	NS	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate
Extrapyramidal symptoms								
Olanzapine	OR 0.19 (0.06, 0.60)	+	Low	Indirect	Consistent	Precise	Suspected	Low
Haloperidol	OR 0.83 (0.51, 1.34)	NS	Low	Direct	Consistent	Imprecise	Suspected	Low
Nausea and vomiting								
Parecoxib	OR 0.56 (0.31, 1.00)	+	Low	Direct	Unknown*	Precise, but borderline significance	Unsuspected	Moderate
Ketamine	OR 0.93 (0.64, 1.35)	NS	Low	Direct	Unknown*	Imprecise	Unsuspected	Low
Dexmedetomidine	OR 0.83 (0.23, 2.99)	NS	Low	Direct	Consistent	Imprecise	Unsuspected	Moderate

OR: odds ratio. SMD: standardized mean difference. NS: statistically not significant. DFP: diazepam plus flunitrazepam plus pethidine. SoE: Strength of evidence. +: the intervention is significantly favorable compare to placebo/-: the intervention is significantly unfavorable compare to placebo. *: unable to assess inconsistency due to lack of sufficient data (a single study). †: too large 95% CI. ‡: small sample size. Smaller OR corresponds to better preventive efficacy (lower incidence of delirium), while greater OR corresponds to better treatment efficacy (higher response rate).

Rationale:

1. Study limitation: We assigned 'low level' when the contributions from high risk of bias (RoB) comparisons were greater than 20% or contributions from low risk of bias comparisons were less than 30%.
2. Imprecision: We assigned 'imprecision' when sample size is too small or confidential interval (CI) is too large. Since we considered clinically meaningful threshold for OR to be 0.80 or 1.25, we judged CI to be large if the OR value is 1 or greater and the lower limit of CI is below 0.80 or if OR value is less than 1 and the upper limit of CI is above 1.25
3. Inconsistency: We assigned 'inconsistency' when the result of direct (pairwise meta-analysis) and indirect evidence is not equivalent. If there is no direct evidence, we assessed local inconsistency.
4. Indirectness. We assigned 'indirectness' when assumption of transitivity is being challenged or result is solely derived from indirect comparison.
5. Reporting bias: we assigned 'suspected' when substantial asymmetry is observed in funnel plot.

AHRQ Grade Definition (suggested by Berkman ND et al):

1. High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
2. Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
3. Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
4. Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

guarantee the cure of delirium. Second, the results of quetiapine and morphine in treatment analysis and dexmedetomidine plus acetaminophen in prevention analysis derived from a single RCT, and therefore these results should be interpreted with caution (low SoE). However, the results of dexmedetomidine alone in both treatment and prevention analyses are still well supported by several high-quality RCTs and have moderate to high SoE; therefore, dexmedetomidine may be a good alternative. Third, some of the results derived from a single study or studies with high risk of bias and have conflicting results between direct and indirect evidence. To consider such evidence deficiencies, we assessed SoE for each significant outcome as summarized in Table 1. This may help readers to identify the credibility of each evidence. Lastly, there are some intrinsic limitations of NMA. Due to a large and complex data set comparing numerous (often > 10 items) interventions simultaneously, presenting and communicating various findings from NMA in a reader-friendly and understandable format are challenging. Furthermore, NMA can lead to an inappropriate conclusion if key differences among studies are not sufficiently considered (Li et al., 2011; Higgins and Welton, 2015). Despite these limitations, NMA is still an attractive methodology as it provides a single coherent ranking of interventions and answers to the questions of interest for decision-makers, who frequently encounter a wide range of treatment options, not just two (Higgins and Welton, 2015). In addition, the methodological power of NMA is credible as NMA incorporates both direct and indirect evidence, while conventional pairwise meta-analysis is only dependent on direct evidence. There was empirical evidence that NMA was 20% more likely to provide stronger evidence and 4 years earlier evidence against the null hypothesis of treatment differences than conventional pairwise meta-analysis (Nikolakopoulou et al., 2018). Accordingly, this NMA can offer meaningful implication for guiding management of delirium until future studies build up stronger evidence.

5. Conclusion

The etiology of delirium is complex and multifactorial, and thus clinical contexts should be considered in treatment and prevention strategies. Dexmedetomidine is a potential agent in both treating and preventing delirium of the ICU and postsurgical patients when the hemodynamic instability induced by dexmedetomidine can be adequately

managed. Current evidence does not support routine use of antipsychotics due to either low SoE for its efficacy or low tolerability. For ICU medical patients, oral ramelteon can be convenient and safe alternative for antipsychotics.

Author statement

Corresponding author confirms that authors had access to all the study data. Corresponding author takes responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. Corresponding author confirms that all authors approve the manuscript and agree to adhere to all terms outlined in Journal of Psychiatric Research. Information for authors including terms for copyright.

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Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Not required.
Data sharing.

Transparency

The manuscript's guarantor (CSH) affirms that this manuscript is an honest, accurate, and transparent account of study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

CRediT authorship contribution statement

Min Seo Kim: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft. **Hye Chang Rhim:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft. **Ariel Park:** Data curation, Investigation, Writing - original draft. **Hanna Kim:** Data curation, Investigation, Writing - original draft. **Kyu-Man Han:** Methodology, Supervision, Writing - review & editing. **Ashwin A. Patkar:** Writing - review & editing. **Chi-Un Pae:** Writing - review & editing. **Changsu Han:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Declaration of competing interest

Min Seo Kim, Hye Chang Rhim, Ariel Park, Hanna Kim, Kyu-Man Han, Ashwin A. Patkar, Chi-Un Pae, and Changsu Han have no commercial associations that may present a conflict of interest in relation to this manuscript.

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Appendix A. Supplementary data

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