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Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium
A Network Meta-analysis

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IMPORTANCE Although several pharmacological interventions for delirium have been investigated, their overall benefit and safety remain unclear.

OBJECTIVE To evaluate evidence regarding pharmacological interventions for delirium treatment and prevention.

DATA SOURCES PubMed, Embase, ProQuest, ScienceDirect, Cochrane Central, Web of Science, ClinicalKey, and ClinicalTrials.gov from inception to May 17, 2018.

STUDY SELECTION Randomized clinical trials (RCTs) examining pharmacological interventions for delirium treatment and prevention.

DATA EXTRACTION AND SYNTHESIS To extract data according to a predetermined list of interests, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were applied, and all meta-analytic procedures were conducted using a random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcomes were treatment response in patients with delirium and the incidence of delirium in patients at risk of delirium.

RESULTS A total of 58 RCTs were included, in which 20 RCTs with 1435 participants (mean age, 63.5 years; 65.1% male) compared the outcomes of treatment and 38 RCTs with 8168 participants (mean age, 70.2 years; 53.4% male) examined the prevention of delirium. A network meta-analysis demonstrated that haloperidol plus lorazepam provided the best response rate for delirium treatment (odds ratio [OR], 28.13; 95% CI, 2.38-333.08) compared with placebo/control. For delirium prevention, the ramelteon, olanzapine, risperidone, and dexmedetomidine hydrochloride groups had significantly lower delirium occurrence rates than placebo/control (OR, 0.07; 95% CI, 0.01-0.66 for ramelteon; OR, 0.25; 95% CI, 0.09-0.69 for olanzapine; OR, 0.27; 95% CI, 0.07-0.99 for risperidone; and OR, 0.50; 95% CI, 0.31-0.80 for dexmedetomidine hydrochloride). None of the pharmacological treatments were significantly associated with a higher risk of all-cause mortality compared with placebo/control.

CONCLUSIONS AND RELEVANCE This network meta-analysis demonstrated that haloperidol plus lorazepam might be the best treatment and ramelteon the best preventive medicine for delirium. None of the pharmacological interventions for treatment or prophylaxis increased the all-cause mortality.

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Supplemental content

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Delirium is an acute confusional state characterized by inattention and global cognitive dysfunction. It is a multifactorial neuropsychiatric condition that develops owing to a complex interplay of risk factors and noxious insults.[1] Delirium is a prevalent yet underdiagnosed disturbance that is particularly common among elderly inpatients. For instance, the prevalence of delirium is between 11% and 42% among medical inpatients[2] and between 9% and 87% among older people undergoing surgery.[3] Delirium is associated with a myriad of detrimental outcomes, including a higher risk of falls, functional decline, permanent cognitive decline (eg, dementia), prolonged hospitalization, institutionalization, and increased mortality.[4] Nevertheless, it has been estimated that 30% to 40% of delirium cases are potentially preventable.[1,5]

Several risk factors, such as age, pre-intensive care unit (ICU) emergency surgery or trauma, or mechanical ventilation,[6] and neurobiological aberrations may contribute to the emergence of delirium, including dopamine imbalance,[7] cholinergic deficiency,[8] alterations of serotonergic activity,[9] and disruption of circadian rhythms.[10,11] Accordingly, several pharmacological agents targeting those neurochemical abnormalities (eg, antipsychotics and melatonergic agents) have been assessed for use in the treatment and prevention of delirium.

Despite the widespread use of various psychopharmacological agents for the management of delirium, the relative balance between benefit and harm of the various available treatments remains unclear.[12] Previous randomized clinical trials (RCTs) have provided evidence to support a benefit of antipsychotics, such as quetiapine fumarate, for the treatment of agitated delirium.[13-16] However, a pairwise meta-analysis failed to support the effectiveness of antipsychotics.[17] In addition, there is a pressing need to understand the role of pharmacological interventions in preventing delirium among high-risk patients. Numerous medications have been suggested to have a role in the prevention of delirium.[18,19] However, there have been concerns that some pharmacological interventions may increase mortality in this high-risk population.[2] Therefore, we conducted a systematic review and network meta-analysis (NMA) of RCTs that investigated various pharmacological agents used for both the treatment and prevention of delirium. We aimed to synthesize evidence and compare different drugs that have been tested regarding their delirium response rate and delirium occurrence rate for the treatment and prevention of delirium. Moreover, these agents were assessed in terms of their propensity to increase the overall mortality in this population.

Key Points

Question Which medications provide the best delirium response rate, the lowest delirium occurrence rate, and the best tolerability for the treatment and prevention of delirium?

Findings From the results of a network meta-analysis of 58 randomized clinical trials among 9603 individuals, haloperidol plus lorazepam had the best response rate for delirium treatment, and ramelteon had the lowest delirium occurrence rate. No pharmacological management was significantly associated with a higher risk of all-cause mortality compared with placebo or control groups during delirium treatment or prevention.

Meaning The use of a combination of haloperidol plus lorazepam and ramelteon is suggested for the treatment and prevention of delirium.

Methods

Detailed information regarding the methods and materials is available in the eMethods in the Supplement. In brief, this NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension guidelines (eTable 1 in the Supplement).[20] By searching PubMed, Embase, ProQuest, ScienceDirect, Cochrane Central, Web of Science, ClinicalKey, and ClinicalTrials.gov, we identified RCTs with both placebo-controlled and active-controlled designs conducted in adults. The present work involved no individual patient data, so informed consent of participants was not applicable. Peer-reviewed articles published in any language were considered for inclusion. The following 2 types of pharmacological intervention were considered for inclusion (1) therapeutic interventions and (2) preventive interventions that could alter the incidence of delirium.

We evaluated the risk of bias using the Cochrane risk of bias tool.[21] Studies were then further classified into categories according to their overall risk of bias. Frequentist random-effects NMA, which consisted of direct and indirect comparisons, was conducted to compare the effect sizes between studies within the same type of intervention (ie, treatment or prevention).[22] Heterogeneity among the included studies was evaluated by the τ statistic. Comparison-adjusted funnel plots[23] and Egger tests were used to examine potential small-study bias (ie, publication bias) after treatments were ordered from the oldest to the newest.

Subgroup analysis was used to evaluate the potential confounding associations of the route of administration (ie, intravenous) or the rescue medication used in each trial. We ranked the relative probabilities for the delirium response rate or delirium occurrence rate of all medications in terms of the target outcomes using the surface under the cumulative ranking curve (SUCRA), which reflected the percentage of effectiveness each medication can achieve relative to an imaginary intervention that was the best without uncertainty.[24] Meta-regression analysis was used to assess the associations between the delirium response rate and delirium occurrence rate of treatments and characteristics of participants. Finally, we evaluated the potential local inconsistency between the direct and indirect evidence within the network using the loop-specific approach and the node-splitting models.[25,26] Furthermore, we also used the design by treatment interaction models to evaluate the global inconsistency within the whole NMA.[27]

Results

After the initial screening procedure, 157 articles in total were considered for full-text review (eFigure 1 in the Supplement).

However, 99 were excluded for various reasons (eTable 2 and eFigure 1 in the Supplement). Finally, 58 articles were included in the present study (eTable 3A and B in the Supplement).

Among the 58 articles, 20 provided evidence relating to different therapeutic interventions for delirium, while 38 assessed preventive interventions for delirium. The whole geometric distribution of the treatment arms is shown in **Figure**, A and B, and in eFigure 2A-D in the Supplement.

Characteristics of the Included Studies

Among the 20 RCTs investigating the treatment of delirium, a total of 1435 participants (mean age, 63.5 years; 65.1% male) were included at baseline with different health conditions, including AIDS, hospitalization in general wards or ICUs, cancer, elderly delirium, patients who underwent major surgical procedures, and hospice patients. The rating scales for the evaluation of delirium varied widely across the included trials, including delirium rating scales,[28] the Intensive Care Delirium Screening Checklist,[29] the Confusion Assessment Method for the ICU,[30] the Richmond Agitation-Sedation Scale,[31] the delirium severity index,[32] and the Memorial Delirium Assessment Scale.[33]

Among the 38 RCTs assessing different drug interventions for the prevention of delirium, a total of 8168 participants (mean age, 70.2 years; 53.4% male) were included with a variety of baseline diseases, including critically ill patients, patients who underwent major surgery, patients with major burns, patients hospitalized in general wards or ICUs, patients receiving flap surgery, patients with cancer, or elderly patients. The rating scales for the evaluation of delirium included delirium rating scales,[28] the Confusion Assessment Method for the ICU,[30] the Neelon and Champagne (NEECHAM) Confusion Scale,[34] the Delirium Detection Score,[35] the Delirium Observation Screening scale,[36] the medical record-based method for the identification of delirium,[37] and the Intensive Care Delirium Screening Checklist.[29]

Response Rates of Treatment Interventions for Delirium

In total, 20 included articles stated the response rates to different treatments for delirium, totaling 14 treatment arms, including haloperidol plus lorazepam, rivastigmine tartrate, chlorpromazine hydrochloride, lorazepam, quetiapine fumarate, amisulpride, ziprasidone hydrochloride, olanzapine, haloperidol, dexmedetomidine hydrochloride, haloperidol plus rivastigmine tartrate, risperidone, ondansetron hydrochloride, and placebo/control (**Table 1** and Figure, A). In the NMA, only the response rates for haloperidol plus lorazepam (odds ratio [OR], 28.13; 95% CI, 2.38-333.08) and haloperidol (OR, 2.37; 95% CI, 1.04-5.43) were significantly superior to those for placebo/control. However, rivastigmine tartrate, chlorpromazine hydrochloride, lorazepam, quetiapine fumarate, amisulpride, ziprasidone hydrochloride, olanzapine, dexmedetomidine hydrochloride, haloperidol plus rivastigmine tartrate, risperidone, and ondansetron hydrochloride did not show significantly better response rates compared with placebo/control. In addition, the response rate for the haloperidol plus lorazepam group was significantly higher than the rates for the haloperidol, risperidone, ondansetron hydrochloride, and placebo/control groups (Table 1 and Figure, C). According to the SUCRA for response rate, haloperidol plus lorazepam was ranked the best among all treatments (eTable 4A in the Supplement). A meta-regression using restricted maximum likelihood estimators did not find that age had any potential moderating association with treatments when the mean age of patients in a trial was used as a moderating variable.

In total, 8 articles provided evidence related to the response rates to different treatments for delirium without the use of rescue medications. In total, 10 treatment arms (placebo/control, chlorpromazine hydrochloride, lorazepam, risperidone, quetiapine fumarate, haloperidol, amisulpride, olanzapine, dexmedetomidine hydrochloride, and ondansetron hydrochloride) were included (eTable 5A and eFigure 2A in the Supplement). In the NMA, compared with placebo/control, the response rates of the chlorpromazine hydrochloride (OR, 45.34; 95% CI, 5.29-388.42), lorazepam (OR, 36.30; 95% CI, 2.98-442.10), haloperidol (OR, 16.16; 95% CI, 5.88-44.40), amisulpride (OR, 18.14; 95% CI, 1.57-209.42), quetiapine fumarate (OR, 16.74; 95% CI, 3.13-89.44), ondansetron hydrochloride (OR, 13.44; 95% CI, 2.82-64.11), and olanzapine (OR, 10.14; 95% CI, 3.86-26.62) groups were significantly superior (eFigure 3A in the Supplement). Moreover, the response rates for the chlorpromazine hydrochloride and haloperidol groups were significantly superior to the response rate of the dexmedetomidine hydrochloride group (eTable 5A in the Supplement). Finally, chlorpromazine hydrochloride exhibited the best response rate when trials that did not use rescue medications were considered (eTable 4B in the Supplement).

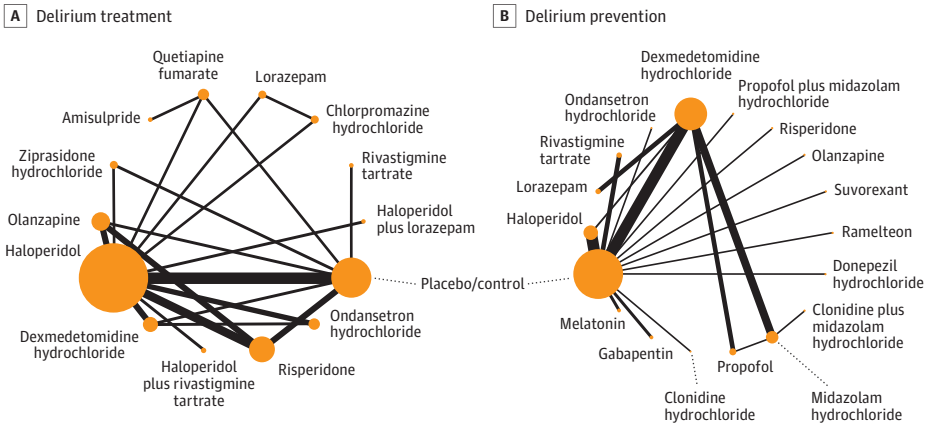
Association Between Individual Therapeutic Interventions for Delirium and All-Cause Mortality

Ten eligible articles provided data relative to the all-cause mortality rates across 10 treatment arms, including placebo/control, chlorpromazine hydrochloride, lorazepam, risperidone, quetiapine fumarate, haloperidol, haloperidol plus lorazepam, haloperidol plus rivastigmine tartrate, ziprasidone hydrochloride, and rivastigmine tartrate groups (eTable 5B and eFigure 2B in the Supplement). Compared with placebo/control, there were no statistically significant differences in all-cause mortality across all medications tested in the NMA. eFigure 3B in the Supplement shows the forest plot of the all-cause mortality rates across different treatment groups relative to placebo/control. Using the SUCRA, we ranked the relative safety (ie, a lower likelihood of increasing the all-cause mortality rate) across different treatments for delirium. In brief, rivastigmine tartrate had the best overall safety (lowest all-cause mortality rate) (eTable 4C in the Supplement). The results of a meta-regression revealed that the mean age of patients did not moderate the outcome.

Preventive Interventions for Delirium

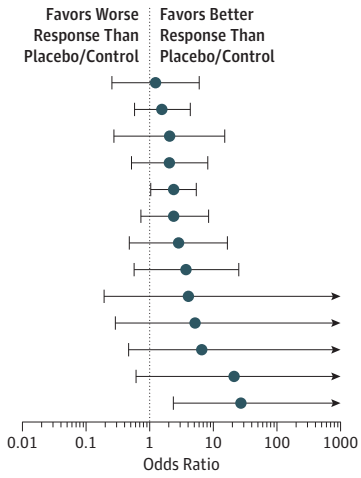
Thirty-eight articles provided evidence related to different preventive interventions for delirium. In total, 18 treatment arms (comprising ramelteon, suvorexant, olanzapine, donepezil hydrochloride, risperidone, propofol plus midazolam

Figure. Network Structure and Forest Plot of the Present Network Meta-analysis in Reference to Placebo/Control



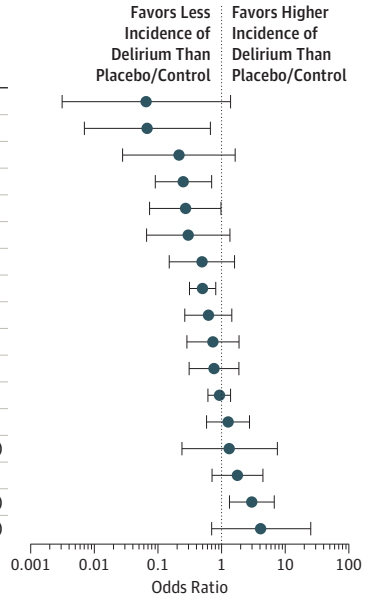
C Treatment response

Source	Odds Ratio With 95% CI and 95% Prediction Interval	
Ondansetron hydrochloride	1.23 (0.24-6.22)	(0.03-53.71)
Risperidone	1.57 (0.56-4.38)	(0.07-37.78)
Haloperidol plus rivastigmine tartrate	2.06 (0.27-15.71)	(0.03-147.19)
Dexmedetomidine hydrochloride	2.06 (0.51-8.34)	(0.06-70.60)
Haloperidol	2.37 (1.04-5.43)	(0.12-48.80)
Olanzapine	2.46 (0.71-8.57)	(0.08-72.49)
Ziprasidone hydrochloride	2.89 (0.48-17.29)	(0.05-153.40)
Quetiapine fumarate	3.78 (0.55-25.84)	(0.06-235.65)
Amisulpride	4.10 (0.18-91.61)	(0.01-1256.98)
Lorazepam	5.34 (0.28-101.95)	(0.02-1308.79)
Chlorpromazine hydrochloride	6.68 (0.47-95.24)	(0.04-1089.82)
Rivastigmine tartrate	21.87 (0.61-790.15)	(0.04-13477.64)
Haloperidol plus lorazepam	28.13 (2.38-333.08)	(0.22-3563.80)



D Occurence rate of delirium

Source	Odds Ratio With 95% CI and 95% Prediction Interval	
Suvorexant	0.06 (0.00-1.36)	(0.00-1.91)
Ramelteon	0.07 (0.01-0.66)	(0.00-0.92)
Donepezil hydrochloride	0.21 (0.03-1.62)	(0.02-2.27)
Olanzapine	0.25 (0.09-0.69)	(0.06-1.05)
Risperidone	0.27 (0.07-0.99)	(0.05-1.45)
Propofol plus midazolam hydrochloride	0.30 (0.07-1.33)	(0.05-1.92)
Ondansetron hydrochloride	0.49 (0.15-1.60)	(0.10-2.38)
Dexmedetomidine hydrochloride	0.50 (0.31-0.80)	(0.17-1.47)
Rivastigmine tartrate	0.62 (0.26-1.46)	(0.17-2.32)
Lorazepam	0.73 (0.28-1.89)	(0.18-2.94)
Melatonin	0.76 (0.30-1.87)	(0.19-2.94)
Haloperidol	0.91 (0.60-1.38)	(0.32-2.61)
Gabapentin	1.26 (0.58-2.77)	(0.36-4.49)
Clonidine hydrochloride	1.33 (0.23-7.57)	(0.17-10.72)
Propofol	1.78 (0.70-4.51)	(0.45-7.05)
Midazolam hydrochloride	2.98 (1.30-6.80)	(0.81-10.90)
Midazolam hydrochloride plus clonidine hydrochloride	4.16 (0.69-25.25)	(0.49-35.66)



A and B, Whole network structure. C and D, Forest plots. An effect size exceeding 1 indicates better response (C) and higher occurrence (D) than placebo/control.

hydrochloride, dexmedetomidine hydrochloride, ondansetron hydrochloride, rivastigmine tartrate, lorazepam, melatonin, haloperidol, placebo/control, gabapentin, clonidine hydrochloride, propofol, midazolam hydrochloride, and

Table 1. League Table of Treatment Response in Individuals With Delirium[a]

Haloperidol plus lorazepam								12.05 (2.34-62.50)[b]												
1.29 (0.02-100.28)	Rivastigmine tartrate																			21.74 (0.91-500.00)
4.21 (0.14-130.82)	3.27 (0.04-284.38)	Chlor-promazine hydrochloride	1.25 (0.16-9.52)					2.81 (0.42-18.87)												
5.27 (0.13-205.80)	4.09 (0.04-425.26)	1.25 (0.09-17.33)	Lorazepam					2.25 (0.23-22.22)												
7.43 (0.38-143.91)	5.78 (0.10-338.09)	1.76 (0.08-39.95)	1.41 (0.05-41.10)	Quetiapine fumarate	0.92 (0.16-5.49)			1.04 (0.27-3.94)												11.49 (0.57-250.00)
6.86 (0.15-318.85)	5.33 (0.05-613.42)	1.63 (0.03-85.53)	1.30 (0.02-83.65)	0.92 (0.08-10.60)	Amisulpride															
9.75 (0.52-184.40)	7.58 (0.14-417.54)	2.31 (0.10-51.26)	1.85 (0.06-52.82)	1.31 (0.10-16.44)	1.42 (0.04-47.75)	Ziprasidone hydrochloride		1.52 (0.50-4.55)												2.35 (0.80-6.90)
11.42 (0.83-156.31)	8.87 (0.20-395.82)	2.71 (0.17-44.26)	2.17 (0.10-46.77)	1.54 (0.18-13.26)	1.66 (0.06-43.21)	1.17 (0.15-9.45)	Olanzapine	0.63 (0.29-1.36)							1.17 (0.44-3.15)	10.42 (3.88-27.78)[b]				
11.85 (1.15-121.81)[b]	9.21 (0.23-365.66)	2.81 (0.23-35.16)	2.25 (0.13-38.16)	1.59 (0.26-9.95)	1.73 (0.08-36.53)	1.22 (0.20-7.31)	1.04 (0.32-3.42)	Haloperidol	1.71 (0.64-4.57)	1.15 (0.51-2.60)	1.76 (0.39-8.00)	1.45 (0.68-3.08)	1.75 (0.48-6.33)							
13.63 (0.91-204.94)	10.59 (0.23-497.44)	3.24 (0.18-57.71)	2.59 (0.11-60.51)	1.83 (0.19-17.66)	1.99 (0.07-55.50)	1.40 (0.16-12.52)	1.19 (0.21-6.89)	1.15 (0.29-4.60)	Dexmede-tomidine hydrochloride		2.23 (0.51-9.80)									
13.67 (0.69-268.88)	10.62 (0.17-655.97)	3.24 (0.14-74.57)	2.60 (0.09-76.63)	1.84 (0.14-24.95)	1.99 (0.06-70.90)	1.40 (0.11-18.53)	1.20 (0.13-10.88)	1.15 (0.18-7.39)	1.00 (0.10-10.18)	Haloperidol plus rivastigmine tartrate										
17.91 (1.42-226.13)[b]	13.92 (0.33-580.82)	4.25 (0.28-64.37)	3.40 (0.17-68.51)	2.41 (0.31-18.74)	2.61 (0.11-63.32)	1.84 (0.26-13.23)	1.57 (0.47-5.26)	1.51 (0.55-4.12)	1.31 (0.26-6.62)	1.31 (0.16-10.81)	Risperidone			2.56 (0.94-6.94)						
22.86 (1.46-357.98)[b]	17.77 (0.35-910.16)	5.43 (0.29-100.52)	4.34 (0.18-105.07)	3.08 (0.30-31.80)	3.33 (0.11-97.76)	2.34 (0.24-23.22)	2.00 (0.31-12.92)	1.93 (0.45-8.33)	1.68 (0.30-9.30)	1.67 (0.16-17.79)	1.28 (0.22-7.32)	Ondansetron hydrochloride	1.46 (0.33-6.54)							
28.13 (2.38-333.08)[b]	21.87 (0.61-790.15)	6.68 (0.47-95.24)	5.34 (0.28-101.95)	3.78 (0.55-25.84)	4.10 (0.18-91.61)	2.89 (0.48-17.29)	2.46 (0.71-8.57)	2.37 (1.04-5.43)[b]	2.06 (0.51-8.34)	2.06 (0.27-15.71)	1.57 (0.56-4.38)	1.23 (0.24-6.22)	Placebo/ control							

[a] Pairwise (upper right portion) and network (lower left portion) meta-analysis results are presented as the response rates for the outcome of delirium treatment. Drugs are reported in order of the mean ranking of delirium treatment, and outcomes are expressed as odds ratios (95% CIs). For the pairwise meta-analyses, odds ratios greater than 1 indicate that the treatment specified in the row is more effective than that specified in the column. For the network meta-analysis, odds ratios greater than 1 indicate that the treatment specified in the column is more effective than that specified in the row.

[b] Statistically significant.

clonidine hydrochloride plus midazolam hydrochloride groups) were included (**Table 2** and Figure, B). For the NMA, Figure, D, shows the forest plot of delirium occurrence rates for different preventive treatments relative to placebo/control. Only ramelteon (OR, 0.07; 95% CI, 0.01-0.66), olanzapine (OR, 0.25; 95% CI, 0.09-0.69), risperidone (OR, 0.27; 95% CI, 0.07-0.99), and dexmedetomidine hydrochloride (OR, 0.50; 95% CI, 0.31-0.80) yielded a significantly greater decrease in the occurrence of delirium than placebo/control did. However, midazolam hydrochloride was significantly associated with a greater delirium occurrence than placebo/control for the prevention of delirium (OR, 2.98; 95% CI, 1.30-6.80). The other preventive interventions, such as propofol plus midazolam hydrochloride, clonidine hydrochloride plus midazolam hydrochloride, ondansetron hydrochloride, clonidine hydrochloride, melatonin, propofol, haloperidol, lorazepam, rivastigmine tartrate, gabapentin, or suvorexant, did not show significantly different risks of delirium occurrence compared with placebo/control. According to the SUCRA, ramelteon was ranked the best for the prevention of delirium occurrence (eTable 4D in the Supplement). In addition, the mean age of patients did not have a significant association with the occurrence rate according to a meta-regression analysis.

Twenty-three articles provided evidence of different preventive interventions for delirium that were delivered intravenously (eTable 5C and eFigure 3C in the Supplement). Those intervention groups comprised placebo/control, haloperidol, lorazepam, ondansetron hydrochloride, dexmedetomidine hydrochloride, midazolam hydrochloride plus propofol, midazolam hydrochloride plus clonidine hydrochloride, midazolam hydrochloride, propofol, and clonidine hydrochloride groups. In the pairwise meta-analysis, the dexmedetomidine hydrochloride group had a significantly lower delirium occurrence rate than placebo/control (OR, 0.50; 95% CI, 0.31-00.80). According to the SUCRA, propofol plus midazolam hydrochloride and dexmedetomidine hydrochloride were the 2 top-ranked intravenously delivered preventive interventions (eTable 4E in the Supplement).

Association Between Individual Preventive Interventions for Delirium and All-Cause Mortality

Fifteen articles provided evidence of the association between different preventive interventions for delirium and all-cause mortality, including 9 treatment arms (comprising placebo/control, propofol plus midazolam hydrochloride, dexmedetomidine hydrochloride, midazolam hydrochloride, rivastigmine tartrate, melatonin, lorazepam, haloperidol, and propofol groups) (eTable 5D and eFigure 2D in the Supplement). When different pharmacological interventions for the prevention of delirium were considered, there were no nominally significant differences in the all-cause mortality rate according to the NMA. eFigure 3D in the Supplement shows the forest plot of the all-cause mortality rates across different preventive interventions for delirium relative to placebo/control. According to the SUCRA, dexmedetomidine hydrochloride had the lowest likelihood of increasing the all-cause mortality rate among all preventive interventions for delirium examined (eTable 4F in the Supplement). The mean age of patients did not moderate outcomes according to a meta-regression analysis.

Twelve articles provided data on all-cause mortality after different intravenous preventive treatments for delirium, including placebo/control, haloperidol, lorazepam, dexmedetomidine hydrochloride, midazolam hydrochloride plus propofol, midazolam hydrochloride, and propofol. In the pairwise meta-analysis, the all-cause mortality rate during dexmedetomidine hydrochloride treatment was significantly less likely to increase than that for placebo/control (OR, 0.56; 95% CI, 0.32-0.99). According to the SUCRA, dexmedetomidine hydrochloride and midazolam hydrochloride were associated with the least increase in overall mortality among all intravenously delivered preventive interventions for delirium.

Risk of Bias and Publication Bias

We found that 59.4% (241 of 406) of studies had an overall low risk of bias, 20.0% (81 of 406) of studies had an overall unclear risk of bias, and 20.7% (84 of 406) of studies had an overall high risk of bias. In addition, the occurrence of an unclear risk of bias due to unclear reporting of randomization procedures or blinding was frequently observed (eFigure 4A-D in the Supplement).

Funnel plots of publication bias across the included studies (eFigure 5A-L in the Supplement) revealed general symmetry, and Egger test results indicated no significant publication bias among the articles included in the NMA. Detailed information on the inconsistency evaluation and the estimated between-study variance are listed in eTable 6 and eTable 7 in the Supplement. In general, NMAs did not demonstrate inconsistency in terms of either local inconsistency, as assessed using the loop-specific approach and the node-splitting method, or global inconsistency, as assessed using the design by treatment interaction method, with the exception of response rates to therapeutic interventions for delirium. Specifically, there was significant inconsistency between the direct and indirect evidence for olanzapine vs placebo. The direct evidence between these 2 arms was based on a single study[38] with an extreme OR. Therefore, we performed a sensitivity test with removal of that study. The main result of the sensitivity test showed the same results as the previous findings. Haloperidol plus lorazepam still had the best response rate.

Discussion

To our knowledge, the present study is the first NMA to investigate treatment and prevention interventions for delirium, and numerous novel results were revealed. In brief, haloperidol plus lorazepam provided the best response rate for the treatment of delirium. To prevent the occurrence of delirium, ramelteon appeared to be the optimal preventive intervention with the lowest delirium incidence rate. Compared with previous pairwise meta-analyses, our study provided clearer evidence regarding the relative benefit and safety of different pharmacological treatments for delirium. Specifically,

Table 2. League Table of Occurrence Rate of Delirium During Delirium Prevention in Individuals at High Risk of Delirium[a]

Ramelteon																	0.07 (0.01-0.54)[b]					
1.04 (0.02-47.04)	Suvorexant																0.06 (0.00-1.19)					
0.27 (0.02-3.29)	0.26 (0.01-6.45)	Olanzapine															0.25 (0.15-0.40)[b]					
0.32 (0.01-6.74)	0.30 (0.01-11.86)	1.17 (0.12-11.38)	Donepezil hydrochloride														0.21 (0.03-1.32)					
0.25 (0.02-3.45)	0.24 (0.01-6.59)	0.92 (0.18-4.81)	0.79 (0.07-8.81)	Risperidone													0.27 (0.10-0.69)[b]					
0.23 (0.01-3.48)	0.22 (0.01-6.50)	0.84 (0.14-5.14)	0.71 (0.06-8.97)	0.91 (0.12-6.63)	Propofol plus midazolam hydrochloride												0.30 (0.09-0.99)[b]					
0.13 (0.01-1.38)	0.13 (0.01-2.81)	0.50 (0.16-1.52)	0.42 (0.05-3.41)	0.54 (0.13-2.14)	0.59 (0.12-2.86)	Dexmede-tomidine hydrochloride				0.70 (0.37-1.32)						0.22 (0.05-0.91)[b]	0.49 (0.28-0.84)[b]			0.24 (0.06-0.92)[b]	0.13 (0.06-0.29)[b]	
0.14 (0.01-1.80)	0.13 (0.00-3.47)	0.51 (0.11-2.42)	0.43 (0.04-4.56)	0.55 (0.09-3.20)	0.61 (0.09-4.11)	1.02 (0.29-3.67)	Ondansetron hydrochloride										0.49 (0.22-1.07)					
0.11 (0.01-1.24)	0.10 (0.00-2.46)	0.40 (0.11-1.51)	0.34 (0.04-3.10)	0.43 (0.09-2.05)	0.48 (0.08-2.69)	0.81 (0.31-2.13)	0.79 (0.18-3.39)	Rivastigmine tartrate									0.60 (0.21-1.73)					
0.09 (0.01-1.09)	0.09 (0.00-2.15)	0.34 (0.08-1.37)	0.29 (0.03-2.75)	0.37 (0.07-1.85)	0.41 (0.07-2.42)	0.69 (0.30-1.58)	0.67 (0.15-3.07)	0.85 (0.24-3.06)	Lorazepam													
0.09 (0.01-1.04)	0.09 (0.00-2.05)	0.33 (0.08-1.28)	0.28 (0.03-2.60)	0.36 (0.07-1.74)	0.39 (0.07-2.27)	0.66 (0.24-1.81)	0.65 (0.15-2.88)	0.82 (0.24-2.83)	0.97 (0.26-3.56)	Melatonin							0.50 (0.07-3.73)					
0.07 (0.01-0.75)[b]	0.07 (0.00-1.53)	0.27 (0.09-0.81)[b]	0.23 (0.03-1.85)	0.29 (0.08-1.15)	0.32 (0.07-1.55)	0.55 (0.30-1.02)	0.54 (0.15-1.88)	0.68 (0.26-1.76)	0.80 (0.28-2.25)	0.83 (0.30-2.26)	Haloperidol						0.88 (0.63-1.21)					
0.07 (0.01-0.66)[b]	0.06 (0.00-1.36)	0.25 (0.09-0.69)[b]	0.21 (0.03-1.62)	0.27 (0.07-0.99)[b]	0.30 (0.07-1.33)	0.50 (0.31-0.80)[b]	0.49 (0.15-1.60)	0.62 (0.26-1.46)	0.73 (0.28-1.89)	0.76 (0.30-1.87)	0.91 (0.60-1.38)	Placebo/ control	0.82 (0.58-1.14)	0.75 (0.17-3.32)								
0.05 (0.00-0.59)[b]	0.05 (0.00-1.18)	0.20 (0.05-0.71)[b]	0.17 (0.02-1.48)	0.21 (0.05-0.97)[b]	0.23 (0.04-1.28)	0.40 (0.16-0.99)[b]	0.39 (0.09-1.60)	0.49 (0.15-1.57)	0.58 (0.17-1.98)	0.60 (0.18-1.99)	0.72 (0.30-1.75)	0.79 (0.36-1.73)	Gabapentin								
0.05 (0.00-0.89)[b]	0.05 (0.00-1.61)	0.19 (0.02-1.39)	0.16 (0.01-2.30)	0.20 (0.02-1.77)	0.22 (0.02-2.21)	0.38 (0.06-2.27)	0.37 (0.04-3.00)	0.47 (0.07-3.23)	0.55 (0.08-3.96)	0.57 (0.08-4.02)	0.68 (0.11-4.08)	0.75 (0.13-4.26)	0.95 (0.14-6.37)	Clonidine hydrochloride							
0.04 (0.00-0.44)[b]	0.04 (0.00-0.87)[b]	0.14 (0.04-0.55)[b]	0.12 (0.01-1.11)	0.15 (0.03-0.75)[b]	0.17 (0.03-0.97)[b]	0.28 (0.12-0.63)[b]	0.27 (0.06-1.24)	0.35 (0.10-1.23)	0.41 (0.13-1.30)	0.42 (0.11-1.56)	0.51 (0.19-1.41)	0.56 (0.22-1.42)	0.71 (0.21-2.39)	0.75 (0.10-5.36)	Propofol	1.00 (0.36-2.75)					
0.02 (0.00-0.26)[b]	0.02 (0.00-0.51)[b]	0.08 (0.02-0.31)[b]	0.07 (0.01-0.64)[b]	0.09 (0.02-0.42)[b]	0.10 (0.02-0.55)[b]	0.17 (0.08-0.34)[b]	0.16 (0.04-0.70)[b]	0.21 (0.06-0.69)[b]	0.24 (0.08-0.72)[b]	0.25 (0.07-0.87)[b]	0.31 (0.12-0.77)[b]	0.34 (0.15-0.77)[b]	0.42 (0.14-1.33)	0.45 (0.07-3.06)	0.60 (0.24-1.49)	Midazolam hydrochloride	0.71 (0.19-2.70)				
0.02 (0.00-0.29)[b]	0.02 (0.00-0.53)[b]	0.06 (0.01-0.47)[b]	0.05 (0.00-0.77)[b]	0.06 (0.01-0.60)[b]	0.07 (0.01-0.74)[b]	0.12 (0.02-0.69)[b]	0.12 (0.01-1.02)	0.15 (0.02-1.10)	0.17 (0.03-1.21)	0.18 (0.02-1.37)	0.22 (0.03-1.39)	0.24 (0.04-1.46)	0.30 (0.04-2.17)	0.32 (0.03-3.91)	0.43 (0.07-2.70)	0.71 (0.14-3.54)	Midazolam hydrochloride plus clonidine hydrochloride				

[a] Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as the delirium occurrence rate for the outcome of delirium prevention. Drugs are reported in order of the mean ranking of delirium prevention, and outcomes are expressed as odds ratios (95% CIs). For the pairwise meta-analyses, odds ratios less than 1 indicate that the treatment specified in the row is more preventive than that specified in the column. For the network meta-analysis, odds ratios less than 1 indicate that the treatment specified in the column is more preventive than that specified in the row.

[b] Statistically significant.

previous meta-analyses did not provide evidence regarding which specific antipsychotic medications are the best candidates for the treatment of delirium compared with a placebo.[17,39] The detailed pharmacodynamic mechanism of each medication investigated in the present network meta-analysis is listed in eTable 8 in the Supplement.

A main finding herein was that haloperidol plus lorazepam provided the highest response rate among the examined therapeutic interventions for delirium. Our findings complement previous meta-analyses that only indicated antipsychotics as a whole to be the best delirium treatment.[17,39] Indeed, current clinical consensus guidelines did not recommend specific pharmacotherapy to manage delirium.[40] In contrast, our results suggest the superiority of haloperidol plus lorazepam for the treatment of delirium and the superiority of ramelteon for the prevention of delirium. Our findings also provide rationales for future RCTs to compare specific treatments and to potentially revise specific treatments and prevention in the treatment guidelines. The effectiveness of haloperidol plus lorazepam may be derived in part from the mitigation of extrapyramidal symptoms associated with this combination drug.[41] Moreover, lorazepam coprescription may further alleviate agitated delirious symptoms.[42] Although there was inconsistency between the direct and indirect evidence among some of the treatment arms herein, the main results and superiority of haloperidol plus lorazepam did not change based on the sensitivity test that removed some studies with extreme ORs. Therefore, haloperidol plus lorazepam seems to be a superior therapeutic choice in patients with delirium.

Our second main finding was that ramelteon, a melatonin agonist, appeared to be the best intervention to prevent the emergence of delirium based on the pairwise meta-analysis, NMA, and SUCRA. Ramelteon is believed to contribute to delirium prevention owing to its high affinity toward melatonin receptors 1 and 2, which are associated with the development of delirium.[43] Furthermore, among antipsychotics, olanzapine was associated with the lowest occurrence rate of delirium. Although previous pairwise meta-analyses have assessed the preventive influence of antipsychotics as a class,[17,44,45] in the present study we were able to consider the overall benefit of individual antipsychotics tested to date as preventive interventions for delirium.

Finally, considering the overall safety of the pharmacological treatments for delirium in terms of all-cause mortality, the present NMA indicated that none of the pharmacological interventions were inferior to placebo/control among the various therapeutic and preventive interventions for delirium examined in this analysis. These findings were consistent in part with the results of previous meta-analyses, which suggested that treatment with antipsychotics does not increase the all-cause mortality in patients with delirium.[17,46] Our NMA further provided evidence that the safety of individual medications examined for delirium treatment or prevention in this study was similar to that of placebo/control.

Limitations

Several limitations of the present NMA need to be considered in the interpretation of our results. First, some of the analyses in this study were limited by underpowered statistics, including heterogeneity in the characteristics of the participants (eg, underlying diseases, initial severity of delirium, and trial duration), the small trial numbers for some treatment arms, heterogeneous psychopathology assessment tools, and the inclusion of few studies on the influence of different interventions for the treatment and prevention of hypoactive delirium. Second, differences in the route of administration (ie, oral vs intravenous) of medications across the included studies may limit the comparability of outcomes in the present NMA; hence, we compared studies involving intravenous medication in subgroup analyses. Third, most of the evidence supporting the benefit of ramelteon was derived from an RCT conducted by Hatta and coworkers.[43] Because the network for delirium prevention is poorly connected, no indirect evidence was available to support this finding. Fourth, the potential confounding associations of the use of rescue medications might have influenced the response rankings because few studies had assessed the therapeutic benefits with rescue medications.

Conclusions

The results of the present NMA suggest that haloperidol plus lorazepam had the best overall response rate for the treatment of delirium, while ramelteon ranked the best in terms of the prevention of delirium occurrence. None of the pharmacological interventions were inferior to placebo/control in terms of all-cause mortality among the various therapeutic and preventive interventions for delirium. However, when delirium occurs, clinicians should not only prescribe medication to manage delirium symptoms but also begin surveillance to identify any potential abnormal physical conditions behind the delirium. Future large-scale RCTs investigating the treatment effect of haloperidol plus lorazepam and the preventive effect of ramelteon are warranted to corroborate the findings of our NMA.

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