**The Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium: a Network Meta-analysis**

*Running title: Management of Delirium – NMA*

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**Key Points:**

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

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

**Meaning.** Regardingthe delirium response rate, delirium occurrence rate and tolerability, the use of a lorazepam/haloperidol combination and ramelteon is suggested for the treatment and prevention of delirium.

**Abstract**

**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 prevention and treatment.

**DATA SOURCES:** PubMed, EMBASE, ProQuest, ScienceDirect, Cochrane CENTRAL, Web of Science, ClinicalKey and ClinicalTrials.gov from inception to May 17th, 2018.

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

**DATA EXTRACTION AND SYNTHESIS:** To extract the data according to a pre-determined list of interest. PRISMA guidelines were applied, and all meta-analytic procedures were conducted under the random effect model.

**MAIN OUTCOMES AND MEASURES:** The primary outcomes were (a) treatment response in delirious patients and (b) the incidence of delirium in patients at risk of delirium.

**RESULTS:** A total of 58 RCTs were included, in which 20 RCTs with a total of 1435 participants comparing the outcomes of treatment and 38 RCTs with a total of 8168 participants examining the prevention of delirium. The network meta-analysis (NMA) demonstrated that lorazepam*+*haloperidol provided the best response rate for delirium treatment [OR (odds ratio) = 28.13, 95%CIs (confidence intervals) = 2.38 to 333.08] and that ramelteon treatment had the lowest delirium occurrence rate for delirium prevention (OR = 0.02, 95%CIs = 0.00 to 0.29) comparing to placebo/control groups. For delirium prevention, the ramelteon, olanzapine, risperidone, and dexmedetomidine groups had significantly lower delirium occurrence rates than those of placebo/control groups [ORs: 0.07 (95%CIs: 0.01 to 0.66), 0.25 (95%CIs: 0.09 to 0.69), 0.27 (95%CIs: 0.07 to 0.99), 0.50 (95%CIs: 0.31 to 0.80)]. None of the pharmacological treatments was significantly associated with a higher risk of all-cause mortality comparing to placebo/control.

**CONCLUSIONS AND RELEVANCE:** This NMA demonstrated that lorazepam*+*haloperidol 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.

*Keywords: tolerability; efficacy; systematic review; network meta-analysis; delirium; management.*

**Abbreviations:** AUC: area under the curve; CI: confidence interval; DSM: the Diagnostic and Statistical Manual of Mental Disorders; ICD: international classification of diseases; ICU: intensive care unit; NEECHAM: Neelon and Champagne; NMA: network meta-analysis; OR: odds ratio; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCT: randomized clinical trial; SUCRA: surface under the cumulative ranking curve.

**Introduction**

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% in medical inpatients2 and between 9 and 87% in 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 (e.g., dementia), prolonged hospitalization, institutionalization, and increased mortality.4 Nevertheless, and most importantly, it has been estimated that 30 to 40% of delirium cases are potentially preventable.1,5

 Several risk factors, such as age, pre-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 (for example, antipsychotics and melatonergic agents) have been assessed for use in the prevention and treatment 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, for the treatment of agitated delirium.13-16 However, a pair-wise 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 medications18,19 have been suggested to have a role in the prevention of delirium. On the other hand, there have been concerns in 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 prevention and treatment 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.

**Methods**

Detailed information regarding the methods/materials is presented in eMethods. In brief, the current NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension guidelines (eTable 1).20 By searching the databases of PubMed, Embase, ProQuest, ScienceDirect, Cochrane Library, ClinicalKey, Web of Science, and ClinicalTrials.gov, we identified randomized controlled trials (RCTs), of both placebo-controlled and active-controlled designs, conducted in adult humans. Peer-reviewed articles published in any language were considered for inclusion.

Two types of pharmacological intervention were considered for inclusion: (a) therapeutic interventions and (b) preventative interventions that could affect 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 effect NMA, which consisted of direct and indirect comparisons, was conducted to compare the effect sizes between studies within the same type of intervention (i.e., treatment or prevention).22 Heterogeneity among the included studies was evaluated by the tau statistic. Comparison-adjusted funnel plot23 and the Egger test were conducted to examine potential small study bias (i.e., publication bias), after treatments were ordered from the oldest to the newest.

Subgroup analysis was used to evaluate the potential confounding effects of the route of administration (i.e., 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 relationships between the delirium response rate/occurrence rate of treatments and characteristics of participants. Finally, we evaluated the potential local inconsistency between direct and indirect evidence within the network using the loop-specific approach and the side-splitting models.25,26 Furthermore, we also employed 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). However, 99 were excluded for various reasons (see eFigure 1 and eTable 2 for a summary). Finally, 58 articles were included in the current study (eTable 3A and 3B).

Among the 58 articles, 20 provided evidence relating to different therapeutic interventions for delirium, whilst 38 assessed preventative interventions for delirium. The whole geometric distribution of the treatment arms is provided in Figure 1A-1B and eFigure 2A-2D (available online).

**Characteristics of the included studies**

Among the 20 RCTs investigating the treatment of delirium, a total of 1435 participants were included at baseline, with different health conditions including acquired immune deficiency syndrome (AIDS), hospitalization in general wards or intensive care units (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 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 intensive care units (ICUs), patients receiving flap surgery, 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 chart-based method for the identification of delirium,37 and the intensive care delirium screening checklist.29

**Treatment interventions for delirium: response rates**

In total, 20 included articles stated the response rates to different treatments for delirium totaling fourteen treatment arms, including placebo/control, chlorpromazine, lorazepam, risperidone, quetiapine, haloperidol, amisulpride, olanzapine, dexmedetomidine, ondansetron, haloperidol *plus* lorazepam, haloperidol *plus* rivastigmine, ziprasidone, and rivastigmine (Table 1A and Figure 1A). In the network meta-analysis, only the response rates for haloperidol and haloperidol *plus* lorazepam were significantly superior to those for placebo/control groups (OR = 2.37 [95%CIs: 1.04 to 5.43] and OR = 28.13 [95%CIs: 2.38 to 333.08], respectively). However, the chlorpromazine, lorazepam, risperidone, quetiapine, amisulpride, olanzapine, dexmedetomidine, ondansetron, haloperidol *plus* rivastigmine, ziprasidone, and rivastigmine did not show significantly better response rates than those of placebo/control groups. In addition, the response rate for the haloperidol *plus* lorazepam group was significantly higher than the rates for the haloperidol, risperidone, ondansetron and placebo/control groups (Table 1A and Figure 1C). According to the SUCRA for response rate, lorazepam *plus* haloperidol was ranked the best among all treatments (eTable 4A, available online). A meta-regression using restricted maximum likelihood estimators did not find that age had the potential moderating effect on 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, ten treatment arms comprising placebo/control, chlorpromazine, lorazepam, risperidone, quetiapine, haloperidol, amisulpride, olanzapine, dexmedetomidine, and ondansetron were included (eTable 5A and eFigure 2A, available online). In the NMA, when compared with placebo/control groups, the response rates of the chlorpromazine, lorazepam, haloperidol, amisulpride, quetiapine, ondansetron, and olanzapine groups were significantly superior (OR= 45.34 [95%CIs: 5.29 to 388.42], OR = 36.30 [95%CIs: 2.98 to 442.10], OR = 16.16 [95%CIs: 5.88 to 44.40], OR = 18.14 [95%CIs: 1.57 to 209.42], OR = 16.74 [95%CIs: 3.13 to 89.44], OR = 13.44 [95%CIs: 2.82 to 64.11], and OR = 10.14 [95%CIs: 3.86 to 26.62], respectively, eFigure 3A). Moreover, the response rates for the chlorpromazine and haloperidol groups were significantly superior to that of the dexmedetomidine group (eTable 5A, available online). Finally, chlorpromazine exhibited the best response rate when trials that did not use rescue medications were considered (eTable 4B, available online).

**Association between individual therapeutic interventions for delirium and all-cause mortality**

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

**Preventative interventions for delirium**

Thirty-eight articles provided evidence related to different preventative interventions for delirium. In total, 17 treatment arms comprising placebo/control, propofol *plus* midazolam, dexmedetomidine, midazolam, clonidine *plus* midazolam, olanzapine, ondansetron, clonidine, melatonin, propofol, haloperidol, lorazepam, rivastigmine, gabapentin, ramelteon, suvorexant and risperidone groups were included (Table 1B and Figure 1B). For the NMA, Figure 1D depicts the forest plot of delirium occurrence rates for different preventative treatments relative to placebo/control groups. Only ramelteon, dexmedetomidine, olanzapine, and risperidone yielded a significantly greater decrease in the occurrence of delirium than a placebo did (ORs: 0.07 [95%CIs: 0.01 to 0.66], 0.50 [95%CIs: 0.31 to 0.80], 0.25 [95%CIs: 0.09 to 0.69], 0.27 [95%CIs: 0.07 to 0.99], respectively). On the other hand, midazolam was significantly associated with a greater delirium occurrence than a placebo/control did for the prevention of delirium (OR: 2.94 [95%CIs: 1.30 to 6.67]). The other preventative interventions such as propofol *plus* midazolam, clonidine *plus* midazolam, ondansetron, clonidine, melatonin, propofol, haloperidol, lorazepam, rivastigmine, gabapentin, or suvorexant did not show significantly different risks of delirium occurrence compared to placebo/control. According to the SUCRA, ramelteon was ranked best for the prevention of delirium occurrence (eTable 4D, available online). In addition, the mean age did not have a significant effect on the occurrence rate according to meta-regression analysis.

Twenty-three articles provided evidence of different preventative interventions for delirium that were delivered intravenously (eTable 5C and eFigure 3C). Those intervention groups comprised placebo/control, haloperidol, lorazepam, ondansetron, dexmedetomidine, midazolam *plus* propofol, midazolam *plus* clonidine, midazolam, propofol, and clonidine groups. In the pairwise meta-analysis, the dexmedetomidine had significantly lower delirium occurrence rate than that of the placebo/control group (OR: 0.5 [95%CIs: 0.31 to 0.8]). According to the SUCRA, propofol *plus* midazolam and dexmedetomidine were the two top-ranked intravenously-delivered preventative interventions (eTable 4E).

**Association between individual preventative interventions for delirium and all-cause mortality**

Fifteen articles provided evidence of the association between different preventative interventions for delirium and all-cause mortality, including nine treatment arms comprising placebo/control, propofol *plus* midazolam, dexmedetomidine, midazolam, rivastigmine, melatonin, lorazepam, haloperidol, and propofol groups (eTable 5D and eFigure 2D, available online). 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 shows the forest plot of all-cause mortality rates across different preventative interventions for delirium relative to placebo/control groups. According to the SUCRA, midazolam had the lowest likelihood of increasing the all-cause mortality rate among all preventative interventions for delirium examined (eTable 4F). The mean age did not moderate outcomes according to meta-regression analysis.

Twelve articles provided data on all-cause mortality after different intravenous preventative treatments for delirium, including placebo/control, haloperidol, lorazepam, dexmedetomidine, midazolam *plus* propofol, midazolam, and propofol. In the pairwise meta-analysis, the all-cause mortality rate during dexmedetomidine treatment was significantly less likely to increase than that under placebo/control treatment (OR: 0.56 [95%CIs: 0.32 to 0.99]). According to the SUCRA, dexmedetomidine and midazolam had the lowest rank of increasing the overall mortality among all intravenously-delivered preventative interventions for delirium.

**Risk of bias and publication bias**

We found that 59.36%, 19.95%, and 20.69% of studies had an overall low, unclear, and high risk of bias, respectively. In addition, the occurrence of an unclear risk of bias due to unclear reporting of randomization procedures or blindness was frequently observed (eFigure 4A to 4D, available online).

Funnel plots of publication bias across the included studies (eFigure 5A to 5L, available online) revealed general symmetry, and the results of Egger’s test indicated no significant publication bias among the articles included in the NMA. The detailed information of inconsistency evaluation and the estimated between-study variance were provided in eTable 6 and eTable 7. In general, NMAs do 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 method, with the exception of response rates to therapeutic interventions for delirium. To be specifically, there is significant inconsistence between the direct and indirect evidences between the olanzapine versus placebo. The direct evidence between these two arms was only based on a single study38 with an extreme odds ratio. Therefore, we did the sensitivity test by removal of this study. The main result of sensitivity test showed the same results as previous findings. The haloperidol *plus* lorazepam was still associated with the best response rate.

**Discussion**

To our knowledge, the current study was the first NMA to investigate prevention and treatment interventions for delirium, and numerous novel results were revealed. In brief, lorazepam *plus* haloperidol provided the best response rate for the treatment of delirium. To prevent the occurrence of delirium, ramelteon appeared to be the optimal preventative 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 pharmacologic treatments for delirium. Specifically, previous meta-analyses did not provide evidence regarding which specific antipsychotic medications are the best candidates for the treatment of delirium when compared with a placebo.17,39 The detailed pharmacodynamic mechanism of each medication is listed in eTable 8.

The main finding was that lorazepam *plus* haloperidol provided the highest response rate among the examined therapeutic interventions for delirium. Our findings fill up the missing pieces of previous meta-analyses, as which only indicated antipsychotics as a whole to be the best delirium treatment.17,39 Indeed, current clinical guidelines did not consensually recommend specific pharmacotherapy to manage delirium.40 Our results, however, suggest the superiority of lorazepam *plus* haloperidol and treatment of ramelteon for prevention. Our findings also provide rationales to conduct future RCTs to compare specific treatments and the potential revision of using specific treatment and prevention in the treatment guidelines. The great efficacy of lorazepam *plus* haloperidol may be partly derived from the mitigation of extrapyramidal symptoms associated with haloperidol by the co-prescription of lorazepam.41 Moreover, lorazepam co-prescription may further alleviate agitated delirious symptoms.42 Although there was some inconsistency between the direct and indirect evidences among some of the treatment arms, the main results and superiority of lorazepam *plus* haloperidol would not change based upon the sensitivity test which removed some studies with extreme odds ratio. Therefore, lorazepam *plus* haloperidol would be a superior therapeutic choice in delirious patients.

Our second main finding was that ramelteon, a melatonin agonist, appeared to be the best intervention to prevent the emergence of delirium based upon pairwise meta-analysis, NMA, and the SUCRA. Ramelteon was believed to contribute to delirium prevention owing to its high affinity towards melatonin receptor 1 and 2 (MT1 and MT2), 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 preventative efficacy of antipsychotics as a class,17,44,45 in the current study, we were able to consider the overall benefit of individual antipsychotics tested to date as preventative interventions for delirium.

Finally, considering the overall safety of pharmacological treatments for delirium in terms of all-cause mortality, the current NMA indicated that none of the pharmacological interventions was inferior to the placebo/control group among the various therapeutic and preventative interventions for delirium examined in this analysis. These findings were partially consistent with the results of previous meta-analyses, which suggested that treatment with overall antipsychotics does not increase the all-cause mortality in delirious patients.17,46 Our NMA further provided evidence as to the safety of individual medications, demonstrating that the safety of the medications employed for therapeutic or preventative intervention for delirium examined in this study was similar to those of placebo/control groups.

Several limitations of the current NMA need to be considered for the interpretation of its results. First, some of the analyses in this study were limited by underpowered statistics, including heterogeneity in the characteristics of the participants (e.g., 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 very few studies of the efficacy of different interventions for the treatment and prevention of hypoactive delirium. Second, differences in the route of administration (i.e., oral versus intravenous) of medications across the included studies may limit the comparability of outcomes in the current NMA, and 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 As the network for delirium prevention is poorly connected, no indirect evidence is available to support this finding. Fourth, the potential confounding effect of the use of rescue medications might affect the response rankings, because relatively few studies had assessed the therapeutic benefits with rescue medications.

**Conclusion**

The current NMA suggested that lorazepam *plus* haloperidol had the best overall response rate for the treatment of delirium, while ramelteon ranked best in terms of the prevention of delirium occurrence. None of the pharmacological interventions was inferior to the placebo/control group in terms of all-cause mortality among the various therapeutic and preventative interventions for delirium. Future large-scale RCTs investigating the treatment effect of lorazepam *plus* haloperidol and preventative effect of ramelteon are warranted to corroborate the findings of our network meta-analysis.

**Declaration of Interest**

The authors report no financial interests or potential conflicts of interest.

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**Figure legends**

**Figure 1. Network structure and forest plot of the current network meta-analysis in reference to placebo/control groups.**

Figure 1A indicated the structures of whole network structure of network meta-analysis of delirium treatment; figure 1B indicated the structures of whole network structure of network meta-analysis of delirium prevention; When ES > 1, it indicates (fig.1C) better response/(fig. 1D) lower occurrence rate by medication

Abbreviations: Ami: amisulpride; Chl: chlorpromazine; CI: confidence interval; Clo: clonidine; Dex: dexmedetomidine; ES: effect size; Gab: gabapentin; H+L: haloperidol+lorazepam; H+R: haloperidol+rivastigmine; Hal: haloperidol; Lor: lorazepam; M+C: midazolam+clonidine; Mel: melatonin; Mid: midazolam; Ola: olanzapine; Ond: ondansetron; P+M: propofol+midazolam; PrI: predictor interval; Pro: propofol; Que: quetiapine; Ram: ramelteon; Ris: risperidone; Riv: rivastigmine; Suv: suvorexant; Zip: ziprasidone.

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**Table 1A:** League table of treatment response in delirium subjects

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| H+L |  |  |  |  |  |  |  | **\*12.05 (2.34,62.50)** |  |  |  |  |  |
| 1.29 (0.02,100.28) | Riv |  |  |  |  |  |  |  |  |  |  |  | 21.74 (0.91,500.00) |
| 4.21 (0.14,130.82) | 3.27 (0.04,284.38) | Chl | 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) | Lor |  |  |  |  | 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) | Que | 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) | Ami |  |  |  |  |  |  |  |  |
| 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) | Zip |  | 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) | Ola | 0.63 (0.29,1.36) |  |  |  | 1.17 (0.44,3.15) | **\*10.42 (3.88,27.78)** |
| **\*11.85 (1.15,121.81)** | 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) | Hal | 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) | Dex |  | 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) | H+R |  |  |  |
| **\*17.91 (1.42,226.13)** | 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) | Ris |  | 2.56 (0.94,6.94) |
| **\*22.86 (1.46,357.98)** | 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) | Ond | 1.46 (0.33,6.54) |
| **\*28.13 (2.38,333.08)** | 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)** | 2.06 (0.51,8.34) | 2.06 (0.27,15.71) | 1.57 (0.56,4.38) | 1.23 (0.24,6.22) | P/C |

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as response rates for the outcome of delirium treatment. Drugs are reported in order of mean ranking of delirium treatment, and outcomes are expressed as odds ratios (ORs) (95% confidence intervals).

For the pairwise meta-analyses, ORs of less than 1 indicate that the treatment specified in the row is more efficacious than that specified in the column.

For the network meta-analysis (NMA), ORs of less than 1 indicate that the treatment specified in the column is more efficacious than that specified in the row.

Bold results marked with \* indicate statistical significance.

Abbreviations: Ami: amisulpride; Chl: chlorpromazine; Dex: dexmedetomidine; H+L: haloperidol+lorazepam; H+R: haloperidol+rivastigmine; Hal: haloperidol; Lor: lorazepam; Ola: olanzapine; Ond: ondansetron; P/C: placebo or control; Que: quetiapine; Ris: risperidone; Riv: rivastigmine; Zip: ziprasidone.

**Table 1B:** League table of occurrence rate of delirium during delirium prevention in high-risk delirium subjects

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ram |  |  |  |  |  |  |  |  |  |  |  | **\*0.07 (0.01,0.54)** |  |  |  |  |  |
| 1.04 (0.02,47.04) | Suv |  |  |  |  |  |  |  |  |  |  | 0.06 (0.00,1.19) |  |  |  |  |  |
| 0.27 (0.02,3.29) | 0.26 (0.01,6.45) | Ola |  |  |  |  |  |  |  |  |  | **\*0.25 (0.15,0.40)** |  |  |  |  |  |
| 0.32 (0.01,6.74) | 0.30 (0.01,11.86) | 1.17 (0.12,11.38) | Don |  |  |  |  |  |  |  |  | 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) | Ris |  |  |  |  |  |  |  | **\*0.27 (0.10,0.69)** |  |  |  |  |  |
| 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) | P+M |  |  |  |  |  |  | **\*0.30 (0.09,0.99)** |  |  |  |  |  |
| 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) | Dex |  |  | 0.70 (0.37,1.32) |  | **\*0.22 (0.05,0.91)** | **\*0.49 (0.28,0.84)** |  |  | **\*0.24 (0.06,0.92)** | **\*0.13 (0.06,0.29)** |  |
| 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) | Ond |  |  |  |  | 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) | Riv |  |  |  | 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) | Lor |  |  |  |  |  |  |  |  |
| 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) | Mel |  | 0.50 (0.07,3.73) |  |  |  |  |  |
| **\*0.07 (0.01,0.75)** | 0.07 (0.00,1.53) | **\*0.27 (0.09,0.81)** | 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) | Hal | 0.88 (0.63,1.21) |  |  |  |  |  |
| **\*0.07 (0.01,0.66)** | 0.06 (0.00,1.36) | **\*0.25 (0.09,0.69)** | 0.21 (0.03,1.62) | **\*0.27 (0.07,0.99)** | 0.30 (0.07,1.33) | **\*0.50 (0.31,0.80)** | 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) | P/C | 0.82 (0.58,1.14) | 0.75 (0.17,3.32) |  |  |  |
| **\*0.05 (0.00,0.59)** | 0.05 (0.00,1.18) | **\*0.20 (0.05,0.71)** | 0.17 (0.02,1.48) | **\*0.21 (0.05,0.97)** | 0.23 (0.04,1.28) | **\*0.40 (0.16,0.99)** | 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) | Gab |  |  |  |  |
| **\*0.05 (0.00,0.89)** | 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) | Clo |  |  |  |
| **\*0.04 (0.00,0.44)** | **\*0.04 (0.00,0.87)** | **\*0.14 (0.04,0.55)** | 0.12 (0.01,1.11) | **\*0.15 (0.03,0.75)** | **\*0.17 (0.03,0.97)** | **\*0.28 (0.12,0.63)** | 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) | Pro | 1.00 (0.36,2.75) |  |
| **\*0.02 (0.00,0.26)** | **\*0.02 (0.00,0.51)** | **\*0.08 (0.02,0.31)** | **\*0.07 (0.01,0.64)** | **\*0.09 (0.02,0.42)** | **\*0.10 (0.02,0.55)** | **\*0.17 (0.08,0.34)** | **\*0.16 (0.04,0.70)** | **\*0.21 (0.06,0.69)** | **\*0.24 (0.08,0.72)** | **\*0.25 (0.07,0.87)** | **\*0.31 (0.12,0.77)** | **\*0.34 (0.15,0.77)** | 0.42 (0.14,1.33) | 0.45 (0.07,3.06) | 0.60 (0.24,1.49) | Mid | 0.71 (0.19,2.70) |
| **\*0.02 (0.00,0.29)** | **\*0.02 (0.00,0.53)** | **\*0.06 (0.01,0.47)** | **\*0.05 (0.00,0.77)** | **\*0.06 (0.01,0.60)** | **\*0.07 (0.01,0.74)** | **\*0.12 (0.02,0.69)** | 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) | M+C |

Pairwise (upper-right portion) and network (lower-left portion) meta-analytic results are presented as the delirium occurrence rate for the outcome of delirium prevention. Drugs are reported in order of mean ranking of delirium prevention, and outcomes are expressed as odds ratios (ORs) (95% confidence intervals).

For the pairwise meta-analyses, ORs of 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 (NMA), ORs of less than 1 indicate that the treatment specified in the column is more preventive than that specified in the row.

Bold results marked with \* indicate statistical significance.

Abbreviations: Chl: chlorpromazine; Clo: clonidine; Dex: dexmedetomidine; Don: donepezil; Gab: gabapentin; Hal: haloperidol; Lor: lorazepam; M+C: midazolam+clonidine; Mel: melatonin; Mid: midazolam; Ola: olanzapine; Ond: ondansetron; P/C: placebo or control; P+M: propofol+midazolam; Pro: propofol; Ram: ramelteon; Ris: risperidone; Riv: rivastigmine; Suv: suvorexant.