Ther Adv Psychopharmacol

2023, Vol. 13: 1–16

DOI: 10.1177/
20451253231152113

Olanzapine for the treatment of ICU delirium: a systematic review and meta-analysis

Si Bo Liu*, Shan Liu*, Kai Gao*, Guo Zhi Wu, Guo Zu and Jin Jie Liu

Abstract

Background: As an atypical antipsychotic drug, olanzapine is one of the most commonly used drugs for delirium control. There are no systematic evaluations or meta-analyses of the efficacy and safety of olanzapine for delirium control in critically ill adults.

Objectives: In this meta-analysis, we evaluated the efficacy and safety of olanzapine for delirium control in critically ill adults in the intensive care unit (ICU).

Data Sources and Methods: From inception to October 2022, 12 electronic databases were searched. We retrieved randomized controlled trials (RCTs) and retrospective cohort studies of critically ill adults with delirium that compared the effects of olanzapine and other interventions, including routine care (no intervention), nonpharmaceutical interventions and pharmaceutical interventions. The main outcome measures were the (a) relief of delirium symptoms and (b) a decrease in delirium duration. Secondary outcomes were ICU and in-hospital mortality, ICU and hospital length of stay, incidence of adverse events, cognitive function, sleep quality, quality of life, mechanical ventilation time, endotracheal intubation rate and delirium recurrence rate. We applied a random effects model.

Results: Data from 10 studies (four RCTs and six retrospective cohort studies) involving 7076 patients (2459 in the olanzapine group and 4617 in the control group) were included. Olanzapine did not effectively relieve delirium symptoms (OR = 1.36, 95% CI [0.83, 2.28], $p = 0.21$), nor did it shorten the duration of delirium [standardized mean difference (SMD) = 0.02, 95% CI [−1.04, 1.09], $p = 0.97$] when compared with other interventions. Pooled data from three studies showed that the use of olanzapine reduced the incidence of hypotension (OR = 0.44, 95% CI [0.20, 0.95], $p = 0.04$) compared with other pharmaceuticals. There was no significant difference in other secondary outcomes, including ICU or hospital length of stay, in-hospital mortality, extrapyramidal reactions, QTc interval prolongation, or overall incidence of other adverse reactions. The number of included studies was not sufficient for performing a comparison between olanzapine and no intervention.

Conclusion: Compared with other interventions, olanzapine has no advantage in alleviating delirium symptoms and shortening delirium duration in critically ill adults. However, there is some evidence that the rate of hypotension was lower in patients who received olanzapine than in those who received other pharmaceutical interventions. There was a nonsignificant difference in the length of ICU or hospital stay, in-hospital mortality, and other adverse reactions. This study provides reference data for delirium research and clinical drug intervention strategies in critically ill adults.

Registration: Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021277232).

Keywords: delirium, intensive care unit, meta-analysis, olanzapine, systematic review

Received: 20 June 2022; revised manuscript accepted: 4 January 2023.

Correspondence to:
Jin Jie Liu
Department of No. 2 General Medicine, Dalian Municipal Central Hospital Affiliated Dalian University of Technology, Dalian 116033, China

Neurological Intensive Care Unit, Beijing Tiantan Hospital Affiliated Capital Medical University, Beijing 100050, China.
vip2ljj@163.com

Si Bo Liu
Shan Liu
Kai Gao
Guo Zhi Wu
Intensive Care Unit, Dalian Municipal Central Hospital Affiliated Dalian University of Technology, Dalian, China

Guo Zu
Department of Gastrointestinal Surgery, Dalian Municipal Central Hospital Affiliated Dalian University of Technology, Dalian, China

*S.B.L., S.L., and K.G. are co-first authors.

Introduction

The word 'delirium' comes from the Latin *delirare*, which means 'out of the ditch', deviating from a straight line or insane. The *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition; DSM-5)*, published by the American Psychiatric Association, defines delirium as an acute episode of confusion or altered consciousness, accompanied by inattention, confusion, incoherence, and sensory dysfunction.[1] The pathophysiology of delirium is not clear. The etiology includes sepsis, fracture, surgery, changes in medication, hypoglycemia, liver failure and other factors.[2] It involves complex, dynamic and multifactorial interactions among various risk factors.[3,4] Delirium is common among older and hospitalized people, and one-third of general medical patients who are 70 years of age or older have delirium.[5] A systematic review of 33 clinical studies in 2020 showed that the overall prevalence of delirium in hospitalized patients was 23%.[6] A recent meta-analysis study with patients from North America, South America, Europe, and Asia showed that 31.8% of critically ill patients in the intensive care unit (ICU) developed delirium. These patients had an increased risk for in-hospital mortality, a longer ICU and hospital stay, a longer duration of mechanical ventilation, and cognitive impairment after discharge.[7] Delirium has a huge economic impact, with the United States spending more than 164 billion dollars a year and 18 European countries spending more than 182 billion dollars a year.[2] Due to the serious negative impact of delirium on the prognosis of ICU patients and the heavy economic burden on the health system, the prevention and treatment of delirium has become one of the most concerning problems in the field of critical care medicine.

At present, there are some guidelines for the use of nonpharmacologic approaches for critically ill patients with high risk factors for delirium.[8–10] For example, the Society of Critical Care Medicine (SCCM) guidelines found limited evidence to support nonpharmacologic approaches (early mobilization);[8] however, whether nonpharmacologic approaches can effectively improve delirium outcomes remains to be fully studied.[11] Leona Bannon *et al.*[12] included 15 studies that evaluated the effectiveness of nonpharmacological interventions on the incidence and duration of delirium, in-hospital mortality, sleep quality, cognitive function, quality of life, or adverse events in critically ill patients when compared with routine care or other nonpharmaceutical or pharmaceutical interventions and showed that the current evidence did not support the use of nonpharmacological interventions for reducing the incidence and duration of delirium in critically ill patients. Burry *et al.*[13] conducted a systematic review and network meta-analysis to compare the effects of pharmacological and nonpharmacological prevention interventions on delirium occurrence in critically ill adults and showed that single and multicomponent nonpharmacological interventions did not connect to any evidence networks.

Haloperidol, a typical antipsychotic drug, is the most widely used pharmaceutical intervention for delirium.[14,15] However, haloperidol may cause a variety of adverse reactions in clinical practice, including extrapyramidal reactions, arrhythmias, QT interval prolongation, sedentary dysfunction and dystonia, especially in older patients and critically ill patients.[5,16] In addition, we should also note that the availability of the drug is an important point to make, especially in the ICU, and because this is not the case for atypical antipsychotics, such as olanzapine. More precisely, haloperidol is commonly used intravenously (and relatively safe, if ECG monitoring), although not approved by the FDA for intravenous use.[17] Atypical antipsychotics, also known as second-generation antipsychotics, are characterized by fewer extrapyramidal symptoms and other adverse reactions than the first generation of antipsychotics,[18] including olanzapine, risperidone, quetiapine, aripiprazole, etc. Therefore, more researchers focus on treatment with atypical antipsychotics.[19,20]

In the guidelines of the National Institute for Health and Clinical Excellence (NICE), olanzapine was recommended as an alternative to haloperidol.[21] As an atypical antipsychotic drug, olanzapine is one of the most commonly used drugs to treat delirium.[9,14,15] According to the clinical prescribing practices of more than 8500 delirium patients in the ICU, olanzapine accounted for 52.6% of antipsychotic recipients.[15] However, there are no systematic evaluations or meta-analyses of the efficacy and safety of olanzapine for delirium control in critically ill patients. Therefore, we conducted a systematic review of randomized controlled trials (RCTs) and retrospective cohort studies to assess the advantages and disadvantages of olanzapine *versus* placebo or any intervention for delirium control in critically ill patients.

Methods

Using the internationally acclaimed and commonly used PICOS framework for systematic review, we asked the following research question: Can olanzapine be used as a routine treatment for delirium control in critically ill adults? The program was prospectively registered with PROSPERO (CRD42021277232). The focus of this article is the results of RCTs and retrospective cohort studies. We used the Cochrane review method for framework formulation and review. This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[22]

Search strategy

The synonyms for delirium, olanzapine and critical illness were searched in PubMed, CINAHL, EMBASE, PsychINFO, Web of Science, Scopus, Cochrane Library, CNKI, Wan Fang, VIP, several clinical trial registration centers, and gray literature databases. There were no restrictions on literature types or language as of October 2022. The gray literature databases NICE Evidence and Opengrey were searched. Ongoing and unpublished trials were from the ISRCTN Registry, ClinicalTrials.gov, ICTRP Search Portal, and EU Clinical Trials Register. Publication bias was minimized to confirm positive results and incorporate unpublished negative results. In addition, we manually searched the reference lists for relevant articles to identify other trials to include in the study. Due to the lack of sufficient data, studies with only a meeting summary were excluded. The search strategy for each database is detailed in Appendix A of the supplementary document.

Inclusion and exclusion criteria

We included RCTs and retrospective cohort studies on critical illness in which researchers evaluated the effectiveness of treatment-targeted olanzapine drug intervention for relieving delirium symptoms and shortening the duration of delirium compared with other interventions, including routine care (no intervention), nonpharmaceutical intervention and pharmaceutical interventions. Critically ill patients are defined as patients who are cared for in the ICU or any professional, highly dependent department after a selective or emergency admission, including internal medicine, surgery, cardiology/cardiac surgery, neurology/neurosurgery, or comprehensive ICU department. The exclusion criteria were as follows: (a) studies focusing on treatment after ICU or discharge, (b) studies of no delirium, (c) duplicate publications, (d) lack of research on predetermined outcome data, and (e) other types of studies except RCTs and retrospective cohort studies.

Study selection, data extraction and quality evaluation

Three researchers (L.S.B., L.S., and G.K.) independently searched for titles and abstracts to determine whether they should be included. The same researcher reviewed the full text and extracted the data. The Cochrane bias risk tool was used to assess the quality of RCTs.[22] The Newcastle Ottawa scale was used to assess the risk of bias in retrospective cohort studies.[23] The extracted data included study characteristics, participant characteristics, intervention measures and intervention environment, adverse events, bias risk, and outcome data. If necessary, we tried to contact the literature author to obtain the missing data. See Appendix B for the study selection and data extraction table.

Outcome indicators

The primary outcomes were (a) improvement of delirium symptoms and (b) a decrease in delirium duration. Secondary outcomes were ICU and in-hospital mortality, ICU and length of stay, adverse events and overall incidence, cognitive function, sleep quality and quality of life measured with validated tools, mechanical ventilation time, endotracheal intubation rate, and delirium recurrence rate. All outcome indicators reported by the authors were included.

Statistical analysis

The data were analyzed in Review Manager (version 5.4) software. The standardized mean difference (SMD) and 95% confidence interval (CI) of continuous results were calculated. If necessary, the mean and standard deviation of the median and interquartile spacing were estimated using standard methods.[24] For binary data, odds ratios (ORs) and 95% CIs were used to describe the treatment effect. When there were results of two or more similar intervention studies, a meta-analysis was performed. The random effects were calculated using the combination model.

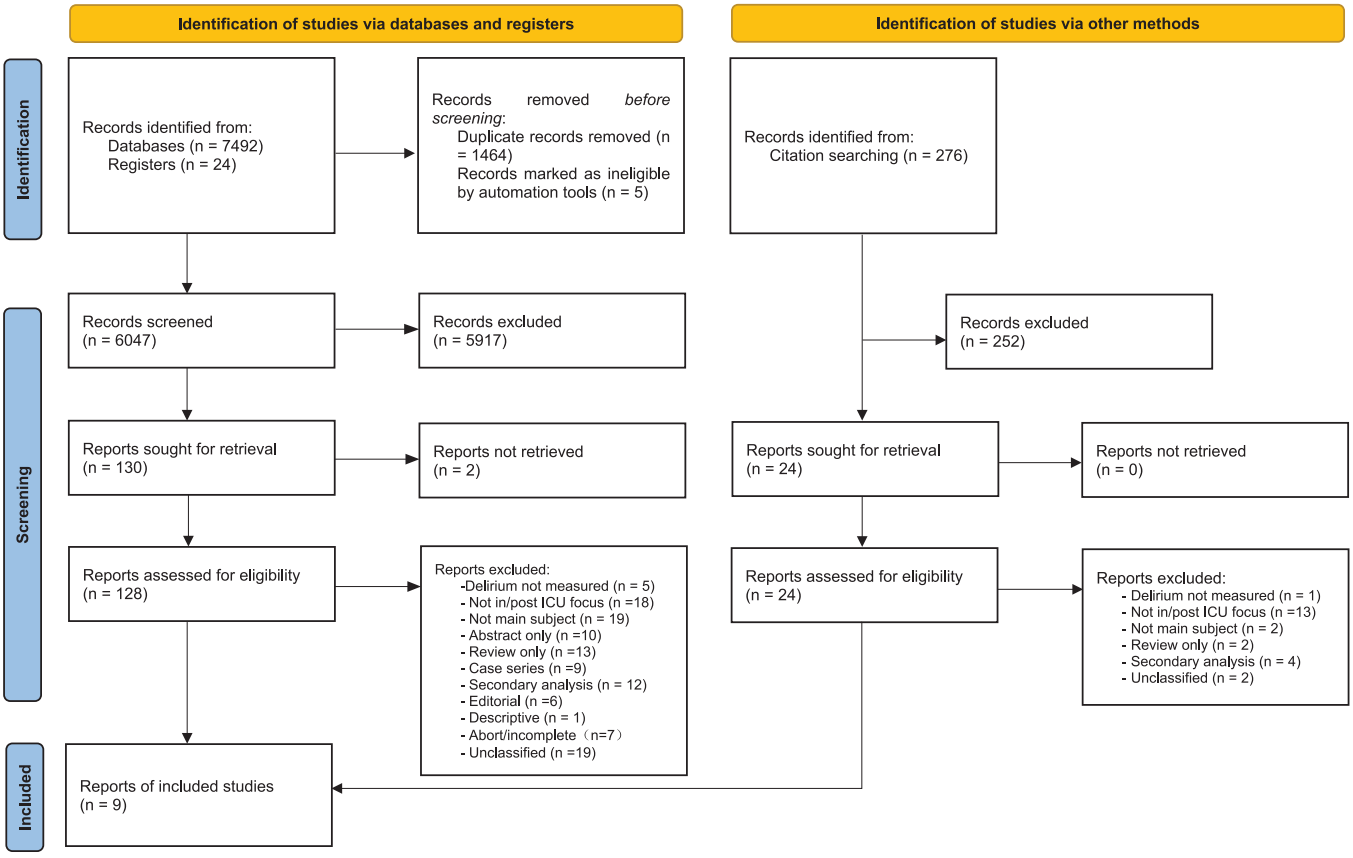

Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 flow diagram.

Clinical heterogeneity was assessed by qualitative assessment of study and intervention differences. Statistical heterogeneity was assessed by the chi-square test ($p < 0.1$ for significant heterogeneity) and I^2 statistics ($I^2 > 50\%$ for significant heterogeneity).

Subgroup analysis of pediatric patients, patients with mechanical ventilation and patients without mechanical ventilation was planned, and interventions aimed at delirium control were studied. However, there were not enough subgroup data for this analysis. Funnel plots were planned to assess possible publication bias. However, there were too few included studies to judge the symmetry of the funnel plot. We undertook sensitivity analyses on studies judged as having a high risk of bias for sequence generation and allocation concealment, as well as the random-effects and fixed-effects models. In addition, the studies included were not sufficient for statistical analysis for the comparison between olanzapine and no intervention.

Results

According to the meta-analysis report specification,[25] the screening strategy flow chart is shown in Figure 1. According to the search strategy, a total of 7792 references were identified. Among them, a total of 1469 repetitive and unqualified studies marked by automatic tools were excluded. After reviewing the titles and abstracts of the literature, 6169 items unrelated to the research topic were excluded. The remaining 152 studies were considered relevant, and the full text was carefully screened. Six had unmeasured delirium, 31 post ICU/non-ICU occurrence, 21 study subjects non-olanzapine, 10 abstracts only, 15 reviews only, nine case/case series, 16 secondary analyses, six editorials/reviews, one descriptive study, seven terminated/incomplete, and 21 unclassified studies were excluded. Finally, nine quantitative studies (four RCTs and five retrospective cohort studies)[15,26–33] were included. The main characteristics of the included studies are shown in Table 1.

The sample sizes ranged from 35 to 6311. A total of 7228 ICU delirium patients were included in the analysis (2496 in the treatment group and 4732 in the other intervention group). The diagnostic criteria of delirium were not all the same among the enrolled studies. Seven studies used CAM or CAM-ICU diagnostic criteria,[15,28–33] and two studies used *DSM-IV* or *DSM-5* diagnostic criteria.[26,27] All nine studies enrolled adult ICU patients.[15,26–33] Three studies quantitatively analyzed the control of delirium severity.[26,27,29] Table 2 lists the bias risk assessment of RCTs, and Table 3 lists the bias risk assessment of retrospective cohort studies.

Olanzapine and delirium symptom relief

Data on the improvement of delirium symptoms were explored in seven studies (three RCTs and four retrospective cohort studies).[15,26,27,29,30,32,33] However, only three studies with data on delirium symptom relief could be combined for statistical analysis.[29,32,33] The effective rates of delirium symptom improvement in the olanzapine group and other intervention groups were 64.38% (103/160) and 57.70% (90/156), respectively. Heterogeneity was not statistically significant ($I^2 = 0\%$, $p = 0.68$). Pooled data based on the random-effects model showed that the use of olanzapine correlated with delirium symptom improvement (OR = 1.36, 95% CI [0.83, 2.28], $p = 0.21$, Figure 2). In the subgroup analysis of two retrospective cohort studies (OR = 1.29, 95% CI [0.76, 2.19], $p = 0.34$, $I^2 = 0\%$), there were also no beneficial effects of olanzapine use.[32,33]

Olanzapine and delirium duration

Four studies[28–30,33] provided data on the control of delirium duration in the ICU. Pooled data based on the random-effects model showed that the use of olanzapine did not affect the duration of delirium (days) (SMD = 0.29, 95% CI [−0.82, 1.39], $p = 0.61$, $I^2 = 96\%$, Figure 3). There was no significant difference in the subgroup analysis of the two RCTs[28,29] (SMD = 0.87, 95% CI [−1.84, 3.59], $p = 0.53$, $I^2 = 98\%$). In the subgroup analysis of two retrospective cohort studies[30,33] (SMD = −0.28, 95% CI [−1.58, 1.03], $p = 0.68$, $I^2 = 93\%$), there was also no significant difference. The study in which the control group received no intervention was excluded, and sensitivity analysis showed no significant difference in other studies (SMD = 0.55, 95% CI [−0.94, 2.04], $p = 0.47$, $I^2 = 97\%$).

Olanzapine and ICU length of stay

Five studies[28,30–33] reported data on ICU length of stay. Meta-analysis did not show that the use of olanzapine and other interventions had different effects on ICU hospitalization time (days) (SMD = −0.14, 95% CI [−1.19, 0.91], $p = 0.79$, $I^2 = 98\%$, Figure 4). In the subgroup analysis of four retrospective cohort studies[30–33] (SMD = −0.05, 95% CI [−1.35, 1.24], $p = 0.94$, $I^2 = 98\%$), there was no beneficial effect. The study in which the control group received no intervention was excluded, and sensitivity analysis showed no significant difference in other studies (SMD = -0.05, 95% CI [−1.35, 1.24], $p = 0.94$, $I^2 = 98\%$).

Olanzapine and hospital stay

Four studies[27,30,31,33] reported data on the length of hospital stay. The summary results showed that hospital stay (days) was not significantly different between patients treated with olanzapine and other interventions (SMD = −0.22, 95% CI [−0.87, 0.20], $p = 0.12$, $I^2 = 84\%$, Figure 5). In the subgroup analysis of three retrospective cohort studies [30, 31, 33] (OR = −0.37, 95% CI [−1.04, 0.30], $p = 0.28$, $I^2 = 89\%$), there was also no significant difference.

Olanzapine and the overall incidence of adverse reactions

Six studies[26,27,29–32] reported the incidence of complications under the use of olanzapine and other interventions. The overall complication rate of the olanzapine group was 14.74% (56/380), which was lower than the rate of 27.25% (112/411) in the other intervention groups. However, the meta-analysis showed that the use of olanzapine did not reduce the overall incidence of adverse reactions (OR = 0.39, 95% CI [0.06, 2.71], $p = 0.34$, $I^2 = 91\%$, Figure 6). Olanzapine had no beneficial effect in the subgroup analysis of three RCTs[26,27,29] (OR = 1.27, 95% CI [0.01, 163.50], $p = 0.92$, $I^2 = 82\%$). Subgroup analysis of three retrospective cohort studies[30–32] (OR = 0.22, 95% CI [0.02, 2.36], $p = 0.21$, $I^2 = 95\%$) also showed that this difference was not statistically significant.

Olanzapine and extrapyramidal reactions

Two studies[26,30] reported the incidence of extrapyramidal reactions under the use of olanzapine and other interventions. The incidences of extrapyramidal reactions in the olanzapine group and

Table 1. Summary of studies included in the meta-analysis.

Authors, year (country)	Design	Population	Diagnostic criteria	Number of participants (intervention)	Dose (intervention)	Control	Number of participants (control)	Dose (control)
Skrobik *et al.*, 2004 (Canada)[26]	RCT	Medical-surgical ICU	*DSM-IV*	28	Olanzapine started with 2.5–5 mg/d. Subsequent titration was based on clinical judgment.	Haloperidol	45	Haloperidol was initially taken 0.5–5 mg every 8 hours. Subsequent titration was based on clinical judgment.
Mesbahi J *et al.*, 2021 (Iran)[27]	RCT	ICU	*DSM-5*	19	Olanzapine 5 mg was taken orally every 8 hours for three consecutive days.	Haloperidol	16	Haloperidol 3 mg was taken orally every 8 hours for three consecutive days.
Ji *et al.*, 2021 (China)[28]	RCT	ICU	CAM-ICU	43	Olanzapine was taken orally 2.5–10 mg/d.	Routine therapy	43	Routine therapy.
Zan, 2019 (China)[29]	RCT	ICU	CAM	42	Olanzapine was taken orally 1.25–10 mg/d.	Taohe Chengqi Decoction	42	Taohe Chengqi Decoction.
Liu S, *et al.*, 2021 (China)[30]	Retrospective	ICU	CAM-ICU	145	Olanzapine was administered orally or through nasogastric tube, 2.5–10 mg/d.	Dexmedetomidine	118	The dose of dexmedetomidine was 0.1–0.7 mcg/kg/h.
Hanna *et al.*, 2021 (USA)[31]	Retrospective	Cardiology ICU	CAM-ICU	50	The initial dose of olanzapine was 5 ± 3.0 mg and the maximum dose was 7 ± 4.6 mg. The median treatment time was 2 (1.0–5.8) days.	Quetiapine	94	The initial dose of quetiapine was 28 ± 14.2 mg and the maximum dose was 43 ± 32.1 mg. The median treatment time was 3 (1.0–7.0) days.
Wang *et al.*, 2019 (USA)[32]	Retrospective	Medical, cardiac, cardiothoracic, neurology, surgical, and trauma ICU	CAM-ICU	96	The initial dose of olanzapine for intravenous injection was 1.25–5 mg, and the maximum recommended cumulative dose within 24 hours was 10 mg.	Haloperidol	96	The initial dose of haloperidol for intravenous injection was 0.25–5 mg. The maximum recommended cumulative dose within 24 hours was 40 mg.
Fitz, K. *et al.*, 2011 (USA)[33]	Retrospective	ICU	CAM-ICU	22	No information.	Sodium valproate	18	No information.
Boncyk *et al.*, 2021 (USA)[15]	Retrospective	Medical, surgical, trauma, or cardiovascular ICU	CAM-ICU	2051	The median daily dose of olanzapine was 7.5 (5–12.5) mg.	Haloperidol, quetiapine	2395, 1865	The median daily dose of haloperidol was 5^{3-10} mg. The median daily dose of quetiapine was 50^{25-125} mg.

CAM, confusion assessment method; CAM-ICU, confusion assessment method for the intensive care unit; *DSM*, Diagnostic and Statistical Manual of Mental Disorders; ICU, intensive care unit; RCT, randomized controlled trial.

Table 2. Risk-of-bias assessment of RCTs.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified
Skrobik *et al.*, 2004 (Canada)[26]	High risk of bias Based on odd or even days	Unclear risk of bias	Low risk of bias Blinding of all participants	Low risk of bias Outcome assessor is blinded	Low risk of bias Outcome data complete	Low risk of bias	Unclear risk of bias
Mesbahi J *et al.*, 2021 (Iran)[27]	Low risk of bias Using a randomization scheme generated	Low risk of bias Sealed envelope	Low risk of bias Blinding of all participants	Low risk of bias Outcome assessor is blinded	Low risk of bias Outcome data complete	Low risk of bias	Unclear risk of bias
Ji *et al.*, 2021 (China)[28]	Low risk of bias Using a randomization scheme generated	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias Outcome data complete	Low risk of bias	Unclear risk of bias
Zan, 2019 (China)[29]	High risk of bias According to the order of incidence	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias Outcome data complete	Low risk of bias	Unclear risk of bias

RCT, randomized controlled trial.

Table 3. Risk-of-bias assessment for the retrospective cohort studies.

		Liu S, *et al.*, 2021 (China)[30]	Hanna *et al.*, 2021 (USA)[31]	Wang *et al.*, 2019 (USA)[32]	Fitz, K. *et al.*, 2011 (USA)[33]	Boncyk *et al.*, 2021 (USA)[15]
Selection	Representativeness of the exposed cohort	Truly representative	Truly representative	Truly representative	Truly representative	Truly representative
	Selection of the nonexposed cohort	Same hospital	Same hospital	Same hospital	Same hospital	Same hospital
	Ascertainment of exposure	Secure record	Secure record	Secure record	Secure record	Secure record
	Demonstration that outcome of interest was not present at start of study	Yes	Yes	Yes	Yes	Yes
Comparability outcome	Comparability of cohorts on the basis of the design or analysis	Age- and gender-matched	Age- and gender-matched	Age- and gender-matched	Age- and gender-matched	Age- and gender-matched
	Assessment of outcome	Reliable hospital records	Reliable hospital records	Reliable hospital records	Reliable hospital records	Reliable hospital records
	Was follow-up long enough for outcomes to occur	No, 90 days	No, In-hospital	No, In-hospital	No, In-hospital	No, 90 days
	Adequacy of follow-up of cohorts	Complete follow-up	Complete follow-up	Complete follow-up	Complete follow-up	Complete follow-up

other intervention groups were 1.16% (2/173) and 3.68% (6/163), respectively. Heterogeneity was not statistically significant ($I^2 = 66\%$, $p = 0.09$). Pooled data based on the random-effects model showed that the use of olanzapine did not increase the incidence of extrapyramidal reactions (OR = 0.65, 95% CI [0.02, 23.71], $p = 0.81$, Figure 7).

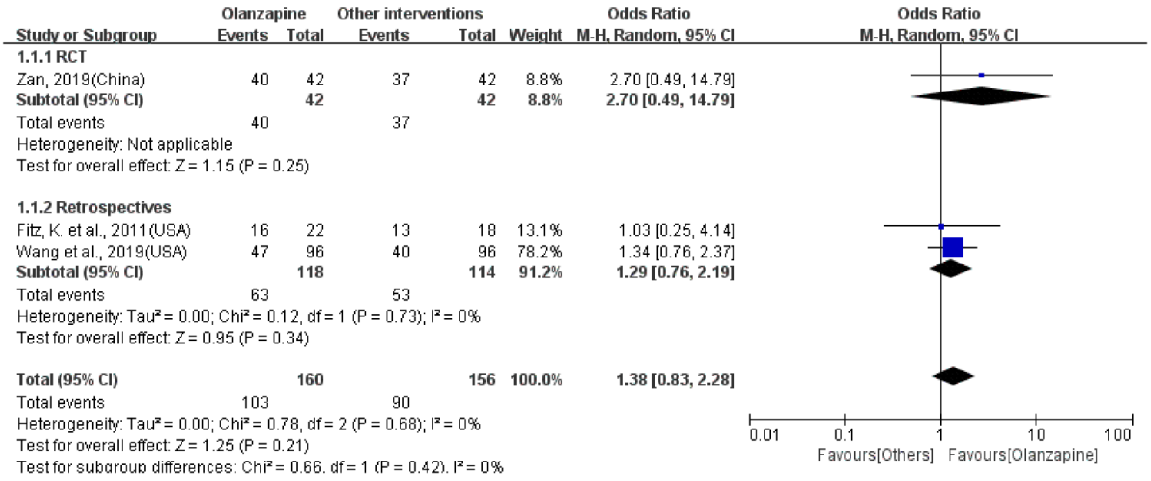

Figure 2. Olanzapine and delirium symptom relief.

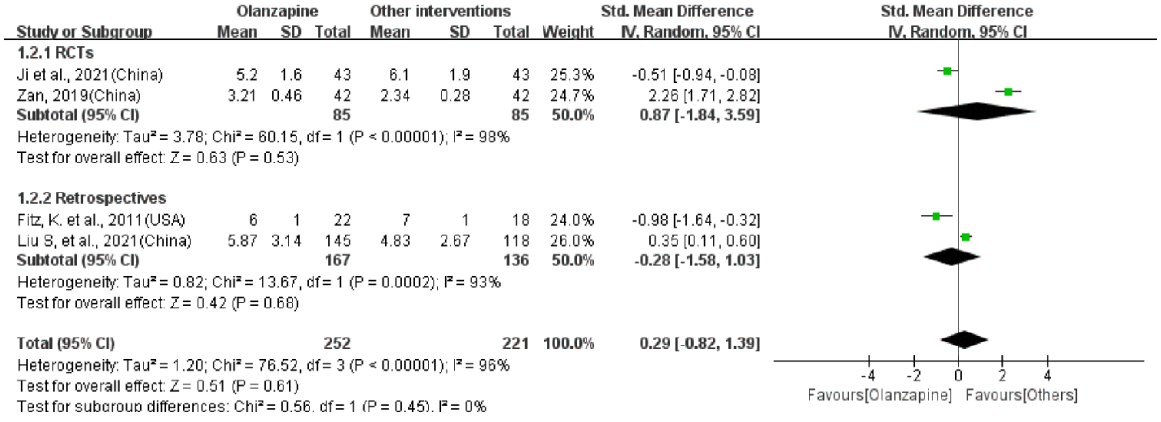

Figure 3. Olanzapine and delirium duration.

Olanzapine and QTc interval prolongation

Two studies[31,32] reported the incidence of QTc interval prolongation under the use of olanzapine and other interventions. The incidence of QTc interval prolongation in the olanzapine group was similar to that in the other intervention groups, 3.42% (5/146) and 4.21% (8/190), respectively. Pooled data based on the random-effects model showed that the use of olanzapine did not increase the incidence of QTc interval prolongation (OR = 1.08, 95% CI [0.01, 112.98], $p = 0.98$, Figure 8). The heterogeneity was significant ($I^2 = 81\%$, $p = 0.02$). Both studies were retrospective cohort studies without subgroup analysis.

Olanzapine and incidence of hypotension

Three studies[30–32] reported the incidence rate of hypotension under the use of olanzapine and other interventions. The incidence of hypotension in the olanzapine group was 5.84% (17/291), which was lower than the 11.04% (34/308) in the other intervention groups. This beneficial effect was demonstrated by pooled data based on the random-effects model, and the use of olanzapine reduced the incidence of hypotension compared with other interventions (OR = 0.44, 95% CI [0.20, 0.95], $p = 0.04$, Figure 9). All three studies were retrospective cohort studies without subgroup analysis. Heterogeneity was not statistically significant ($I^2 = 21\%$, $p = 0.28$).

Olanzapine and in-hospital mortality

Two studies[28,30] reported data on in-hospital mortality. The in-hospital mortality rate of the olanzapine group was 19.68% (37/188), which was lower than that of the other intervention

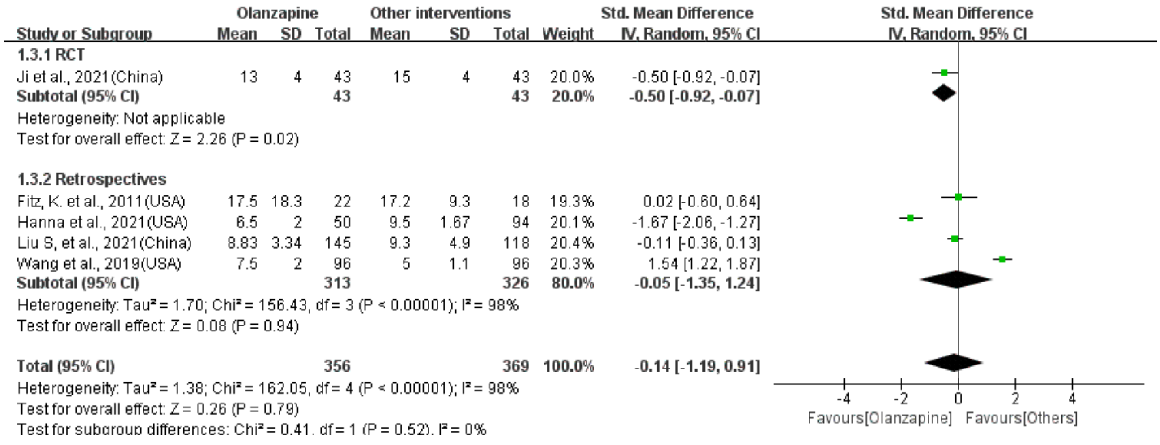

Figure 4. Olanzapine and ICU length of stay.

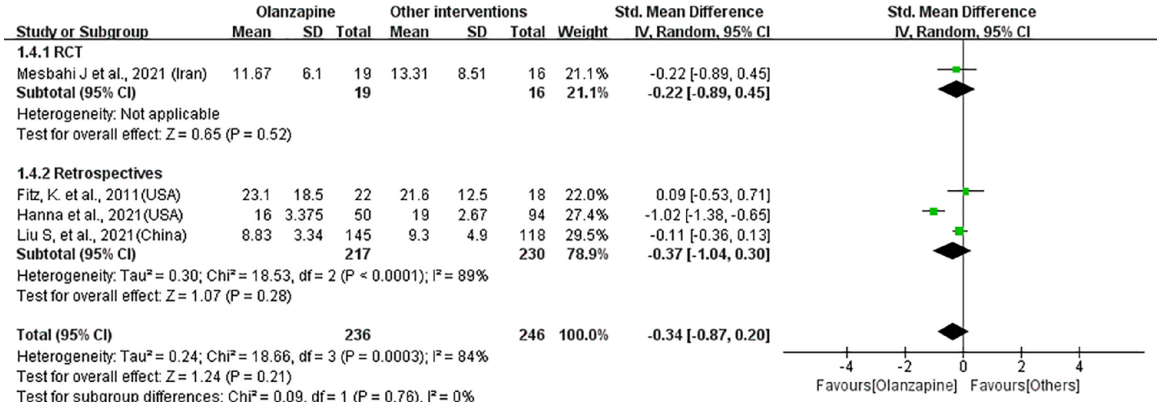

Figure 5. Olanzapine and hospital stay.

groups [26.71% (43/161)]. However, pooled data based on the random-effects model showed that the use of olanzapine did not reduce in-hospital mortality (OR = 0.60, 95% CI [0.25, 1.41], $p = 0.24$, $I^2 = 53\%$, Figure 10). The study in which the control group received no intervention was excluded, and sensitivity analysis showed no significant difference in other studies (OR = 0.83, 95% CI [0.47, 1.49], $p = 0.54$).

Discussion

This systematic review included nine studies for which we evaluated the effects of olanzapine on delirium symptom relief, delirium duration, ICU and hospital stay, in-hospital mortality, incidence of adverse events, and overall delirium incidence in critically ill patients compared with other interventions, including routine care or other pharmaceutical or nonpharmaceutical interventions. Research interventions and outcome indicators vary widely, so it is impossible to collect data from many studies, including mechanical ventilation time, endotracheal intubation rate, delirium recurrence rate, cognitive function, and continued medication rate after discharge. The data collected from a few studies showed that compared with other interventions, olanzapine was not significantly more efficacious at alleviating delirium symptoms and reducing delirium duration in critically ill patients. In addition, the use of olanzapine did not shorten the length of stay in the ICU or hospital, nor did it show an effect on reducing in-hospital mortality. In patients treated with olanzapine, extrapyramidal reactions, QTc interval prolongation, and overall adverse reactions did not show significant differences compared with other interventions. However, there is evidence that, compared with other pharmaceutical interventions, olanzapine was associated with a

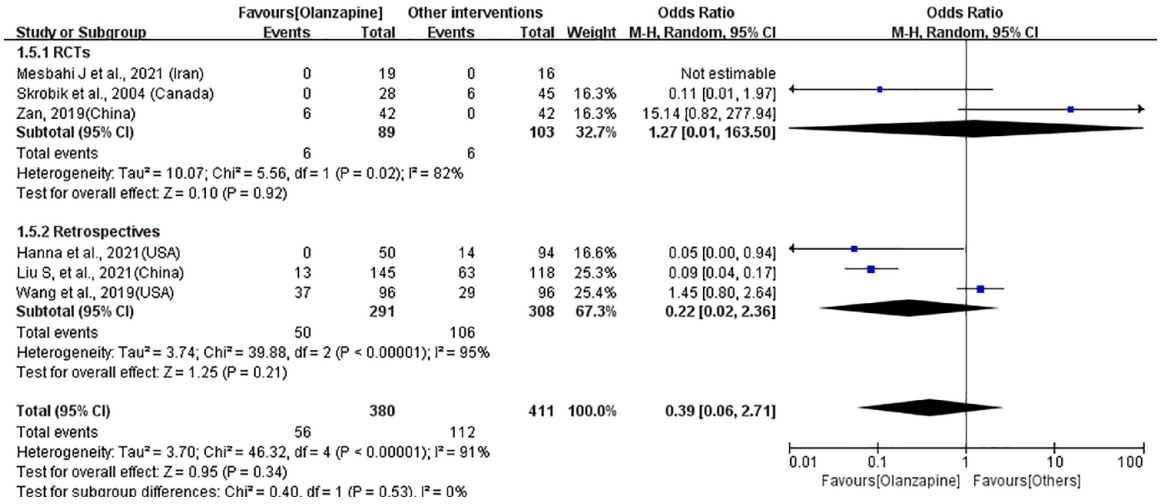

Figure 6. Olanzapine and the overall incidence of adverse reactions.

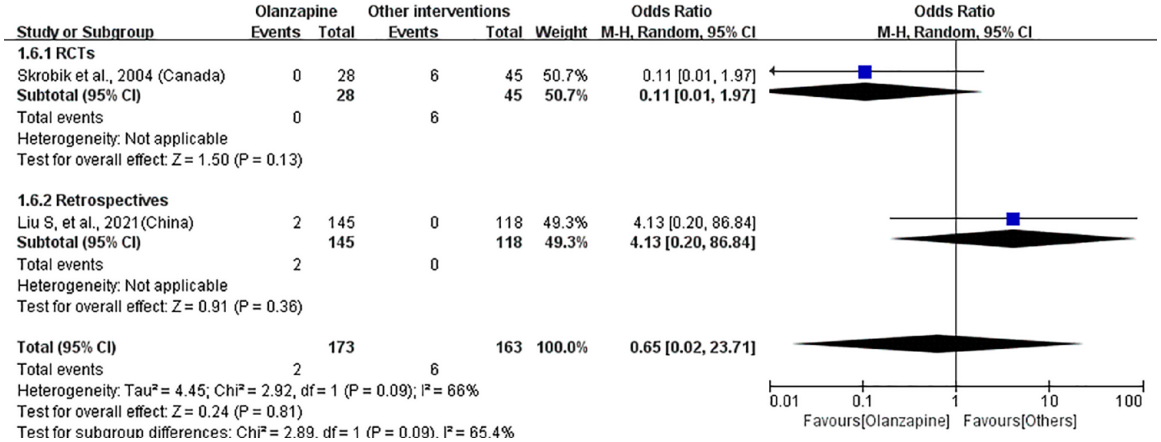

Figure 7. Olanzapine and extrapyramidal reactions.

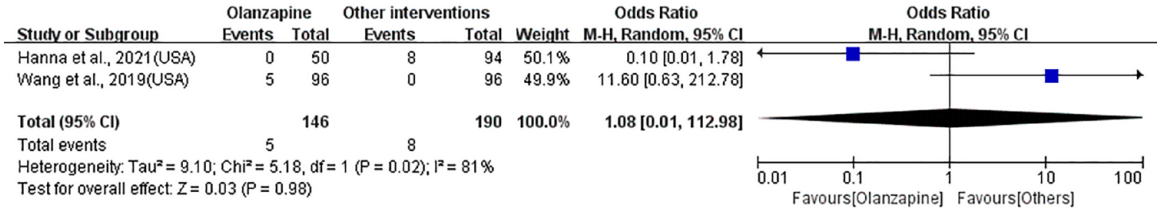

Figure 8. Olanzapine and QTc interval prolongation.

lower rate of hypotension in ICU patients with delirium.

In previous meta-analysis studies on antipsychotics for treating delirium, interventions usually included all antipsychotics[34–36] or second-generation antipsychotics.[37,38] In addition, the target population was selected for all inpatients or postoperative patients. We believe that interventions involving multiple drugs and differences between different target populations may lead to huge heterogeneity in these studies, thus

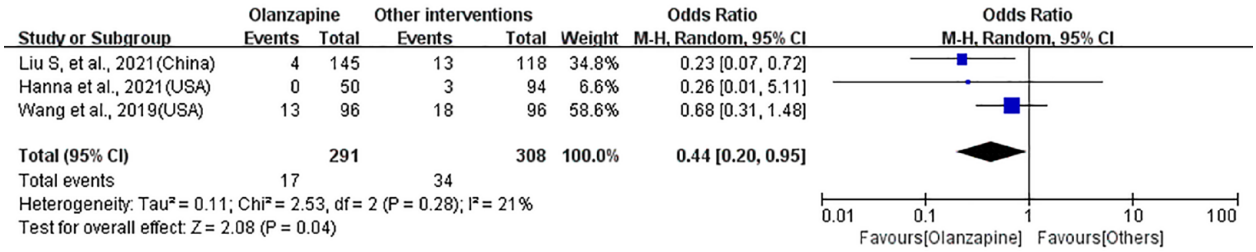

Figure 9. Olanzapine and incidence of hypotension.

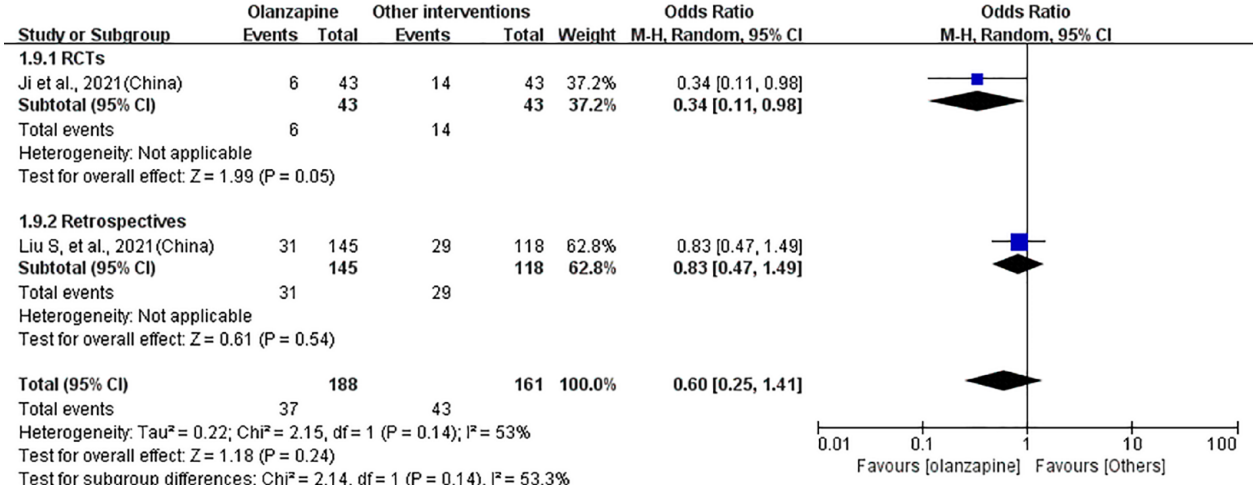

Figure 10. Olanzapine and in-hospital mortality.

affecting the research results. This review only tested olanzapine as the representative drug for second-generation antipsychotics in ICU delirium patients in an attempt to eliminate these influencing factors. This review included nine studies (a total of 7228 ICU delirium patients) and systematically considered more outcomes, including potential hazards. Unfortunately, although the study was limited to a single drug and a single target population, the main results of this systematic evaluation did not differ from those of the recent systematic evaluation.[34,36,39–41] From inception to October 2022, we searched the PubMed, CINAHL, EMBASE, PsychINFO, Web of Science, Scopus, Cochrane Library, CNKI, WanFang, and VIP databases to obtain relevant systematic reviews. A systematic review of adult hospitalized patients with and without serious diseases showed that antipsychotics were not beneficial for treating delirium, improving its severity or shortening its duration and were not associated with ICU and hospital length of stay or mortality.[34] Another study also pointed out that haloperidol or other second-generation antipsychotics could not prevent delirium in hospitalized patients. No beneficial effects were observed on delirium duration, mortality, or other adverse reactions.[42] A recent Cochrane Review (up to July 2017), focusing only on RCTs in noncritically ill hospitalized patients, also proved that antipsychotics did not reduce delirium severity or alleviate delirium-related symptoms. There was no difference in reporting extrapyramidal symptoms or mortality.[39]

In a network meta-analysis, researchers evaluated delirium treatment in critically ill and noncritically ill adult inpatients and compared RCTs of 20 different drug treatment measures, including antipsychotics. The results showed that antipsychotic treatment alone lacked advantages in eliminating delirium and all-cause mortality compared with placebo or control treatment.[40] It is worth noting that this network meta-analysis only assessed delirium duration, delirium response rate and all-cause mortality but did not assess other clinically important outcomes, such as

circulatory, respiratory and neurological adverse reactions. This review systematically evaluated the overall incidence of extrapyramidal reactions, QTc interval prolongation, hypotension, and adverse reactions caused by olanzapine treatment. It was found that olanzapine had no effect on other indicators when compared with other interventions but had a smaller effect on blood pressure in patients with delirium in the ICU. Different antipsychotics have different affinities for the adrenergic α1 receptor, which plays a sedative role. In addition, they can also cause systemic venous dilation, which could lead to orthostatic hypotension. The order of orthostatic hypotension caused by antipsychotics is clozapine = chlorpromazine > risperidone > quetiapine > olanzapine = ziprasidone.[43] Dexmedetomidine stimulates α2 adrenaline receptors to cause bradycardia and vasodilatory hypotension. The affinity of dexmedetomidine for α2 adrenaline receptors was eight times higher than that of other sedatives.[44,45] This may be why the effect of olanzapine on blood pressure is very slight, which is different from other pharmaceutical interventions. Compared with other treatment measures, the superiority of olanzapine in the circulatory system of delirium patients has also been confirmed in other studies.[30,46]

The findings of this review show that olanzapine does not significantly benefit the main outcomes of patients with delirium in the ICU, which is consistent with recent clinical practice guidelines, which do not recommend the routine use of antipsychotics in the treatment of delirium. The 2018 SCCM guidelines for critically ill patients recommend not routinely using haloperidol, second-generation antipsychotics (including olanzapine) or HMG CoA reductase inhibitors (i.e. statins) to treat delirium (conditional recommendation, low quality of evidence).[11] The 2019 Scottish Intercollege Guidance Network (SIGN) also did not recommend the routine use of any drug to treat delirium (insufficient evidence).[47] The 2018 guidelines for analgesia and sedation in the Chinese adult ICU did not recommend haloperidol, statins, donepezil, and antipsychotics to prevent and treat delirium (weak recommendation and intermediate quality of evidence).[48] However, we should also note that some guidelines put different opinions forward.[21,49] The psychiatrist group for hospitalized patients with novel coronavirus-19 (COVID-19) recommended olanzapine as a first-line antipsychotic drug for restless delirium and recommended that quetiapine be avoided.[49] According to the guidelines of the NICE, short-term treatment with olanzapine or haloperidol should be considered when delirium patients feel pain, are considered to be a danger to themselves or others, or nonpharmaceutical interventions are ineffective or inappropriate.[21] In a prospective randomized trial with a small study sample in which researchers evaluated the efficacy of olanzapine in the treatment of delirium in ICU patients, the results showed that olanzapine could lower the delirium index (DI) without any side effects.[26] In another randomized controlled observation trial with a small study sample, Hu *et al.* compared the efficacy of olanzapine, haloperidol, and the control group in the treatment of delirium. There was a significant difference in the treatment efficacy between the two groups and the control group, but olanzapine produced a faster effect.[50] Significantly, it has been more than 10 years since the NICE guideline was published,[21] and there is limited evidence[26,50] for recommending the use of olanzapine. During this period, researchers also performed other studies.[38,51–53] Meagher *et al.*[53] found that previous studies did not suggest significant differences in efficacy for atypical agents *versus* haloperidol but reported higher rates of extrapyramidal side effects with haloperidol. Rivière *et al.*[38] also believed that olanzapine and quetiapine seem to be adequate alternatives to haloperidol, especially in patients who are vulnerable to extrapyramidal symptoms, who require sedation or who have a history of haloperidol intolerance. However, to date, there is a lack of high-quality evidence on the use of psychotics, including first- and second-generation antipsychotics, for delirium control in critically ill patients.

We retrieved ongoing trials on the ISRCTN Registry, ClinicalTrials.gov, ICTRP Search Portal, and EU Clinical Trials Register (up to October 2022). There were three RCTs. The three trials plan to recruit 270 (IRCT20200927048852N1), 210 (ChiCTR1900027708), and 100 (IRCT20141209020258N114) participants, and all use olanzapine intensively in the ICU. The purpose of these three trials is to evaluate the efficacy of olanzapine and other pharmaceutical interventions in treating ICU delirium. We expect that the results of these trials may provide better evidence to support the use of certain drugs in the future.

Some limitations should be considered when interpreting the results of this systematic review. First, the studies in this review have considerable clinical heterogeneity, including different patient

groups (MICU, SICU, or CICU), different intervention measures (drug dose, frequency, route of administration, etc.), different control populations (haloperidol, dexmedetomidine, quetiapine, sodium valproate, traditional Chinese medicine, and no intervention), different outcome indicators (efficiency of delirium treatment was reported in many ways, etc.), and different study designs. In particular, the different interventions (olanzapine dose, medication frequency, administration time, administration route) included in the studies hinder the comparative study of the dose-effect relationship between different doses of the same drug or between different doses of different drugs, which is of great significance for the safety, effectiveness and clinical decision-making of drugs. This is the inherent weakness of system evaluation, which limits its ability. Although we performed subgroup analysis and sensitivity analysis, we cannot completely eliminate the impact of this heterogeneity. Presenting the data and analyzing the results in a differentiated way is unavoidable. This limitation highlights the significance of studying standardization and homogenization when circumstances permit. At present, different teams are developing reporting standards for conversion between different delirium measurement tools and related outcome indicators to evaluate all studies of antipsychotic treatment of delirium.[54–56] Researchers are encouraged to use the intervention description and replication template (TIDieR) list and guidelines to clearly and comprehensively describe their interventions, methods, and outcomes so that other researchers and readers can use their information.[57] Second, other indicators were systematically evaluated, including mechanical ventilation time, endotracheal intubation rate, delirium recurrence rate, cognitive function, and continued medication rate after discharge. However, the combined analysis could not be carried out due to the insufficient number of studies or inconsistent data reporting standards. Only two studies mentioned mechanical ventilation time data,[31,33] one study mentioned endotracheal intubation rate data,[30] two studies mentioned the delirium recurrence rate,[30,33] two studies mentioned ventricular tachycardia,[30,31] one study mentioned cognitive function data,[30] and one study mentioned continued medication after discharge.[31] None of the studies mentioned the effects of olanzapine on sleep quality and quality of life. Finally, due to insufficient data, we could not evaluate the difference in prognosis between mechanically ventilated and nonmechanically ventilated populations in the ICU or the benefits and hazards of olanzapine under different types of delirium. The number of studies included was insufficient for performing a comparison between olanzapine and no intervention. Further study with well-designed clinical trials is required in this area, especially double-blind, randomized, placebo-controlled trials.

Conclusion

In conclusion, in the results of this systematic review, compared with routine care or other pharmaceutical interventions, the application of olanzapine was not significantly more efficacious at relieving delirium symptoms in ICU adults with delirium. In addition, the duration of delirium and ICU and hospital stays were not shortened. It also did not show the effect of reducing in-hospital mortality. In patients treated with olanzapine, extrapyramidal reactions, QTc interval prolongation, and overall adverse reactions did not decrease. One study suggested that olanzapine could effectively alleviate symptoms and reduce the mortality rate of ICU patients with delirium when compared with the no intervention group, but this one study was not sufficient for statistical analysis. However, there is evidence that olanzapine has a weaker effect on blood pressure in ICU delirium adults than other pharmaceutical interventions. These data will provide some reference for delirium research and clinical drug intervention strategies in critically ill patients. It is suggested that future clinical trials describe intervention measures, methods, and outcomes in a standardized manner. For some clinically important results and specific patient subgroups (such as mechanical ventilation and patients with different types of delirium), there is no or insufficient evidence. Further research in this field is necessary.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have seen the manuscript and approved to submit this article to your journal.

Author contributions

Si Bo Liu: Conceptualization; Funding acquisition; Investigation; Methodology; Software; Writing – original draft.

Shan Liu: Formal analysis; Investigation; Methodology; Software.

Kai Gao: Formal analysis; Investigation; Methodology; Software.

Guo Zhi Wu: Supervision; Visualization.

Guo Zu: Supervision; Visualization.

Jin Jie Liu: Funding acquisition; Project administration; Writing – review & editing.

Acknowledgements
The authors acknowledge Prof. Yong Ming Yao from the Trauma Research Center, Fourth Medical Center of the Chinese PLA General Hospital for helping with the manuscript writing.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Open Project Program of Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Ministry of Education (grant number 2019GDND03) and Dalian High-Level Talents Innovation Support Plan (grant number 2021RQ029).

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
Not applicable.

ORCID iD
Jin Jie Liu https://orcid.org/0000-0002-5922-8216

Supplemental material
Supplemental material for this article is available online.

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