JOURNAL OF PSYCHOPATHOLOGY 2020;26:155-161
doi: 10.36148/2284-0249-349

Review

Atypical antipsychotic medications in the treatment of delirium: a systematic review

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SUMMARY

Objective

Delirium is an acute neuropsychiatric condition with high mortality rate if untreated. Haloperidol has long been the drug of choice when treating patients with delirium, however more recently atypical antipsychotics have increasingly been used in the management of this condition. We conducted a systematic literature review to assess the effectiveness of atypical antipsychotics in the treatment of delirium.

Methods

We devised a search strategy according to the methodology outlined in the Prisma guidelines on systematic literature reviews to identify randomised controlled trials comparing atypical antipsychotic medications with placebo, haloperidol, or other atypical antipsychotics in adult patients with delirium. We excluded studies where validated rating instruments were not employed and where antipsychotic medications were used to prevent delirium. Multiple risks of bias were estimated and taken into account.

Results

Our initial search yielded 238 articles. Following screening and application of inclusion and exclusion criteria, a total of 8 studies were included in the qualitative synthesis. The results of the reviewed studies showed that atypical antipsychotics can be useful interventions for the treatment of delirium: in addition to superiority to placebo, these medications demonstrated similar levels of effectiveness to conventional antipsychotics, with a better tolerability profile.

Conclusions

The available evidence from randomised controlled trials suggests that atypical antipsychotics are both safe and effective in the treatment of adult patients diagnosed with delirium. The findings of comparative studies indicate that these medications could be a valuable alternative to conventional antipsychotics. The limitations of the reviewed literature include the recruitment of clinical samples that are limited in size and heterogeneous in clinical presentation. Further clinical research should be conducted in patients with different aetiologies and clinical presentations of delirium, including hypoactive forms.

Key words: atypical antipsychotics, delirium, haloperidol pharmacotherapy; trials.

Received: September 14, 2019
Accepted: October 17, 2019

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Conflict of interest
The Authors declare no conflict of interest

How to cite this article: Shastri A, Bangar S, Cavanna AE. Atypical antipsychotic medications in the treatment of delirium: a systematic review. Journal of Psychopathology 2020;26:155-61. https://doi.org/10.36148/2284-0249-349

Introduction

Delirium is a neuropsychiatric condition characterised by alterations in cognition and consciousness or impairment in perception that develop over a short period of time (usually hours to days) and fluctuates throughout the course of the day [1]. Occurring in approximately 10 to 30% of hospitalised medically ill patients and in up to 80% of terminally ill patients, delirium often presents with psychiatric symptoms such as hallucinations, delusions, confusion, and disorientation[2]. Since delirium is essentially a

manifestation of an underlying medical or surgical illness, the management of delirium should primarily involve treating the underlying pathology [3]. Delirium is associated with increased mortality, morbidity, length of hospital stay, and long-term cognitive impairment [4,5].
Although the pathophysiological processes underlying delirium are not fully understood, it is thought that cholinergic neurotransmission and brain plasticity play a key role [6,7]. Treatment protocols combine management of the acute brain syndrome with general and specific procedures to control the underlying condition. Dealing with the symptom-complex involves the principles and practice of sedation, hydration, nutrition, nursing care, and supportive measures. Over the years, haloperidol, albeit not licensed, has been the preferred medication in the pharmacological management of delirium. More recently, in consideration of the adverse effects associated with haloperidol, atypical antipsychotic medications such as olanzapine have increasingly been used. Compared to haloperidol, relatively little is known about the use of atypical antipsychotic agents in patient with delirium. We therefore conducted a systematic literature review to assess the effectiveness of atypical antipsychotics in the treatment of delirium.

Methods

We devised a search strategy according to the methodology outlined in the Prisma guidelines on systematic literature reviews to identify randomised controlled trials comparing atypical antipsychotic medications with placebo, haloperidol, or other atypical antipsychotics in adult patients with delirium [8]. Both PubMed and Cochrane databases were searched using the following strategy: antipsychotic* (OR amisulpride OR aripiprazole OR asenapine OR clozapine OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR ziprasidone) AND delirium AND random*. Only studies on patients aged at least 18 years and published in English language were included in the review. A further criterion for inclusion was the use of validated rating instruments such as the Delirium Rating Scale (DRS) or DRS Revised 98 (DRS-R-98), the Memorial Delirium Assessment Scale (MDAS), or the Delirium Index (DI). Thus, we excluded studies where validated rating instruments were not employed, as well as studies where antipsychotic medications were used to prevent delirium. Multiple risks of bias were estimated using the Cochrane risk-of-bias criteria and taken into account.

Results

The initial search of our systematic literature review yielded 238 articles, out of which 43 were excluded as duplicates. We screened 195 articles: 149 articles were excluded based on the content of their title and abstract. Out of the 149 articles, 51 were review articles, 49 were original studies with a different protocol from randomised controlled trials, 31 had non-delirium diagnosis, and 18 were published in languages other than English. We retrieved 46 full text articles from the remaining number of articles: of these, 38 were excluded as they did not meet the inclusion criteria. Specifically, 7 articles focused on typical antipsychotics, 5 used adjuvant therapy, 8 were prophylactic studies, 5 were review articles, 6 were observational studies, and 7 used less established rating scales that were not part of our inclusion criteria. Therefore, a total of 8 randomised controlled trials were included in our review (Fig. 1).
Table I shows a summary of the main characteristics of the reviewed studies on atypical antipsychotics in the treatment of delirium.
Table II shows a summary of the risk of bias of the reviewed studies based on Cochrane risk-of-bias criteria, whereas Figure 2 shows an overall quantification of such risk.

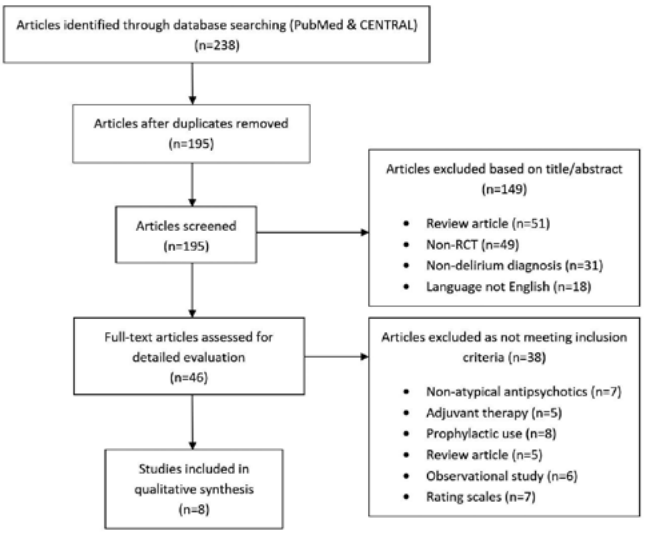

FIGURE 1. *PRISMA flowchart illustrating the selection process of the reviewed articles.*

Discussion

The available evidence from randomised controlled trials suggests that atypical antipsychotics are both safe and effective in the treatment of adult patients diagnosed with delirium. According to the results of our systematic literature review, there was only one placebo-controlled double-blind, randomised trial that compared an atypical antipsychotic medication (quetiapine) with placebo. Only adult patients who met Diagnostic and Statistical

TABLE I. *Summary of the main characteristics of the studies on atypical antipsychotics in the treatment of delirium.*

Study	Sample size	Type of RCT	Medication	Setting	Rating scale
Placebo controlled randomised studies					
Tahir et al., 2010	42	Double-blind	Quetiapine (n = 21) Placebo (n = 21)	Medical and surgical wards	DRS-R-98
Randomised studies comparing an atypical antipsychotic with haloperidol					
Grover et al., 2016	63	Single-blind	Quetiapine (n = 31) Haloperidol (n = 32)	Liaison psychiatry	DRS-R-98
Maneeton et al., 2013	52	Double-blind	Quetiapine (n = 24) Haloperidol (n = 28)	Liaison psychiatry	DRS-R-98
Grover et al., 2011	64	Single-blind	Risperidone (n = 21) Olanzapine (n = 23) Haloperidol (n = 20)	Liaison psychiatry	DRS-R-98
Han and Kim, 2004	24	Double-blind	Risperidone (n = 12) Haloperidol (n = 12)	Psychiatry	MDAS
Skobrik et al., 2004	73	Single-blind	Olanzapine (n = 28) Haloperidol (n = 45)	Intensive care unit	DI
Randomised studies comparing two or more atypical antipsychotics					
Kim et al., 2010	32	Single-blind	Risperidone (n = 17) Olanzapine (n = 15)	Psychiatry	DRS-R-98
Lee et al., 2005	31	Single-blind	Amisulpride (n = 16) Quetiapine (n = 15)	Liaison psychiatry	DRS-R-98

Abbreviations: RCT: randomised controlled trial; DI: Delirium Index; DRS-R-98: Delirium Rating Scale - Revised 98; MDAS: Memorial Delirium Assessment Scale

TABLE II. *Summary of the risk of bias of the reviewed studies.*

	Grover et al., 2016	Maneeton et al., 2013	Grover et al., 2011	Han and Kim, 2004	Skobrik et al., 2004	Kim et al., 2010	Lee et al., 2005	Tahir et al., 2010
Random sequence allocation (selection bias)	+	+	+	+	-	+	+	+
Allocation concealment (selection bias)	+	+	+	+	-	+	+	+
Blinding of participants and personnel (performance bias)	-	+	-	+	-	-	-	+
Blinding of outcome assessment (detection bias)	-	+	-	+	?	?	-	+
Incomplete outcome data (attrition bias)	-	+	-	-	-	?	-	+
Selective reporting (reporting bias)	+	+	+	-	-	-	-	+
Other bias	+	+	+	+	?	+	+	+

Note: +: low risk; -: high risk; ?: unknown risk

Manual for Mental Disorders (DSM) criteria for delirium and whose DRS-R-98 total score was 15 or higher were included in the study by Tahir et al. [9]. Patients with major pre-existing cognitive deficits or psychosis, patients presenting with alcohol withdrawal symptoms, and patients taking medications that were known to interact with quetiapine were excluded. A total of 372 patients were screened and 42 of them were recruited in the

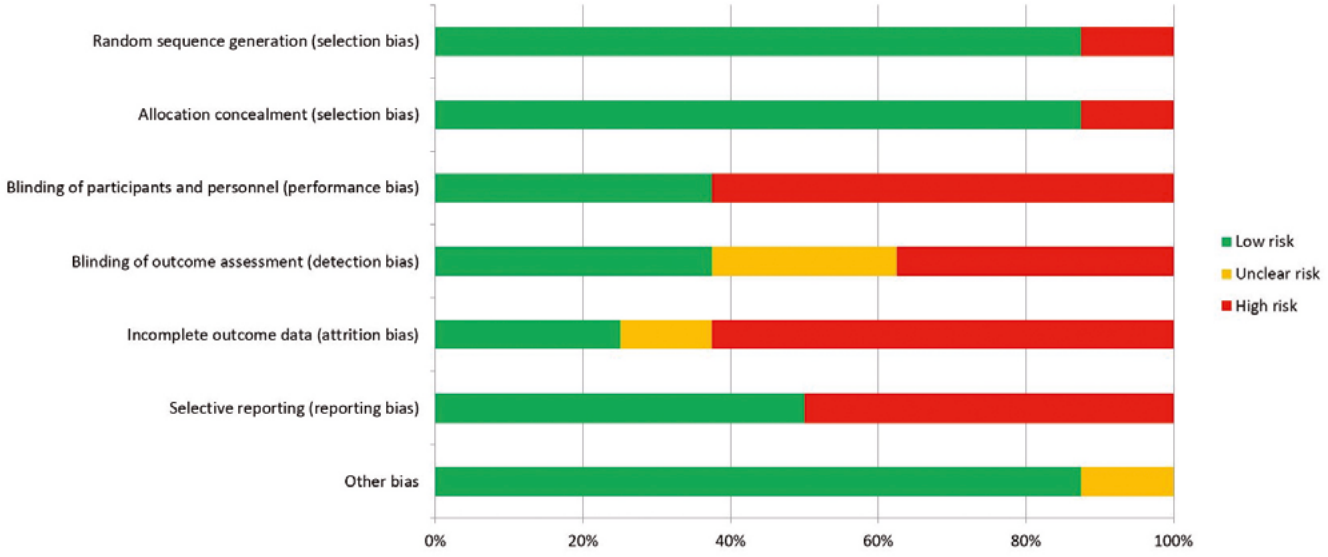

FIGURE 2. *Quantification of the risk of bias in the reviewed studies.*

study. The participants were split into two groups: 21 patients were allocated to the active treatment group and received quetiapine, whereas the remaining 21 patients received a placebo. The mean age of the patients recruited for the trial was 84.2 ± 8.3 years, with ages ranging from 58 to 98 years. The majority of patients (30 out of 42) were female. The trial was completed by 16 patients in the quetiapine group and 13 patients in the placebo group. Participants were assessed on Days 1, 2, 3, 4, 7, and 10 after randomisation, and a follow up assessment was conducted on Day 30. After randomisation, the participants in the active treatment group received a starting dose of quetiapine of 25mg per day. The dose was increased to 175mg per day in divided doses if there was no clinical response or DRS-R-98 score improvement. The authors found a significant difference in severity scores between the quetiapine group and the placebo group. Further analyses on the cognitive and non-cognitive subscales revealed a statistically significant improvement in non-cognitive scores in the quetiapine group. There were a total of 7 deaths within 30 days of the study onset (4 in the quetiapine group and 3 in the placebo group). One patient had to discontinue quetiapine due to sedation as adverse effect. The incidence of involuntary movements was low (4.8% in the quetiapine group and 14.3% in the placebo group). Among the strengths of this study there was the low risk of selection, performance, and attrition bias; its main limitation was the small sample, suggesting that the study could have been underpowered. Importantly, this study was terminated earlier than originally planned, due to concerns from Food and Drug Administration regarding the use of antipsychotics in the elderly. However, the participants of this study reported a significant improvement in DRS-R-98 scores, as well as non-cognitive symptoms of delirium, with the use of quetiapine.

Out of the eight studies included in our systematic literature review, seven were comparative studies: in five of these, atypical antipsychotics were compared to haloperidol.

The study by Han and Kim [10] was a double-blind randomised trial to compare the effectiveness of risperidone and haloperidol in the treatment of delirium. Patients referred to the psychiatry team who met DSM-validated criteria for delirium were included in the trial. Patients who had dementia or other psychiatric diagnoses and those who had received injectable antipsychotics during admission were excluded. A total of 28 patients were randomised to receive either risperidone or haloperidol in a flexible dosing manner, as deemed appropriate by clinical judgement. The trial was completed by 12 patients in each group. The mean daily dose of risperidone was 1.02 ± 0.41 mg per day (range 0.5-2.0 mg per day) and that of haloperidol was 1.71 ± 0.84 mg per day (range 1.0-3.0 mg per day). A validated rating scale (MDAS) was used to measure the severity of delirium at baseline and subsequently daily for 7 days. The authors found a significant difference in MDAS scores from baseline to day 7 in both groups, without significant differences between the groups. No clinically significant adverse effects were reported in the study. The

relatively small sample size was one of the main limitations of this study. Based on their findings, the authors concluded that risperidone is as effective as haloperidol in the treatment of delirium, with an overall better tolerability profile.

The study by Skobrik et al. [11] was a single-blind, prospective, randomised controlled trial comparing olanzapine and haloperidol in the treatment of delirium. Patients aged between 18 and 75 years following admission to intensive care unit were screened and diagnosed with delirium using DSM-validated criteria. Pregnant patients, patients who had received antipsychotic medication within 10 days prior to admission, or those with Parkinson disease, prolonged QTc interval, liver/renal/oropharyngeal dysfunction were excluded from the study. Randomisation was done on an odd/even day basis to receive olanzapine or haloperidol and the dosing regimen depended on clinical judgement. Out of 80 patients for whom informed consent was obtained, 73 patients provided data that were included in the final analysis. The mean age of patients receiving olanzapine was 67.5 ± 6.0 years and of those receiving haloperidol was 63.3 ± 11.7 years. The daily dose for olanzapine was 4.54mg per day (range 2.5-13.5 mg per day) and for haloperidol was 6.5 mg per day (range 1-28 mg per day). A validated rating scale (DI) was used to measure the severity of delirium, which decreased significantly in both groups with no difference between them. No side effects were reported in the olanzapine group, while 6 patients in the haloperidol group reported extrapyramidal adverse effects. The main limitations of this study included the high risk of bias, with odd/even randomisation leading to selection and performance bias. The results on the treatment of delirium suggested that olanzapine has equal efficacy when compared to haloperidol, with a better tolerability profile.

The first study by Grover et al. [12] was a prospective, single-blind randomised controlled trial assessing the efficacy and safety of olanzapine and risperidone versus haloperidol for the treatment of delirium. Patients referred to liaison psychiatry from medical and surgical wards were considered for enrolment in the study. Eligible participants had a diagnosis of delirium, with quantification of symptoms based on psychometric tools (DRS-R-98 and Confusion Assessment Method). Patients presenting with delirium associated with alcohol/benzodiazepine withdrawal or associated with dementia (based on clinical history), co-morbid psychosis or affective disorders, as well as those suffering from terminal illness, were excluded from the study. Patients with profound hearing or visual loss, aphasia, Parkinson disease, history of neuroleptic malignant syndrome, prolonged QTc interval of more than 500ms and history of sensitivity to drugs involved in the study were also excluded. A total of 115 patients were assessed, of whom 25 were excluded as they did not meet the inclusion/exclusion criteria. Consent was obtained from 74 participants, who were randomly allocated to one of three groups: 26 to the olanzapine group, 22 to the risperidone group, and 26 to the haloperidol group. Out of these, 64 participants completed the study (23 in the olanzapine group, 20 in the risperidone group, and 21 in the haloperidol group). The doses of these medications were adjusted on a daily basis according to clinical judgement. The mean doses were as follows: olanzapine 3.05 ± 1.44 mg per day (range 1.25-10.0 mg per day), risperidone 0.95 ± 0.28 mg per day (range 0.5-2.0 mg per day), haloperidol 0.88 ± 0.98mg per day (range 0.25-5.0 mg per day). All participants were assessed on a daily basis for 6 days. There was a statistically significant improvement in DRS-R-98 scores at Day 3 and Day 6 when compared to baseline across the three groups. Clinically significant adverse effects were reported by 2 patients in the olanzapine group, 6 in the risperidone group, and 4 in the haloperidol group. There were no significant differences in the incidence of adverse effects across the groups. The main limitations of this study were the relatively small sample size and the high risk of performance bias and attrition bias. The study showed that olanzapine and risperidone were not only effective, but also better tolerated in terms of adverse effects when compared to haloperidol.

The study by Maneeton et al. [13] compared quetiapine and haloperidol in a 7-day prospective, double-blind randomised controlled trial in patients with delirium. Patients aged 18-75 years who were referred to liaison psychiatry and met the DSM criteria for delirium were included in the trial. Patients who had substance-induced delirium, had known allergy to quetiapine or haloperidol, were pregnant or breastfeeding at the time of the study, were on any other antipsychotic agent, as well as those who had renal/liver failure, were excluded from the trial. A robust randomisation method that involved a computer-generated randomisation system was employed. The patients were randomised to either quetiapine or haloperidol. Patients, staff, investigators and raters were all blinded. A flexible-dosing regimen based on clinical indications was used. Both medications were concealed in identical capsules. Co-administration of other psychopharmacological agents, including benzodiazepines, was not allowed. A total of 52 patients were recruited: 24 were allocated to the quetiapine group and 28 to the haloperidol group. The mean daily dose of quetiapine and haloperidol was 67.6 ± 9.7 mg and 0.8 ± 0.3 mg, respectively. A total of 13 patients in the quetiapine group and 22 patients in the haloperidol group completed the trial. Data were analysed for all the patients who took part in trial, indicating a low risk

of attrition bias. The DRS-R-98 was used to measure the severity of delirium. Clinically significant responses were defined as reductions in DRS-R-98 scores of at least 50% from baseline and scores of 12 or less without relapse. The rate of clinically significant responses was high with both quetiapine (79.2%) and haloperidol (78.6%), and did not differ significantly between the two. Few adverse effects were observed, with hypersomnia being the most common adverse effect in both groups.

The second study by Grover et al. [14] assessed quetiapine and haloperidol in the treatment of delirium. This was a single-blind randomised study in patients referred to liaison psychiatry, aged at least 18 years, who met the DSM criteria for delirium. Patients who had delirium due to alcohol or benzodiazepine withdrawal or delirium associated with dementia were excluded. Patients with prolonged QTc interval, patients unresponsive to verbal or physical stimuli, and patients who had hypersensitivity to quetiapine and haloperidol were excluded. A total of 35 patients were randomised to each group: 31 in the quetiapine group and 32 in the haloperidol group completed the trial. The DRS-R-98 was used to measure the severity of delirium, both at baseline and over the following 6 days. The dose of medication was adjusted according to clinical judgement. The mean dose for quetiapine was 26.63 ± 15.61mg per day and for haloperidol was 0.67 ± 0.35mg per day. Out of the 63 patients who completed the trial, 55 patients had the hyperactive type of delirium, 5 had the hypoactive type, and 3 had the mixed type. The DRS-R-98 scores improved significantly in both groups, with no significant differences between the groups. The main limitations of this study included attrition bias and the lack of placebo arm. Moreover, the treating psychiatrist was not blind to randomisation, resulting in high risk of performance and detection bias. The results of this study suggested that quetiapine is as effective as haloperidol in treatment of delirium.

Finally, our systematic literature search identified two randomised controlled trials comparing two or more atypical antipsychotics.

The study by Lee et al. [15] assessed the effectiveness and tolerability of amisulpride and quetiapine in the treatment of delirium. Forty patients who had been referred to a psychiatric consultation service participated in the study. Patients with a history of psychiatric disorders, as well as those who had been taking antipsychotics, were excluded. Patients were randomised to receive either amisulpride or quetiapine with a flexible dosing regimen, according to the clinician's experience and preference. Other antipsychotics or benzodiazepines were not allowed for the duration of the study. The DRS-R-98 was used to measure the response to treatment in terms of delirium severity and effectiveness. Complete data were obtained from 16 patients in the amisulpride group (mean age 60.8 ± 18.4 years; mean amisulpride dose 156.4 ± 97.5 mg per day; mean treatment duration 6.3 ± 4.4 days) and 15 patients in the quetiapine group (mean age 63.1 ± 14.5 years; mean quetiapine dose 113 ± 85.5mg per day; mean treatment duration 7.4 ± 4.1 days). DRS-R-98 scores showed a significant decrease in both treatment groups, and there was no significant difference between the groups. No serious adverse effects were reported. The main limitations of the study included its single-blind design (performance bias), the variable dosing regimen, and the relatively small sample size. Overall, the results of this study provided evidence of the efficacy and tolerability of atypical antipsychotics in the clinical management of delirium.

The study by Kim et al. [16] was a 7-day trial comparing risperidone and olanzapine in the treatment of delirium. Patients who met DSM-validated criteria of delirium were included in the study, whereas those with dementia, hepatic problems, bone marrow suppression, or those who had previously taken antipsychotics for behavioural problems or patients undergoing intubation were excluded. The DRS-R-98 was used to measure the severity of delirium. A total of 32 patients were enrolled, out of which 17 were randomised to receive risperidone and 15 to receive olanzapine. The trial was completed by 12 patients in the risperidone group and 8 in the olanzapine group. The dosage was adjusted according to clinical judgement over the 7 days and rescue intramuscular injections of haloperidol or benzodiazepine were permitted and recorded. The mean starting doses were 0.6 ± 0.2 mg per day (range 0.25-1 mg per day) for risperidone and 1.8 ± 0.6mg per day (range 1.25-2.5 mg per day) for olanzapine. The mean doses at last observation were 0.9 ± 0.6mg per day (range 0.25-2.0 mg per day) for risperidone and 2.4 ± 1.7 mg per day (range 1.25-7.5 mg per day) for olanzapine. Significant improvement was seen in both groups, and no significant differences were found between the groups. Both medications were well tolerated and adverse effects such as extrapyramidal adverse effects were graded as mild-to-moderate and were tolerable in both groups. The main limitations of this study were its relatively small sample size and high dropout rate; moreover, this was a single-blind study in which only the investigators were blinded. Despite its limitations, this study showed that both risperidone and olanzapine were effective in the treatment of delirium and had a good tolerability profile.

Conclusions

The results of our systematic literature review showed that atypical antipsychotics can be useful interventions for the treatment of delirium: in addition to superiority to placebo, these medications demonstrated similar levels

of effectiveness to conventional antipsychotics, with a better tolerability profile. Our findings are in line with the results of previous reviews [17,18]. Moreover, a Cochrane review found no difference in effectiveness of olanzapine and risperidone when compared with haloperidol; the same review found that higher doses of haloperidol were associated with extrapyramidal adverse effects [19]. Out of the eight studies included in our systematic literature review, seven were comparative studies, in which atypical antipsychotics were compared to either haloperidol or to another atypical antipsychotic medication. The reviewed literature has two main limitations: the sample sizes of the reviewed studies were small, and the clinical samples were heterogeneous in terms of several parameters, including the aetiology of delirium. To reach definitive and firm conclusions, larger sample sizes and well-controlled randomised trials are needed. Our systematic literature review also has intrinsic limitations, which limit the generalizability of its findings: we included only studies published in English language that used established rating scales, such as the DRS-R-98, MDAS, and DI. Moreover, studies on critically ill patients were excluded.

The overall results of our systematic literature review confirm the effectiveness of atypical antipsychotics in the treatment of delirium. Future studies should include pharmacological trials in patients with different subtypes of delirium, including hypoactive presentations that are often undiagnosed due to their clinical features.

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