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Is muscarinic receptor agonist effective and tolerant for schizophrenia?

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Abstract

Background Several randomized clinical trials (RCTs) have recently examined the efficacy and tolerability of muscarinic receptor agonists in schizophrenia. However, whether therapeutics targeting muscarinic receptors improve symptom management and reduce side effects remains systemically unexplored.

Methods Embase, PubMed, and Web of Science were searched from inception until Jan 9, 2025. Altogether, the efficacy and safety outcomes of four RCTs (397 individuals in the muscarinic receptor agonists group, and 374 in the placebo control group) were meta-analyzed. To compare scores of positive and negative syndrome scale (PANSS), response rate, discontinuation rate, and adverse events with muscarinic receptor agonists vs. placebo in patients with schizophrenia, scale changes were pooled as mean difference (MD) for continuous outcomes and risk ratio (RR) for categorical outcomes.

Results It revealed that muscarinic receptor agonists were superior to placebo in terms of decrease in the total PANSS score (MD, −9.92; 95% CI, -12.46 to -7.37; $I^2 = 0\%$), PANSS positive symptom subscore (MD, −3.21; 95% CI, -4.02 to -2.40; $I^2 = 0\%$), and PANSS negative symptom subscore (MD, -1.79; 95% CI, -2.47 to -1.11; $I^2 = 48\%$). According to the study-defined response rate, the pooled muscarinic receptor agonists vs. placebo RR was 2.08 (95% CI, 1.59 to 2.72; $I^2 = 0\%$). No significance was found in the discontinuation rate. Muscarinic receptor agonists were associated with a higher risk of nausea (RR = 4.61, 95% CI, 2.65 to 8.02; $I^2 = 3\%$), and in particular, xanomeline-trospium was associated with risks of dyspepsia, vomiting, and constipation.

Conclusions The findings highlighted an efficacy advantage with tolerated adverse event profiles for muscarinic receptor agonists in schizophrenia.

Keywords Schizophrenia, Muscarinic receptor agonist, Xanomeline-trospium

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Background

Schizophrenia is a complicated and debilitating psychiatric disorder, ranking among the top 10 causes of disability worldwide [1, 2]. Driven by the dopamine hypothesis, the promising therapeutic effect of antipsychotics in D2 dopamine receptor blockade was a milestone in the management of schizophrenia [3, 4], especially with clozapine [5–7]. However, due to their limited effectiveness in addressing the entire core symptoms (especially negative and cognitive symptoms) and burdensome adverse effects (e.g., extrapyramidal motor symptoms, hyperprolactinemia, and metabolic aberrations), the rates of discontinuing the traditional oral antipsychotic treatment reached as 74% before 18 months [8]. Thus, there is an urgent need for mechanistically distinct, and better-tolerated therapeutic agents to treat schizophrenia effectively [9–17].

The development of novel drugs targeting muscarinic acetylcholine receptors (mAChRs), has been the first novel class of antipsychotic medications after the launch of second-generation antipsychotic drugs [10, 14, 15]. Unlike traditional D2 receptor antagonism in treating psychosis, muscarinic receptors including M1 and M4 offer a potential beneficial alternative due to the absence of postsynaptic and nonselective dopamine D2 receptor blockade and its associated side effects. Specifically, M4 muscarinic autoreceptor agonism reduces presynaptic dopamine release in the striatum (an essential region responsible for dysregulated dopamine in patients with schizophrenia) by decreasing cholinergic input from the hindbrain to the midbrain and reducing acetylcholine release from cholinergic interneurons within the striatum [18]. Additionally, as reported, M1 receptors are located on projection neurons in the striatum and the prefrontal cortex [19]. Therefore, M1 muscarinic receptor agonism leads to increased acetylcholine release in the frontal cortex, which stimulates GABA transmission and interacts with glutamatergic inputs into the ventral tegmental area, resulting in reduced presynaptic dopamine release in the striatum. Furthermore, M1 receptor stimulation also increases dopamine in the frontal cortex, potentially leading to precognitive effects. Therefore, the mAChRs agonists, which are devoid of direct D2 dopamine receptor-blocking activity, indirectly modulate dopaminergic systems in tandem with cholinergic function [20–22], possibly achieving an antipsychotic effect and without neuromotor side effects caused by dopamine release in the sensorimotor striatum.

In preclinical studies, compounds targeting mAChRs have proved great efficacy in antipsychotic-like effects as well as negative and/or cognitive symptoms [15, 17, 23–26], stimulating interest in its potential for treating patients with schizophrenia. Recently, several randomized clinical trials (RCTs) have examined the efficacy, safety, and tolerability of mAChR agonists, especially for cholinergic M1 and M4 [27–33] or M4 [34] receptors, in patients with schizophrenia. Therefore, a quantitative synthesis of the results of these studies could systematically investigate the clinical evidence of mAChR agonists. Thus, we collected efficacy and safety evidence of the mAChR agonists for patients with schizophrenia in RCTs, which might guide research and clinical practice.

Methods

Search strategy and selection criteria

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) [35] and registered a protocol (PROSPERO-ID: CRD42024536119).

We searched electronic databases (Embase, PubMed, Web of Science, Google Scholar) from inception until Jan 9, 2025, with no language restriction. Systematic retrieval was carried out in the first three databases (Embase, PubMed, Web of Science) using MeSH terms and their morphological variations in sequential MeSH and free-text terms search. Manual retrieval was conducted in the latter database (Google Scholar) to ensure the comprehensive coverage of the scope. eMethod in Supplement 1 provided complete information on the search strategy. We limited the search to parallel-group RCTs that compared the treatment effect of mAChRs agonists and placebo in patients with schizophrenia, with efficacy and safety outcomes evaluated. Any effective dosage of different drugs was included. When no heterogeneity existed between different dosages of the same drug, the data were combined in the analyses. Otherwise, respective groups were included in the analyses.

Study screening and data extraction

Evaluations including positive and negative syndrome scale (PANSS) and Clinical Global Impression–Severity (CGI-S) are widely used in measuring clinical manifestations of the patients with schizophrenia. The primary efficacy outcome was a total decrease score in the positive and negative syndrome scale (PANSS) from baseline at the treatment endpoint, which indicated the recovery of the general symptoms of schizophrenia [36]. Secondary efficacy outcomes included score decreases from baseline in positive or negative symptom subscores of PANSS, Clinical Global Impression–Severity (CGI-S) scale (standing for global illness severity) [37], and response rates to the treatment according to the study design at the primary endpoint. The response criteria were recorded. To investigate the tolerability of the mAChRs agonists, the discontinuation rate, and any adverse event rate were extracted. The adverse events were extracted and adverse events that occurred in at least 5% of cases more than

three times were all selected for detailed adverse events analysis.

Study screening, data extraction, and quality assessment were conducted independently by RSD and XNG. Studies that met the inclusion criteria on the title and abstract or could not be excluded based on information provided in the abstract, were reviewed at a full-text level. Data was obtained in the eligible paper. If the graph data cannot be directly extracted from the paper, a semi-automated tool (WebPlotDigitize) would be used to help reverse numerical data from images. For the trial of emraclidine [34], the combined results of the 30 mg qd group and 20 mg bid group in Part B were used in the analyses. The risk of bias for the primary outcomes was evaluated using the *Cochrane Handbook Risk of Bias Tool for RCTs*. After reviewing the primary publications, quality assessment results were visualized *via* Review Manager (5.4.1. version). All discrepancies during each stage of study selection, data extraction, and quality assessment were resolved by re-checking source papers.

Data analysis

Meta-analyses were conducted using Review Manager (5.4.1. version). Statistical tests were used to evaluate the pooled effect and heterogeneity of the whole group or subgroup. Sensitivity analyses were omitted due to the constricted number of trials. Publication bias was not examined due to the constricted number of trials. Continuous variables were reported as mean difference (MD), along with the confidence interval (95% CI). The normal likelihood was used for continuous outcomes. Relative risk (RR) and 95% CI were used for pooling binary variables. Heterogeneity among the included studies was assessed using the I^2 index, with an I^2 of 25%, 50%, and 75% indicating mild, moderate, and high heterogeneity, respectively, and was shown in the forest plots. Results of I^2 lower than 50% would be analyzed with a fixed effect model, and others would be analyzed with a random effect model. For significant adverse events, we calculated the number needed to treat/harm (NNH) with 95%CIs. All *P* values were two-tailed, and significance was considered < 0.05.

Results

Five RCTs [27–29, 34, 38] had been identified according to the search criteria in Embase, PubMed, and Web of Science (Fig. 1). Four trials (NCT03697252, register date: 2018-10-03; NCT04136873, register date: 2019-10-21; NCT04659161, register date: 2020-12-02; NCT04738123, register date: 2021-02-01) had no risk of bias [27, 28, 34, 38]. One pilot trial had unclear risks of bias related to randomization processes and incomplete outcome data reporting [29] (eFigs. 1 and 2 in Supplement 1). Thus, we excluded this trial in the meta-analysis but listed the findings together with evidence in other RCTs (eTable 1 in Supplement 1).

In general, 771 patients with current acute exacerbation or relapse of schizophrenia were enrolled in four trials, with a mean age of 43.5 (SD, 10.9) years, males accounting for 75.8% (584/771), average BMI of 28.9 (SD, 5.3) Kg/m^2, Black and African American for 69.8% (538/771), and White for 27.0% (208/771), and average PANSS score of 97.1 (SD, 9.0), positive subscore of 26.4 (SD, 3.5), and negative subscore of 22.7 (SD, 3.9) at baseline. Altogether, two types of mAChRs were conducted with RCTs. Three trials assessed xanomeline–trospium (KarXT; xanomeline: peripheral and central M1 and M4-preferring agonism; trospium: peripheral restricted pan-muscarinic receptor antagonist to mitigate peripheral cholinergic agonism of xanomeline [39]) lasted five weeks [27, 28, 38], and one trial assessed emraclidine, a novel positive allosteric modulator of cholinergic M4 receptors, lasted six weeks [34]. All trials were conducted in inpatient units and lasted short term.

Efficacy evaluation

In the main analysis, the total PANSS score displayed a significant decrease (MD, − 9.92; 95% CI, -12.46 to -7.37; $I^2 = 0\%$; Cohen's d = 0.56; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 356$, placebo control group = 347) in mAChRs agonist group (Fig. 2A). In terms of positive symptoms, a significant PANSS positive symptom subscore decrease was also detected (MD, − 3.21; 95% CI, -4.02 to -2.40; $I^2 = 0\%$; Cohen's d = 0.60; 4 RCT [27, 28, 34, 38]s; mAChRs agonist group $n = 356$, placebo control group = 347) (Fig. 2B). In terms of negative symptoms, the therapeutic effect was detected in PANSS negative symptom subscore decrease with high heterogeneity (MD, -1.79; 95% CI, -2.47 to -1.11; $I^2 = 48\%$; Cohen's d = 0.49; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 356$, placebo control group = 347) (Fig. 2C). On the scale of CGI-S, mAChRs agonist group showed a significantly lower score than the placebo (MD, − 0.58; 95% CI, -0.73 to -0.42; $I^2 = 0\%$; Cohen's d = 0.60; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 356$, placebo control group = 347) (eFigure 3 in Supplement 1). According to the study-defined response rate, the pooled mAChRs agonist vs. placebo RR was 2.08 (95% CI, 1.59 to 2.72; $I^2 = 0\%$; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 309$, placebo control group = 304) (Fig. 2D). Despite moderate heterogeneity in the PANSS negative symptom subscore, all treatment effects were uncovered with low heterogeneity.

Of note, a subgroup analysis that specifically excluded emraclidine [34], revealed that KarXT was effective in reducing total PANSS score (MD, − 9.74; 95% CI, -12.39 to -7.09; Cohen's d = 0.50; $I^2 = 0\%$; 3 RCTs [27, 28, 38]; KarXT group $n = 314$, placebo control group = 326),

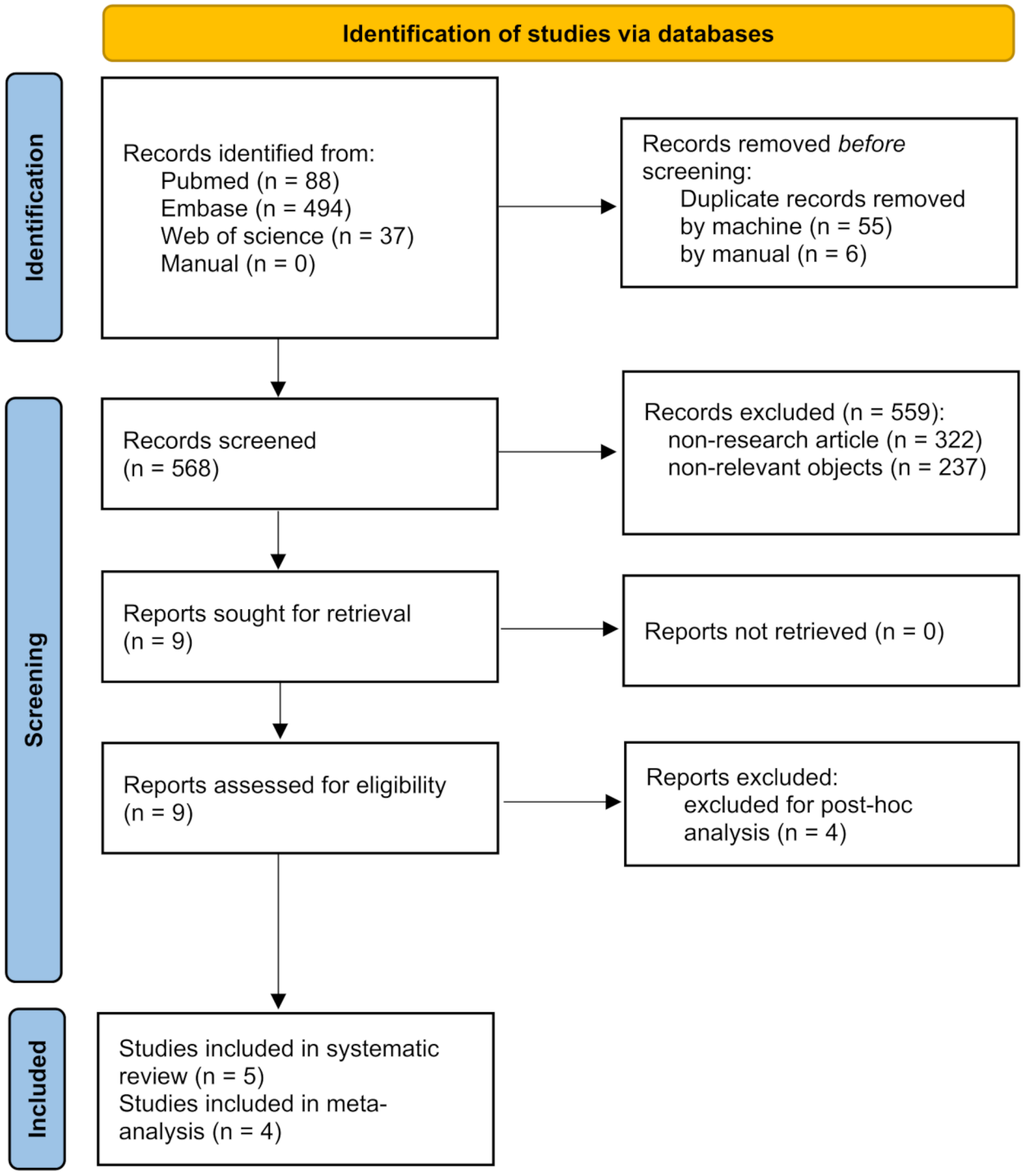

Fig. 1 PRISMA Flowchart

PANSS positive symptom subscore (MD, − 3.20; 95% CI, -4.04 to -2.36; $I^2 = 0\%$; Cohen's d = 0.69; 3 RCTs [27, 28, 38]; KarXT group $n = 314$, placebo control group = 326), and PANSS negative symptom subscore (MD, − 1.55; 95% CI, -2.28 to -0.82; $I^2 = 23\%$; Cohen's d = 0.28; 3 RCTs [27, 28, 38]; KarXT group $n = 314$, placebo control group = 326) (eFigure 4 in Supplement 1). Meanwhile, KarXT also displayed improvement in CGI-S scores (MD, − 0.57; 95% CI, -0.73 to -0.41; $I^2 = 0\%$; Cohen's d = 0.52; 3 RCTs [27, 28, 38]; KarXT group $n = 314$, placebo control group = 326) (eFigure 3 in Supplement 1). Concerning response rate, KarXT was superior to the placebo,

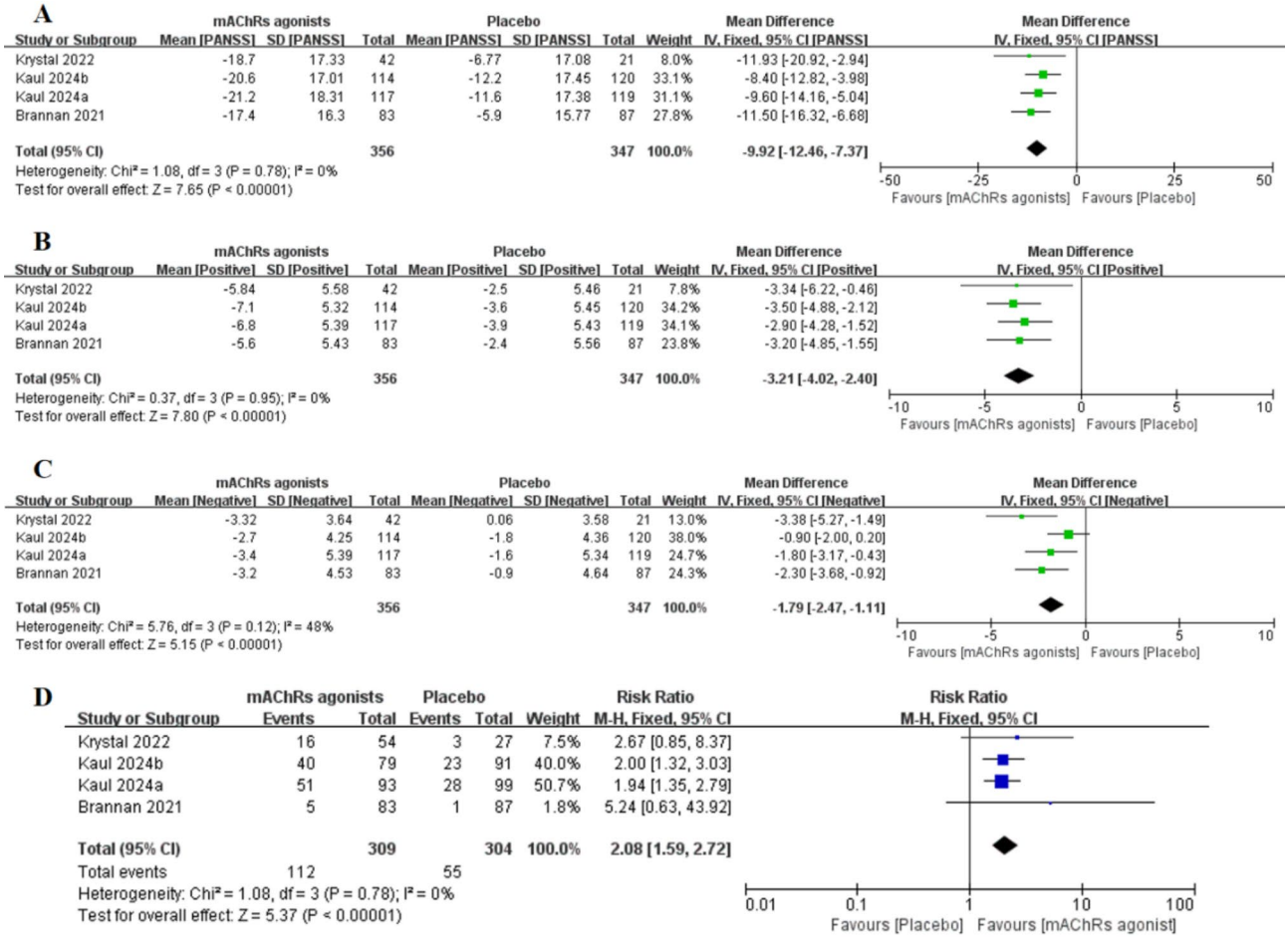

Fig. 2 Efficacy outcomes for mAChRs agonist in patients with schizophrenia. **A**. Total score changes of PANSS. **B**. Score changes of PANSS positive symptom subscore. **C**. Score changes of PANSS negative symptom subscore. **D**. Study-defined response rate at primary endpoint

as the pooled mAChRs agonist vs. placebo RR was 2.03 (95% CI, 1.55 to 2.67; $I^2 = 0\%$; 3 RCTs [27, 28, 38]; KarXT group $n = 255$, placebo control group = 277) (eFigure 4 in Supplement 1).

Safety evaluation

The serious adverse event, severe adverse event, and discontinuation reasons were listed in eTable 2-4 in Supplement 1. The pooled mAChRs agonist vs. placebo RR was 1.18 for discontinuation rate with no significant difference (95% CI, 0.93 to 1.51; $I^2 = 0\%$; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 395$, placebo control group = 376) (Fig. 3A). No significant difference was found in the discontinuation rate caused by adverse events (RR = 1.52, 95% CI, 0.81 to 2.86; $I^2 = 0\%$; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 395$, placebo control group = 376) (Fig. 3B). Similar results can also be observed in the KarXT subgroup analyses (eFigure 5 in Supplement 1).

Considering any adverse events, the pooled mAChRs agonist vs. placebo RR was 1.30 with significance (95% CI, 1.15 to 1.46; $I^2 = 0\%$; NNH = 6.59, 95% CI, 4.54 to 12.01; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 394$, placebo control group = 370) (Fig. 3C). For all the adverse effects, we recorded the details in Supplement 2. The pooled mAChRs agonist vs. placebo RR in nausea was 4.61 with significance (95% CI, 2.65 to 8.02; $I^2 = 3\%$; NNH = 7.31, 95% CI, 5.57 to 10.63; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 394$, placebo control group = 370) (Fig. 3D). However, the discontinuation reason caused by adverse effects was not significant between the mAChRs agonist group and placebo group (RR = 1.52, 95% CI, 0.81 to 2.86; $I^2 = 0\%$; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 395$, placebo control group = 376). The pooled mAChRs agonist vs. placebo RR in headache was 1.07 with no significance (95% CI, 0.73 to 1.56; $I^2 = 0\%$; 4 RCTs [27, 28, 34, 38]; mAChRs agonist group $n = 394$, placebo control group = 370) (eFigure 6 in Supplement 1). The pooled mAChRs agonist vs. placebo MD in body weight increase was −0.28 (95% CI, -0.82 to 0.25; $I^2 = 23\%$; 4 RCTs [27, 28, 34, 38]; mAChRs agonist

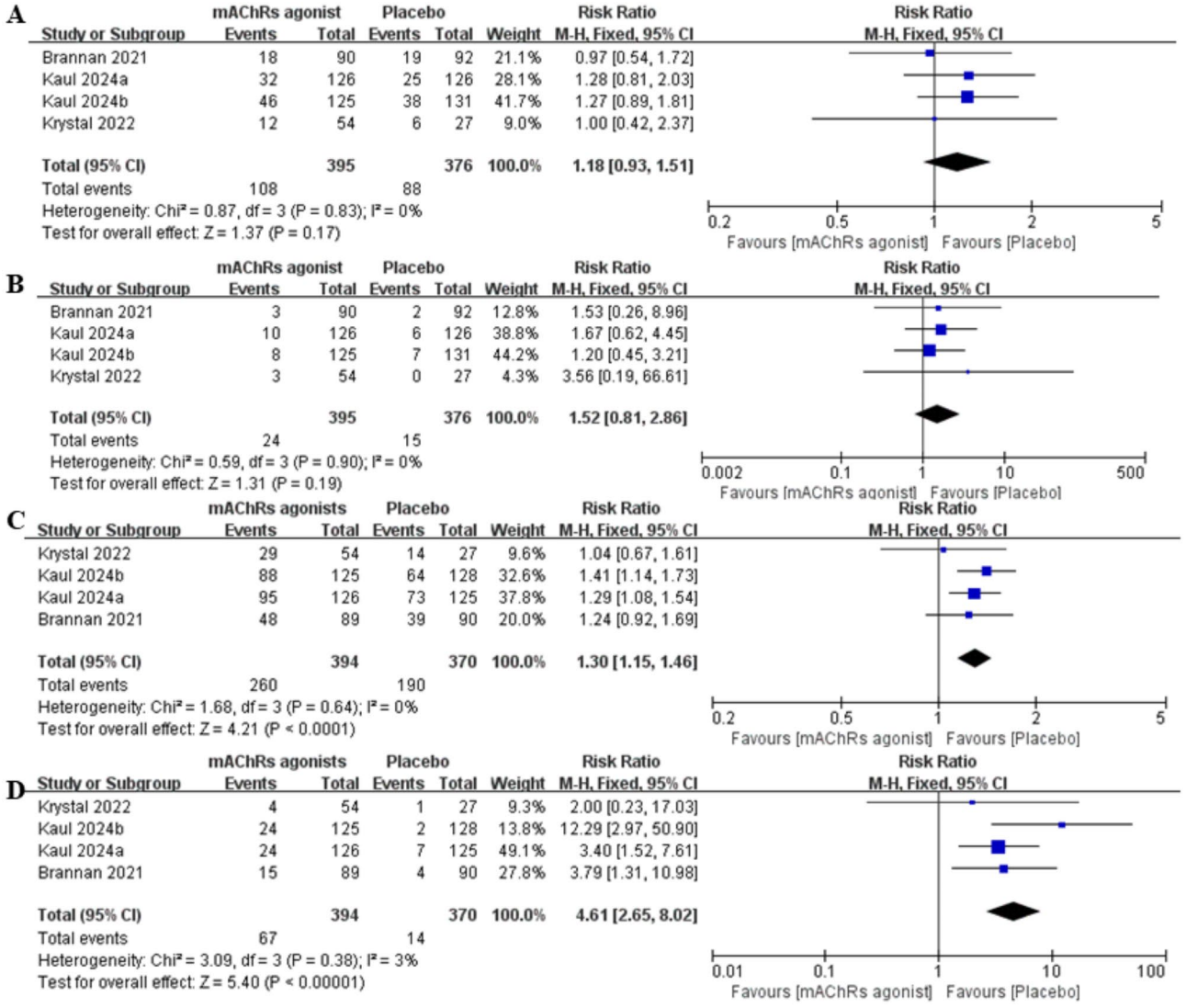

Fig. 3 Safety outcomes for mAChRs agonist in patients with schizophrenia. **A**. Discontinuation rate. **B**. Discontinuation rate caused by adverse events. **C**. Any adverse event rate. **D**. Nausea events

group $n = 362$, placebo control group = 345) (eFigure 7 in Supplement 1).

For KarXT subgroup, the pooled mAChRs agonist vs. placebo RR was 1.32 for any adverse events (95% CI, 1.17 to 1.50; $I^2 = 0\%$; NNH = 6.03, 95% CI, 4.21 to 10.62; 3 RCTs [27, 28, 38]; KarXT group $n = 340$, placebo control group = 343) (eFigure 5 in Supplement 1). Similar frequencies of nausea and headache events in the whole group were observed in the KarXT group (eFigure 5–6 in Supplement 1). Additionally, KarXT was associated with elevated risks of dyspepsia (RR, 3.26; 95% CI, 1.91 to 5.59; $I^2 = 49\%$; NNH = 9.44, 95% CI, 6.67 to 16.14; 3 RCTs [27, 28, 38]; KarXT group $n = 340$, placebo control group = 343), vomiting (RR, 7.81; 95% CI, 1.30 to 46.94; $I^2 = 70\%$; NNH = 8.49, 95% CI, 6.39 to 12.65; 3 RCTs [27, 28, 38]; KarXT group $n = 340$, placebo control group = 343), and constipation (RR, 2.77; 95% CI, 1.73 to 4.45; $I^2 = 0\%$; 3 RCTs [27, 28, 38]; NNH = 9.18, 95% CI, 6.41 to 16.17; KarXT group $n = 340$, placebo control group = 343), while no association risk of diarrhea was found (RR, 1.79; 95% CI, 0.80 to 4.00; $I^2 = 49\%$; 3 RCTs [27, 28, 38]; KarXT group $n = 340$, placebo control group = 343), compared to placebo control (eFigure 8 in Supplement 1). The pooled mAChRs agonist vs. placebo MD in body weight increase was −0.30 with moderate heterogeneity (95% CI, -0.86 to 0.26; $I^2 = 47\%$; 3 RCTs [27, 28, 38]; KarXT group $n = 308$, placebo control group = 318) (eFigure 7 in Supplement 1).

Discussion

Together, in four RCTs [27, 28, 34, 38], mAChRs agonists revealed superior effects to placebo in total PANSS score, PANSS positive symptom subscore, CGI-S score, and study-defined response rate with low heterogeneity, and

PANSS negative symptom subscore with moderate heterogeneity (which possibly caused by the race difference in one trial [38]), at the primary endpoint. Thus, mAChRs agonists have the potential for the management of both acute psychotic and negative symptoms. As reported, the occurrence of cognitive decline was observed following the onset of schizophrenia, despite heterogeneity in cognitive function among patients [40–43]. Traditional antipsychotic treatment for cognitive impairment associated with schizophrenia only exerted limited effect [44, 45]. Importantly, the application of mAChRs agonists for the treatment of dementia served as a marked impetus for studies examining their impact on cognitive benefits in patients with schizophrenia [46]. Of note, both M1 and M4 agonism in the hippocampus appear to enhance neural transmission coordination, benefiting cognitive functioning [47]. However, the cognitive outcomes could not be obtained due to insufficient data on cognition outcomes. Only one trial reported the cognition outcome, showing that emraclidine did not improve cognition performance in the Brief Assessment of Cognition in Schizophrenia symbol coding test [34]. Of note, the administration of xanomeline as a single agent has demonstrated efficacy in enhancing the cognitive function of Alzheimer's disease in a dose-dependent manner (17 sites; $n = 343$) [48], and schizophrenia in a pilot trial, exemplified by improved verbal learning and short-term memory function [29]. In addition, post-hoc analyses yielded a robust and significant benefit in Cogstate Brief Battery among patients with cognitive impairment after taking KarXT (KarXT $n = 23$, placebo $n = 37$, Cohen's $d = 0.50$ [31]; KarXT $n = 71$, placebo $n = 66$, Cohen's $d = 0.54$ [49]). Thus, future studies should be carried out to examine whether or which mAChRs agonist has a treatment role among patients who exhibit a prototypical degree of cognitive impairment. However, caution is warranted to characterize the cognitive outcomes due to the potential pseudospecific effects caused by the mitigation of positive symptoms [31].

Considering the safety and tolerability, the incidences of nausea were more frequent under the intervention of mAChRs agonists due to peripheral mAChR function. However, side effects of antipsychotic drugs including extrapyramidal motor symptoms and hyperprolactinemia were not reported in adverse events that occurred in at least 5% of cases. An absence of neuromotor side effects observed can be attributed to the impact of mAChRs agonists on dopamine release in the sensorimotor striatum. Meanwhile, the discontinuation rate, headache, and body weight changes of mAChRs agonists were similar to placebo control at the primary endpoint, supporting the recommendation for mAChRs agonists with a mild to moderate side-effect profile. Importantly, the management of schizophrenia often involves extended periods of medication therapy, with the potential for side effects to compromise the overall well-being and lifestyle of individuals affected by the condition. Long-term safety considerations have been raised regarding muscarinic agonists due to potential cholinergic side effects like gastrointestinal disturbances and urinary retention that may arise with prolonged usage, which requires further clinical explorations.

For specific mAChRs agonist, KarXT, although the xanomeline monotherapy trial received suspension due to frequent gastrointestinal adverse events [29], the application of trospium chloride, a non-selective muscarinic antagonist that has been previously used for the treatment of overactive bladder [50], has mitigated 46% peripheral cholinergic side effects in the healthy volunteers with co-administration of xanomeline [39, 51]. Indeed, the overall percentage of participants who discontinued the trial was similar between the KarXT and placebo groups (28% vs. 24%). The majority of KarXT-related adverse events still mainly consisted of gastrointestinal reactions (nausea, dyspepsia, vomiting, and constipation), with elevated risks identified in all three trials, compared to placebo control, consistent with previous reports [18, 52–54]. They usually occurred within the early stage and were tolerated before the endpoint of the trial [28, 30, 38]. Subanalyses of the KarXT subgroup displayed consistent efficacy and safety with whole-group analyses of mAChRs agonists, implying the promising future of KarXT in the management of schizophrenia. However, caution should be paid to gastrointestinal reactions, since the side effect impact might be mitigated by inpatient settings. Meanwhile, because the crystal structures of M1 and M4 receptors were identified [55], it was promising to target the specific therapeutic site to design drugs, which might reduce undesirable reactions. Positive allosteric modulators such as emraclidine modulate receptor activity by binding to a site distinct from the natural ligand, potentially offering theoretical advantages such as increased selectivity and safety over orthosteric agonists [56, 57], which can be examined in future studies.

Given the possibility that a quarter of patients with schizophrenia will develop treatment-resistant at the early stages of treatment [58], analyses of the durability of effect and long-term safety after the conduction of larger and longer trials are warranted [59]. The primary endpoints in the studies were around five weeks after the current acute exacerbation or relapse, requiring a longer assessment duration. Fortunately, three 52-week trials for outpatients are underway (KarXT: NCT04659174, register date: 2020-12-02 and NCT04820309, register date: 2021-03-24; Emraclidine: NCT05443724, register date: 2022-06-29). Promisingly, the breakthrough of mAChRs agonists might revolutionize the treatment of

schizophrenia. Additionally, the combination effect of mAChRs agonists with other physical intervention strategies, such as deep transcranial magnetic stimulation [60], transcranial alternating current stimulation [61], and transcranial direct current stimulation [62, 63], can also be examined in the future study for the treatment of patients with schizophrenia.

Key limitations inherent in the systematic review and meta-analysis were listed below. (1) the small number of eligible studies; (2) insufficient data for cognition outcome evaluation; (3) lack of comparable efficacy with traditional antipsychotic drugs [64].

Conclusion

In summary, the systematic meta-analysis highlighted the potential management of mAChRs agonists for individuals with schizophrenia in both positive and negative symptoms. While the overall tolerated adverse event profiles were reported, mAChRs agonists were associated with a risk of nausea, and in particular, KarXT was also associated with risks of dyspepsia, vomiting, and constipation. As such, evidence-based treatment of mAChRs agonists for schizophrenia held the key to characterizing the therapeutic effects on core symptoms and shredded the light on the future drug design [65].

Abbreviations

CI	Confidence interval
CGI-S	Clinical Global Impression–Severity
RCTs	Randomized clinical trials
RR	Risk ratio
mAChRs	muscarinic acetylcholine receptor
MD	Mean difference
PANSS	Positive and negative syndrome scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06662-1 .

Supplementary Material 1

Supplementary Material 2

Acknowledgements

All authors declare no conflict of interest.

Author contributions

XNG, SHH, and JBL conceived the research; XNG and RSD screened, extracted, and analyzed data; XNG wrote the initial manuscript; all the authors polished the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Our manuscript was not applied to human beings and thus requires no ethical approval.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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