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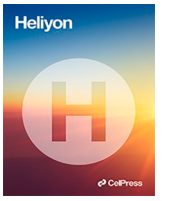

Research article

Side effects and cognitive benefits of buspirone: A systematic review and meta-analysis

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ABSTRACT

Buspirone, a 5-hydroxytryptamine 1A (5-HT1A) receptor agonist, has been investigated for its use in various diseases. However, knowledge about its side effects and potential cognitive benefits in different conditions is limited. Cognitive impairment is also a prevalent symptom in many diseases, yet effective treatments are still lacking. Therefore, to explore the potential side effects of buspirone and the possible cognitive benefits of buspirone, we conducted a comprehensive search of several databases, including PubMed, Embase, Web of Science, Cochrane Review, Cochrane Trial, and ClinicalTrials.gov, to identify eligible randomized clinical trials. Our primary outcome measures included both side effects (adverse events) and cognitive benefits. For continuous variables, we utilized effect size with a 95% confidence interval (CI), whereas for dichotomous variables, we used odds ratios (OR) with a 95% CI. In total, 16 studies were included in this analysis, with 13 studies reporting on buspirone's side effects and 4 studies focusing on cognitive tasks. In terms of side effects, buspirone exhibited a higher rate of dizziness (OR = 4.66, 95% CI: 2.07–10.47), constipation (OR = 4.11, 95% CI: 1.34–12.55), and gastric distress (OR = 1.97, 95% CI: 1.03–3.78) than the placebo group. Regarding cognitive functions, buspirone showed significant benefits (g = 0.20, 95% CI: 0.06–0.34) while the placebo did not. Subgroup analysis indicated superior performance in visual learning and memory (g = 0.49, 95% CI: 0.21–0.78), logical reasoning (g = 0.42, 95% CI: 0.14–0.71), and attention (g = 0.37, 95% CI: 0.13–0.61) when compared to placebo. Our findings indicated that participants in the buspirone group experienced side effects of dizziness, constipation, and gastric distress in different diseases. Despite these adverse events, however, buspirone demonstrated significant cognitive benefits, particularly in the domains of visual learning and memory, logical reasoning, and attention.

1. Introduction

Buspirone is a unique medication with multiple pharmacological properties. It acts as a partial agonist at the post-synaptic serotonin-1A receptors, an antagonist at pre-synaptic dopamine D2, D3, and D4 receptors, and a partial agonist at alpha-1 adrenergic

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receptors [1,2]. Unlike benzodiazepines, buspirone does not directly affect gamma-aminobutyric acid (GABA) receptors or benzodiazepine binding response to GABA or halide ions [1]. Initially, buspirone gained popularity for its efficacy and safety in treating generalized anxiety disorder (GAD) [2]. Nevertheless, recent research has indicated its potential usefulness in treating other disorders and symptoms. Studies have demonstrated that buspirone, either alone or in combination with antidepressants or melatonin, can alleviate depressive symptoms [3–5] and improve cognitive impairment independent of mood symptoms [6,7]. Additionally, Schneider et al. found that buspirone may help alleviate anxious symptoms in individuals with Parkinson's disease [8]. However, researchers cautioned against immediate clinical use due to concerns regarding tolerability and side effects. Furthermore, the same concerns have been observed in gastrointestinal disorders. Interestingly, buspirone has also shown positive effects on digestive system conditions. Recent studies have suggested its potential benefits in treating gastroparesis [9] and improving gastric accommodation [10,11]. Given that gastrointestinal disorders often coexist with other conditions, it is important to exercise caution when considering drug therapy for these patients [12].

Previous studies have examined the side effects of buspirone in patients with generalized anxiety disorder (GAD) [13]. In previous research, certain side effects were significantly more prevalent in the buspirone group compared to the placebo group. These side effects included dizziness, headache, nervousness, light-headedness, diarrhea, paresthesia, excitation, and sweating/clamminess. Gastrointestinal-related complaints were also commonly reported as side effects of buspirone [14]. Nevertheless, despite the ongoing rapid development in the use of buspirone for different diseases, updated evidence regarding its potential side effects is still lacking. This knowledge gap is inconsistent with the increased usage of buspirone across various diseases. It is necessary to collect recent evidence that sheds light on its potential side effects.

Cognitive impairment is a symptom that occurs across a spectrum of diseases. For instance, in Parkinson's disease (PD), cognitive impairments encompass domains such as working memory, executive function, and other cognitive abilities. Studies have shown that up to 80% of PD patients experience cognitive impairments, which have been associated with a reduced quality of life [15]. Likewise, individuals diagnosed with generalized anxiety disorder may exhibit compromised learning, memory, information processing speed, and visuospatial skills [16–18]. These clinical findings provide evidence for the existence of cognitive impairment in multiple conditions, indicating its multidimensional nature and complicating the development of treatment plans. It is worth noting that cognitive impairment is often considered an independent symptom separate from the underlying disease. In schizophrenia, approximately 85% of patients display cognitive deficits related to attention, working memory, and executive function [19]. Surprisingly, these cognitive impairments in schizophrenia have been found to be disconnected from either positive or negative symptoms [20,21]. Even with antipsychotic drug treatment leading to significant improvement or complete remission of other clinical symptoms, about 80% of patients continue to experience persistent cognitive impairments, impeding their ability to live, work, and learn independently [22]. Research on the impact of anxiety symptoms, depressive symptoms, and Parkinson's disease on cognitive impairment has yielded inconsistent results. Nevertheless, some studies propose that cognitive impairment manifests as an independent symptom separate from the aforementioned diseases [23,24]. This indicates that cognitive impairment involves a multifactorial and multistep pathological process, involving oxidative stress, inflammation, neuroplasticity, and other pathophysiological mechanisms [25]. Consequently, addressing cognitive impairment poses significant challenges for clinical treatment while imposing substantial economic and psychological burdens on individuals, families, and society. Given the complexities surrounding cognitive impairment, we strive to further explore it as an independent symptom and investigate potential pharmacological treatments that may effectively address this cognitive deficit.

Currently, therapeutic options available to improve cognitive function are limited. A review published in JAMA suggested that cholinesterase inhibitors may be useful for cognitive treatment of Parkinson's disease, but with limited evidence [26]. Previous studies have indicated that cholinesterase inhibitors can increase the concentration of acetylcholine and enhance the function of the cholinergic system, which is closely related to cognitive function involving attention, learning, and memory. Additionally, cholinesterase inhibitors can increase synaptic plasticity between neurons, promote neuronal growth and repair, and delay brain cortical thinning and basal forebrain atrophy [27–29]. The US Food and Drug Administration (FDA) has approved acetylcholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, for the treatment of mild, moderate, or severe Alzheimer's disease and [editing ok??] dementia [30]. However, patients who take acetylcholinesterase inhibitors to improve cognitive impairment often experience gastrointestinal discomfort as a medication side effect, which may affect their compliance with the medication. More importantly, acetylcholinesterase inhibitors increase cholinergic activity in various systems of the body, which may stimulate vagal nerve activity in the heart, leading to potentially life-threatening conditions such as bradycardia and atrioventricular conduction block [31]. For frail elderly individuals, the risks of treatment may outweigh the benefits [32]. In addition, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine is believed to possibly improve cognitive function by promoting adult hippocampal neurogenesis [33]. A meta-analysis found that memantine may provide some cognitive benefits for patients with Alzheimer's disease and vascular dementia, but the benefits are small [32]. Meanwhile, studies have shown that memantine has no therapeutic effect on dementia in Parkinson's disease [26]. Therefore, it is imperative to search for new drugs with different mechanisms that may improve cognitive function.

Extensive research has suggested that stimulating 5-hydroxytryptamine 1A (5-HT1A) receptors can improve cognitive impairments [7,34,35]. Some clinical studies have shown that after 6 weeks of combined treatment with AAPDs and 5-HT1A receptor agonists, patients exhibited significant improvements in executive function, attention, and verbal memory [32,36]. An animal study showed that chronic treatment with partial agonists of 5-HT1A receptors significantly increased the number of doublecortin (DCX)-positive cells per volume in the dentate gyrus of the rat's brain, strongly indicating that partial agonists of 5-HT1A receptors would be beneficial for improving cognitive dysfunction by increasing hippocampal neurogenesis [37]. In a rat experiment, low-dose buspirone was shown to selectively stimulate 5-HT1A receptors on the dendrites of neurons in the midbrain, leading to reduced serotonin

metabolism in the striatum and release of dopaminergic neurons, improving the performance of rats in the water maze test and enhancing their learning and memory abilities [38]. The above evidence suggests that 5-HT1A receptors may be a potential target for the treatment of cognitive impairments.

Buspirone is a 5-HT1A receptor agonist and one of the most widely used anti-anxiety drugs in clinical practice. As early as 1982, Unrug et al. postulated the cognitive advantages of buspirone. Their research showed that compared with diazepam, buspirone could significantly decrease the score of the cognitive factor [39]. A previous study showed that as a 5-HT1A receptor agonist, buspirone can improve cognition by activating 5-HT1A receptors, increasing extracellular dopamine levels in the prefrontal cortex [40]. At the same time, buspirone can also enhance MK-801-induced cognitive deficits in mice by antagonizing dopamine D3 receptors (D3Rs) [41].

Based on the above evidence (Supplementary F. 1), buspirone may be a promising candidate drug for cognitive therapy. However, thus far, no studies have explored the benefits and overall effects of buspirone on different cognitive domains, as well as its potential side effects. Therefore, we conducted a systematic review and meta-analysis to comprehensively study the side effects of buspirone and the cognitive benefits in different cognitive domains.

2. Methods and materials

2.1. Search strategy and selection criteria

Databases including PubMed, EMBASE, Web of Science, Cochrane Library Review, and Cochrane Library Trial were searched from their inception to April 2023, with a language limitation to English. Two independent researchers reviewed and selected manuscripts based on the inclusion criteria that the title, abstract, keywords, and methods included the terms “Buspirone” and “Randomized” and (“side effect” or “Cognition”). We also conducted a search on ClinicalTrails.gov using the following strategies: “Buspirone” and “Random”.

Studies were included if they were (1) studies published as original articles, (2) randomized, placebo-controlled studies on buspirone treatment, (3) participants aged 18 years or older, and (4) studies providing sufficient information to calculate effect size (ES) statistics. Studies were excluded if they were (1) incomplete trials, (2) not randomized, placebo-controlled studies, and (3) studies that did not have relevant outcomes (including side effects and cognitive tasks).

2.2. Outcome assessment and data extraction

In this study, the primary outcomes were the rates of different treatment-emergent side effects (different adverse events including headaches, dizziness, nausea, insomnia, dry mouth, constipation, diarrhea, drowsiness, fatigue, vertigo, tremor, gastric distress, and sweating), as well as the performance of different cognitive tasks. Previous studies have grouped cognitive results into domains such as attention, visual learning and memory, logical reasoning, psychomotor speed, working memory, general learning ability, executive function, verbal function, and processing speed [36,42] (Supplementary Tab 1). The secondary outcome measures were the acceptability of buspirone in different diseases and dropout rates due to adverse events (AE).

Yue Du and Qing Li extracted the following data from each study: (1) published year; (2) treatment modality (monotherapy or adjunctive treatment) and mean dosage per day; (3) treatment duration; (4) age and gender of participants; (5) number of participants; and (6) number of dropouts. To retrieve relevant studies, Min Wang, Yikai Dou and Yushun Yan imported all retrieved studies into Endnote and removed duplicate studies. Then, Yue Du and Qing Li independently screened the titles and abstracts of each article and reviewed the full text based on our inclusion and exclusion criteria. In case of disagreement (such as the inclusion of study types and evaluation of bias), Xiaohong Ma and Xiao Yang jointly reviewed and made the final decision. Huanhuan Fan and Yu Wang recorded study information, including author name, publication date, sample sizes, and patient characteristics such as diagnose.

2.3. Data analysis

We calculated ORs and the corresponding 95% (CI) for side effects, acceptability, and dropout rate due to AE. Additionally, hedges' g test was utilized to calculate the effect size (ES) of the average cognitive change between two treatment groups. If multiple cognitive tasks are classified into the same domain, the composite ES of these tasks will be used to evaluate changes in cognitive function. Heterogeneity was quantified using I^2 statistics and p values [43]. The Cochrane Risk of Bias (RoB 2) tool, version 2 [44], was used to assess bias in the included trials, with 0–40% heterogeneity values being considered non-significant, 30–60% indicating moderate heterogeneity, 50–90% indicating substantial heterogeneity, and 75–100% indicating significant heterogeneity [45]. RoB 2 has five domains for evaluating bias, including randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Sensitivity analyses were conducted by excluding (1) studies with a high risk of bias, (2) studies with a small sample size (randomized patient number <30) for the two main outcomes, and (3) studies with different diagnoses. Meta-regression was performed to adjust for the effects of publication year and treatment duration. Egger's test was used to investigate publication bias. Analyses were conducted using R 4.2.3 or STATA 17.

This study is registered with PROSPERO, number CRD42023481212.

3. Results

3.1. Characteristics of the included studies

A total of 3916 relevant studies were initially searched, of which 94 trials potentially met the inclusion criteria and were independently screened by two reviewers based on their titles and abstracts. Sixteen randomized clinical trials were selected for qualitative synthesis and data analysis according to the inclusion criteria. The entire literature search process is illustrated in Fig. 1, and the characteristics of the included trials are summarized in Supplementary Table 2. Among the included studies, four (25%) reported 9 different cognitive domains, and 13 (81%) reported side effects. Participants in 4 studies were diagnosed with major depressive disorder, participants in 5 studies were diagnosed with schizophrenia, participants in another 4 studies were diagnosed with generalized anxiety disorder, participants in one study were diagnosed with Parkinson's disease, participants in one study were diagnosed with marijuana dependence, and participants in one study were diagnosed with functional dyspepsia. The included studies were published from 1987 to 2021, and a total of 1061 participants were included in those studies. The treatment duration ranged from 4 weeks to 24 weeks.

3.2. Risk of bias

Of all the studies, two trials (12.5%) showed a high risk of bias due to the lack of information used to estimate the effect of assignment to intervention, while one trial (6.3%) might have a high risk of bias due to the lack of information related to missing samples. Additionally, eleven trials (68.8%) indicated some concerns, and 3 trials (18.8%) had a low risk of bias. The summary assessments of the risk of bias are shown in Supplementary Fig. 2.

3.3. Side effects (adverse events)

Thirteen different adverse events reported across 13 studies were analyzed to investigate the side effects of buspirone. A summary of these findings is presented in Fig. 2 and Supplementary Fig. 3. Ten studies showed a significantly higher rate of dizziness than placebo (OR = 4.66, 95% CI: 2.07–10.47, $I^2 = 22\%$, p = 0.24), four studies showed a significantly higher rate of constipation than placebo (OR = 4.11, 95% CI: 1.34–12.55, $I^2 = 0\%$, p = 0.87), and four studies showed a significantly higher rate of gastric distress than placebo (OR = 1.97, 95% CI: 1.03–3.78, $I^2 = 0\%$, p = 0.78). Other side effects, including headaches, nausea, insomnia, dry mouth, diarrhea, drowsiness, fatigue, vertigo, tremor, and sweating, did not show any difference between buspirone and placebo.

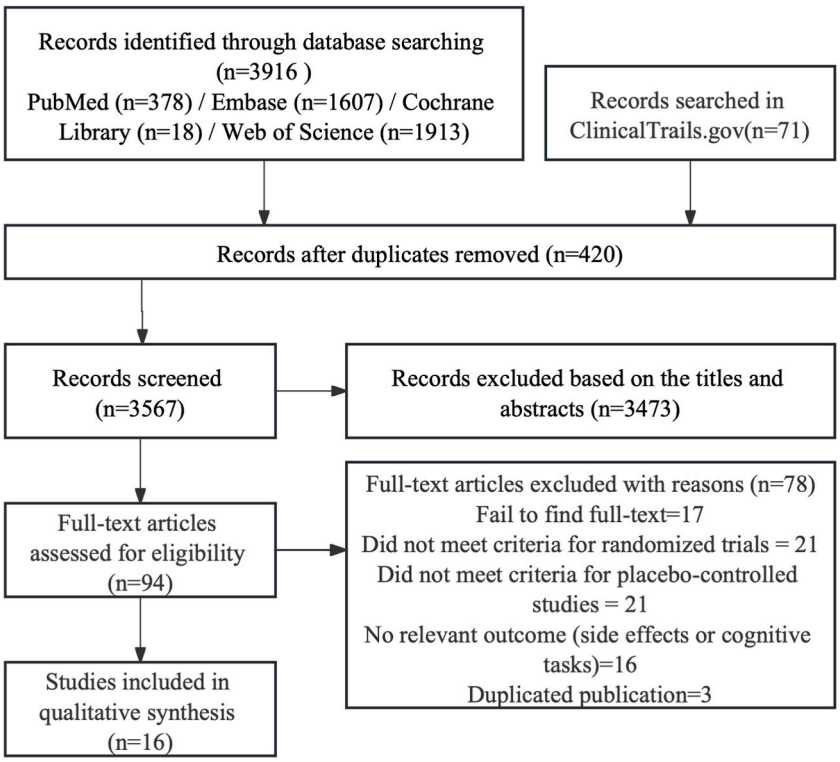

Fig. 1. Literature search and selection.

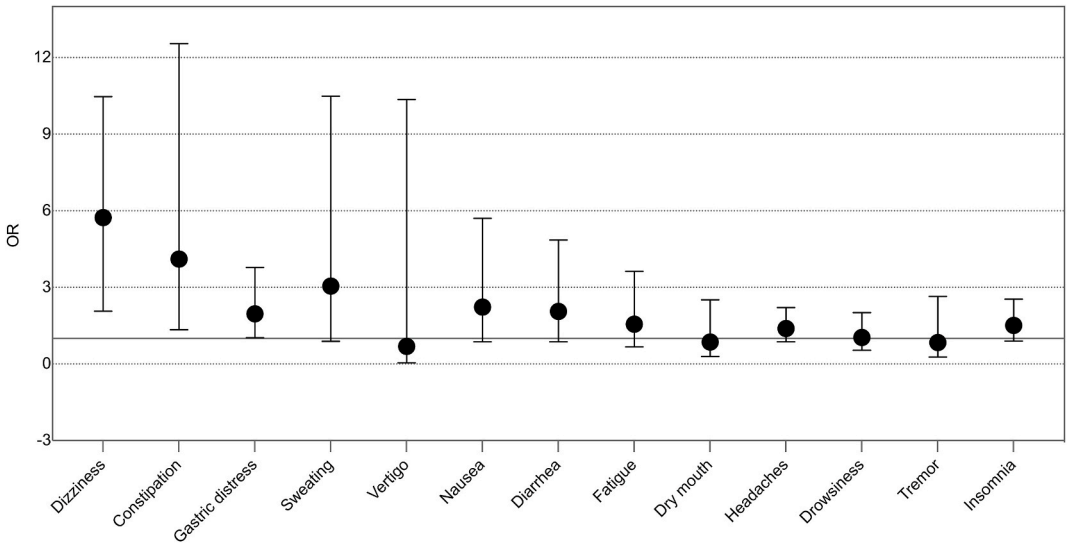

Fig. 2. Side effects of buspirone. The black spots represent the effect sizes calculated by Hedges' test; 95% confidence intervals are depicted for different cognitive domains.

3.4. Neurocognition

Our analysis encompassed four studies that explored the cognitive benefits of buspirone, utilizing a random-effects model to study cognition. The results revealed a significant improvement in cognitive function among participants who received buspirone treatment, with insignificant heterogeneity observed among the included studies ($g = 0.20$, 95% CI: 0.06–0.34, $I^2 = 33\%$, $p = 0.08$), as detailed in Fig. 3 and Supplementary Fig. 4. Subgroup analysis indicated that the buspirone treatment group exhibited significantly greater improvement in visual learning and memory ($g = 0.49$, 95% CI: 0.21–0.78) and logical reasoning ($g = 0.42$, 95% CI: 0.14–0.71) than the placebo group. However, only one study was included in each of these cognitive domains. Participants in the buspirone treatment group also demonstrated significant improvement in attention ($g = 0.37$, 95% CI: 0.13–0.61, $I^2 = 0\%$, $p = 0.40$). No significant cognitive improvement was observed in the other six cognitive domains.

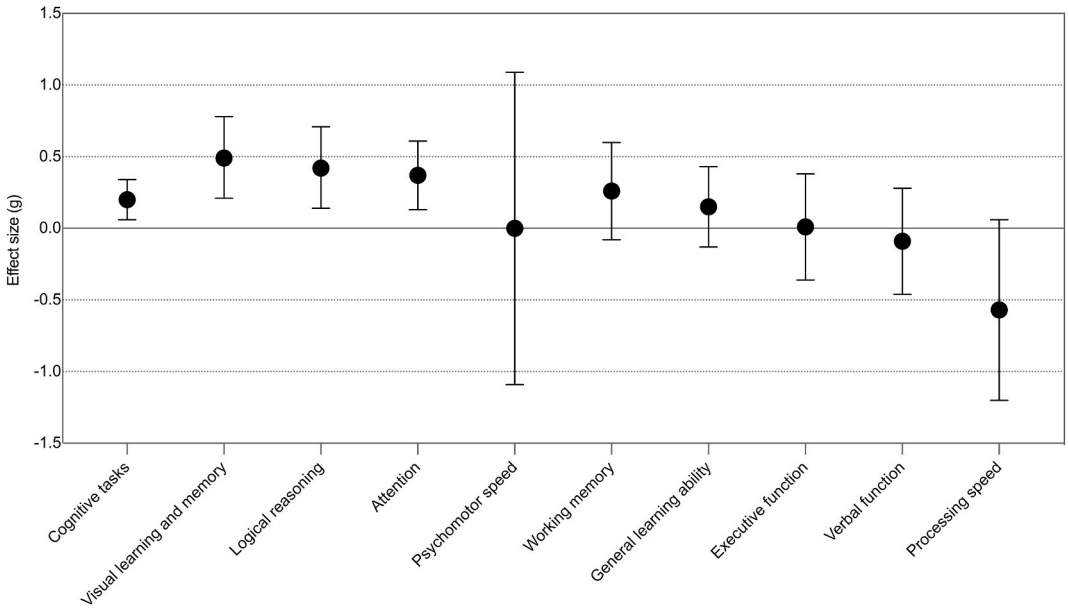

Fig. 3. Cognitive benefits of Buspirone.
The black spots represent the effect sizes calculated by Hedges' test; 95% confidence intervals are depicted for different cognitive domains.

3.5. Acceptability

Of the included trials, fourteen demonstrated the acceptability of buspirone. As shown in Supplementary Fig. 5, acceptability did not differ significantly between buspirone and placebo (OR = 1.11, 95% CI: 0.75–1.64). No heterogeneity was found among the trials (Chi2 = 12.79, df = 12, I^2 = 6%, p = 0.38). In the subgroup analysis, acceptability did not differ significantly between buspirone and placebo in different diseases.

3.6. Dropout rate due to AE

Ten studies reported dropout rates due to adverse events (AE). No significant difference in dropout rates was found between buspirone and placebo (OR = 1.65, 95% CI: 0.77–3.52) (Supplementary F. 6). There was no heterogeneity among the studies (Chi^2 = 4.96, df = 9, p = 0.84, I^2 = 0%). In the subgroup analysis, buspirone and placebo did not differ significantly in the dropout rate due to AE in different diseases.

3.7. Sensitivity analysis, meta-regression, and publication bias

After excluding high-risk studies, no study that reported cognitive benefits was excluded. However, in the side effect studies, buspirone only showed dizziness (OR = 3.27, 95% CI: 1.21–8.88, I^2 = 20%, p = 0.17) as a side effect. After excluding studies with small sample sizes, buspirone still demonstrated cognitive benefits but with high heterogeneity (OR = 0.21, 95% CI: 0.05–0.37, I^2 = 48%, p = 0.03), and the buspirone group showed significant improvement in visual learning and memory (OR = 0.49, 95% CI: 0.21–0.78, p = 0.0006) and logical reasoning (OR = 0.42, 95% CI: 0.14–0.71, p = 0.003) compared to the placebo group (only included one study). In the side effect studies, buspirone showed side effects of dizziness (OR = 4.47, 95% CI: 1.70–11.70, I^2 = 37%, p = 0.13), constipation (OR = 4.79, 95% CI: 1.46–15.64, I^2 = 0%, p = 0.94), gastric distress (OR = 2.01, 95% CI: 1.04–3.91, I^2 = 0%, p = 0.64), and sweating (OR = 3.96, 95% CI: 1.09–14.38, I^2 = 65%, p = 0.06). In a subgroup analysis of studies exclusively involving patients diagnosed with schizophrenia, buspirone showed no significant side effects compared to placebo. Additionally, buspirone displayed a notable improvement in attention when compared to placebo (OR = 0.37, 95% CI: 0.13–0.61, I2 = 0%, p = 0.003). Similarly, in a subgroup analysis limited to studies with patients diagnosed with major depressive disorder, buspirone was reported to cause dizziness, constipation, and gastric distress as side effects, with only two studies reporting these side effects. Furthermore, in a subgroup analysis focusing on studies involving patients diagnosed with generalized anxiety disorder, buspirone did not show any significant side effects when compared to placebo. Meta-regression analysis revealed no significant correlations between cognitive effects and publication year (p = 0.09) or duration of treatment (p = 0.81) or between side effects and publication year (p = 0.95) or duration of treatment (p = 0.99). Egger's test indicated no significant publication bias in cognitive benefits (p = 0.06), side effects (p = 0.83), acceptability (p = 0.96), or dropout rate due to adverse events (p = 0.36). Detailed results are shown in Supplementary F. 7–13.

4. Discussion

We included 16 randomized trials with a total of 1061 participants to investigate the side effects and cognitive benefits of buspirone. We included 13 randomized trials to explore the side effects of buspirone, and 13 different adverse events were reported in these trials. Four studies reported the effect of buspirone on cognitive dysfunction, and a total of 9 different cognitive domains were reported in these studies.

In our study, we found in the buspirone group, patients experienced side effects of dizziness, constipation, and gastric distress, which is consistent with previous studies [13,14]. Gastrointestinal discomfort is a common side effect after treatment with 5-HT receptor agonists. The 5-HT1A receptor is expressed in both the nervous system and gastrointestinal smooth muscle. Activation of the 5-HT1A receptor inhibits the release of acetylcholine after smooth muscle contraction, while buspirone slows gastric emptying by increasing the tone of the lower esophageal sphincter, causing gastric distress and constipation [46,47]. However, in our sensitivity analysis, buspirone did not show a significant increase in constipation and gastric distress compared to placebo, indicating that gastrointestinal discomfort from buspirone may not be as prominent as we previously thought. Our study suggested that buspirone can cause dizziness, which is consistent with previous evidence. Up to 20–80% of patients may experience dizziness after taking buspirone [48]. Previous studies have suggested that this is caused by orthostatic hypotension [49]. However, the mechanism by which 5-HT1A receptor agonists induce dizziness is not yet clear and requires further investigation. However, buspirone has shown the same acceptability and dropout rate due to AE as placebo.

Our research suggested that there were significant cognitive benefits of buspirone compared to placebo. Buspirone can improve patients' visual learning and memory, logical reasoning, and attention. Our results are consistent with previous research findings. A recent meta-analysis showed that buspirone can help improve attention in patients with schizophrenia [50]. As a 5-HT1A receptor agonist, the potential mechanism of the cognitive benefits of buspirone may be related to the activation of 5-HT1A receptors. Previous research has shown that 5-HT1A receptor agonists may improve cognitive function by activating 5-HT1A receptors to increase extracellular dopamine levels in the prefrontal cortex [51]. At the same time, buspirone has strong D3 receptor antagonistic activity, which may enhance memory consolidation by blocking dopamine D3 receptors [52,53]. Other animal experiments have shown that 5-HT1A receptor agonists can improve brain energy metabolism in neonatal rats with NMDA receptor blockade [54] and promote hippocampal neurogenesis in rats [37]. However, a recent meta-analysis on the therapeutic effects of serotonin 1A receptor partial agonists as augmentation therapy for neurocognitive function in patients with schizophrenia revealed no cognitive benefits in verbal

learning, working memory, and executive function [55]. This finding is consistent with the results presented in this article. Therefore, it is important to note that buspirone has therapeutic benefits for only certain cognitive dimensions, rather than all of them. However, the number of trials included in our study was relatively small. More research is needed in the future to explore the effects of buspirone on cognitive dysfunction.

Despite the aforementioned findings, our study has three limitations. Firstly, we did not investigate the effects of varying treatment doses or administration methods (monotherapy or adjunctive therapy) of buspirone on the results. Secondly, there is a scarcity of studies on the cognitive benefits of buspirone, with most of results being derived from the study conducted by Wang et al. [34]. Hence, caution should be exercised when considering the clinical application of these findings. Further research is needed to accurately analyze the effects of buspirone on cognitive impairment caused by different diseases. Thirdly, due to the limited number of trials reporting on adverse events ($n \leq 2$) other than those included in this study, and the exclusion of unpublished data from the search, the potential side effects of buspirone were not comprehensively discussed. Future research is required to conduct a more detailed study on the side effects of buspirone.

5. Conclusion

In this study, participants in the buspirone group experienced side effects such as dizziness, constipation, and gastric distress. Nevertheless, buspirone and placebo did not differ in acceptability or dropout rate due to adverse events. In addition, buspirone showed significantly more cognitive improvement than placebo. Buspirone demonstrated significant benefits in visual learning and memory, logical reasoning, and attention. In sensitivity analysis, buspirone still showed significant cognitive benefits compared to placebo, and buspirone still exhibited the side effect of dizziness.

Funding

None.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Yue Du: Writing – original draft. **Qing Li:** Writing – original draft. **Yikai Dou:** Data curation. **Min Wang:** Data curation. **Yu Wang:** Data curation. **Yushun Yan:** Data curation. **Huanhuan Fan:** Data curation. **Xiao Yang:** Writing – review & editing. **Xiaohong Ma:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28918.

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