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REVIEW

Efficacy and Tolerability of Viloxazine Compared to Placebo on Emotional, Behavioral, and Executive Functioning in Children and Adolescents with ADHD: A Systematic Review and Meta-Analysis

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Introduction: Attention Deficit Hyperactivity Disorder (ADHD) can lead to significant long-term consequences, including emotional and behavioral problems, in addition to difficulties with executive function. While stimulant medications are commonly used to treat ADHD, concerns about the risk of drug abuse have led to interest in non-stimulant options including viloxazine. This study aims to evaluate the effectiveness of viloxazine in improving emotional, behavioral, and executive function in children and adolescents with ADHD, focusing on age-related differences in treatment outcomes, symptom presentation, and medication tolerability to inform tailored approaches to treatment.

Methods: This systematic review assesses the effectiveness of viloxazine in children and adolescents with ADHD. A comprehensive search of electronic databases, including Cochrane Controlled Trials Register, CINAHL, ClinicalTrials.gov, Embase, PubMed, and Scopus, was conducted for randomized controlled trials (RCTs) published by May 4, 2024. Studies were included if they reported mean changes in emotional and behavioral problems and executive function. The review was registered under PROSPERO ID CRD42022302673.

Results: Viloxazine consistently improved emotional, behavioral, and executive function in children with ADHD, with similar but less consistent trends observed in adolescents. Both age groups experienced side effects such as somnolence, decreased appetite, and fatigue, necessitating careful monitoring to enhance tolerability and reduce dropout rates.

Discussion: The limited number of eligible RCTs presents challenges in drawing definitive conclusions. While viloxazine shows the potential to improve ADHD symptoms and executive functioning, its acceptability and tolerability vary between children and adolescents. Further research is essential to explore the long-term safety and efficacy of viloxazine, particularly in adolescents, and to more completely understand the mechanisms of its action. Future studies should also compare viloxazine with other non-stimulant treatments to optimize ADHD management strategies.

Keywords: viloxazine, attention deficit hyperactivity disorder, executive functioning, Conners 3-PS, WFIRS-P

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder affecting from 10.5%-11.4% of children and adolescents.[1] Core symptoms include inattention, impulsivity, and hyperactivity, often leading to

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cognitive and functional impairments such as behavioral and emotional problems. Individuals with ADHD frequently struggle with emotional regulation and executive function, two interconnected cognitive processes. Emotional dysregulation can lead to heightened emotional responses, while executive function deficits hinder planning, decision-making, and impulse control. Additionally, impaired Theory of Mind skills can contribute to social difficulties.[2] These challenges can significantly impact academic performance, social relationships, and overall quality of life. These challenges can persist into adulthood, affecting social interactions, academic and occupational performance, and emotional well-being, highlighting the importance of early intervention and support.

Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with several neurobiological and neuroanatomical factors. Structural abnormalities, such as reduced brain volume in regions including the prefrontal cortex and altered cortical thickness, have been observed. Functional abnormalities include dysregulation of brain networks, decreased activation in the prefrontal cortex, and increased activation in the default mode network. Neurochemical imbalances, particularly as regards dopamine and norepinephrine systems, contribute to the disorder. Genetic and environmental factors also play a role in influencing brain development and function.

Psychostimulants, such as methylphenidate, are commonly used to treat attention deficit hyperactivity disorder (ADHD), especially in children and adolescents. These types of medication act by increasing dopamine and norepinephrine levels in the brain, thereby improving attention and focus. Methylphenidate is a well-established treatment that often leads to significant improvements in academic performance and social functioning. However, its use is associated with several potential risks, particularly adverse effects that may impact treatment adherence. Common side effects include headaches, appetite suppression, tachycardia, hypertension, and sleep disturbances. Additionally, the risk of misuse, —especially among adolescents and young adults, —highlights the importance of careful patient selection and ongoing monitoring to reduce the potential for abuse. Long-term therapy with methylphenidate requires regular evaluation to ensure both safety and effectiveness. Monitoring treatment response and the maintenance of vigilance to ensure the recognition of side effects are crucial. Among the risks, proarrhythmogenic effects,[3] such as increased heart rate and blood pressure, are particularly concerning and may not be adequately addressed by standard protocols. As a result, routine cardiac monitoring should be an integral part of the management plan for children receiving methylphenidate, ensuring comprehensive oversight of safe use.

Non-stimulants such as atomoxetine, clonidine, and viloxazine offer effective and tolerable alternatives for the treatment of ADHD, with atomoxetine functioning as a selective norepinephrine reuptake inhibitor that increases norepinephrine and the modulation of dopamine levels in the prefrontal cortex, and clonidine acting as an alpha-2 adrenergic agonist to reduce norepinephrine release resulting in calming effects. Viloxazine stands out as a unique medication for treatment of ADHD and depression due to its multifaceted approach. It selectively modulates serotonergic activity by acting as a 5-HT_{2B} receptor antagonist and a 5-HT_{2C} receptor agonist. Additionally, it moderately inhibits norepinephrine reuptake. While not a direct dopamine modulator, viloxazine may indirectly increase dopamine levels in certain brain regions, further contributing to its potential therapeutic benefits for conditions including ADHD.[4]

The potential of viloxazine was highlighted in a comparative study with atomoxetine,[5] the results of which demonstrated that viloxazine offers superior efficacy, and tolerability, and has a faster onset of action. Specifically, significant improvements in ADHD symptoms within two weeks of receiving viloxazine were reported in 86% of patients, compared to only 14% of those on atomoxetine. Furthermore, the more favorable side effect profile of viloxazine resulted in only 4% of patients discontinuing treatment due to adverse events, in contrast to 36% for atomoxetine, where gastrointestinal issues and irritability were the primary concerns. An overwhelming 96% of patients expressed a preference for viloxazine over atomoxetine.

Recent studies have shown the potential of viloxazine in treating ADHD, although they often involve small sample sizes, indicating a need for further research. The conducting of meta-analyses could be beneficial in assessing the efficacy, acceptability, and tolerability of viloxazine in treating emotional and behavioral issues. Although viloxazine shows promise, particularly in the case of patients with comorbid emotional disorders due to its dual action, atomoxetine remains the more established treatment with a strong evidence base supporting its efficacy and safety, necessitating additional research to fully understand the comparative advantages of viloxazine in ADHD treatment.

The highlighting of gaps in the evidence, particularly regarding differences in efficacy by age in the context of ADHD treatment, is crucial. The presentation and impact of ADHD symptoms vary across developmental stages, with younger children often exhibiting more hyperactive and impulsive behaviors. At the same time, adolescents may struggle more with inattention and emotional regulation. Understanding how treatment efficacy varies with age can help tailor interventions more effectively. Longitudinal studies tracking the efficacy of ADHD treatments over time, particularly as children transition into adolescence and adulthood, are needed to provide insights into potentially changing treatment needs and long-term outcomes. Comparative effectiveness research directly comparing the efficacy of treatments across different age groups can provide a clearer picture of what works best for whom. This meta-analysis aims to evaluate the efficacy of viloxazine in improving emotional, behavioral, and executive functioning in children and adolescents with ADHD. The analysis will also highlight gaps in the current evidence, particularly regarding differences in treatment efficacy by age.

Methods

Protocol and Registration

The systematic review process was registered under the PROSPERO ID CRD42022302673. Guidelines outlined in the PRISMA 2020 Checklist were followed throughout. The assignments given to NM and BM, the two authors of this review, were carried out independently.

Eligibility Criteria

The inclusion criteria for the randomized controlled trials (RCTs) were: i) Conducted in children or adolescents diagnosed with ADHD, ii) Utilized (SPN-812) as a treatment for ADHD, iii) Reported either the mean change or endpoint scores on standardized rating scales for emotional and behavioral problems, and executive function, or documented dropouts following treatment administration.

Information Sources

The systematic search was conducted across several databases, including Cochrane Library/Cochrane Controlled Trials Register (CCTR), Cumulated Index to Nursing and Allied Health Literature (CINAHL), ClinicalTrials.gov, Excerpta Medica Database (Embase), Public/Publisher MEDLINE (PubMed), and Scopus. The search encompassed studies from their inception up to May 4, 2024, with no language restrictions applied. Reference lists of relevant studies were also manually searched to identify additional pertinent literature.

Search

The typical search terms including (Attention-deficit hyperactivity disorder) AND [(viloxazine) OR (SPN-812) OR (QELBREE)] were applied in all databases. However, the specific strategic searches for each database were as follows:

Cochrane Library: [(Attention-deficit hyperactivity disorder) OR (ADHD) OR (Hyperkinetic disorder)] AND [(viloxazine) OR (SPN-812) OR (QELBREE)]: Filter: Trial

CINAHL: [(Attention-deficit hyperactivity disorder) OR (ADHD) OR (Hyperkinetic disorder)] AND [(viloxazine) OR (SPN-812) OR (QELBREE)]

ClincalTrials.gov: [(Attention-deficit hyperactivity disorder) OR (ADHD) OR (Hyperkinetic disorder)] AND [(viloxazine) OR (SPN-812) OR (QELBREE)]

Embase: [(Attention-deficit hyperactivity disorder) OR (ADHD) OR (Hyperkinetic disorder)] AND [(viloxazine) OR (SPN-812) OR (QELBREE)]: Filter: Randomized controlled trial

PubMed: [(Attention-deficit hyperactivity disorder) OR (ADHD) OR (Hyperkinetic disorder)] AND [(viloxazine) OR (SPN-812) OR (QELBREE)]

Scopus: [(Attention-deficit hyperactivity disorder) OR (ADHD) OR (Hyperkinetic disorder)] AND [(viloxazine) OR (SPN-812) OR (QELBREE)]: Filter: Randomized controlled trial

Study Selection

After the gathering of citations from the specified databases, duplicate records were promptly eliminated. Subsequently, both reviewers (NM and BM) independently evaluated the abstracts and titles of these citations. Following this step, utilizing the full-text versions as references, the reviewers individually selected relevant citations for incorporation into the systematic review. Any discrepancies between reviewers were resolved through consensus.

Data Collection Process

Two reviewers separately extracted the outcomes of interest from included RCTs based on the extraction form. If disputed, a conclusion was reached by the consensus of two reviewers.

Data Items

The data collected included: i) outcomes in alignment with the eligibility criteria, ii) first author and year of publication, iii) study duration, iv) characteristics of subjects, v) viloxazine and its dosage, vi) placebo details, vii) mean change scores from standardized rating scales for each treatment, and viii) response rates and dropout rates for each treatment.

Risk of Bias Within Individual Trials

Two authors (NM and BM) individually assessed the risk of bias in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. The risk of potential bias included the random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcomes assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and any other identified bias.[6]

Summary Measures

In this systematic review, we included assessments of efficacy, acceptability, and tolerability. The efficacy of outcome was primarily evaluated by the difference in means of the pooled mean change scores from standardized rating scales for emotions, behavior, and executive function. In addition to these specific aspects, we also focused on the difference in means of the pooled mean change scores from global assessments of overall treatment outcomes. As indicated in previous systematic reviews, acceptability was estimated by the relative risk (RR) of the overall discontinuation rate,[7] while tolerability was determined by the RR of the rate of discontinuation due to adverse events.[8]

Synthesis of Results

The pooled mean change or endpoint with 95% confidence intervals (CIs) was calculated by using an inverse variance weighing the effect of each RCT.[9] However, the application either weighted mean differences (WMDs) or standardized mean differences (SMDs) relying on the same or different measured rating scales for the included RCTs. Additionally, the RRs estimated the dichotomous outcomes with a 95% confidence interval (95% CI). The Mantel-Haenszel method was applied in the case of all RRs (95% CI).[6] The use of either a fixed or random-effect model for synthesis those outcomes relied on the homogeneity of the included RCTs. In the case of heterogeneity being illustrated in 50% or more, a random effect model was applied. Forest plots are used to display the results from individual studies and pooled analyses. Estimation of the present outcomes was carried out using RevMan 5.4.1.

Risk of Bias Across Studies

If possible, determination of risks of bias for eligible RCTs was carried out by selective reporting within RCTs and publication bias using the Begg's funnel plots test.[6,10] A funnel plot is a simple scatter plot of the intervention effect estimated from each study against a measure of the individual study's size. A symmetrical inverted funnel plot, indicates a lack of bias.[11]

Results

Study Selection

One hundred-seventy-three citations were gathered from the electronic database searches (Cochrane Controlled Trials Register=60, CINAHL=32, ClinicalTrials.gov = 14, Embase=32, PubMed=14, SCOPUS=21). (see Figure 1) Thirty three citations were duplicates, therefore 76 citations were inspected based on their title and abstract. Forty-three citations were collected for the full-text examination, 18 citations were discarded as two were adult ADHD studies,[12,13] eleven were post-hoc analyses,[14–24] two were open-label studies,[25,26] and three were reviews.[27–29] As a result, twenty-five citations of five RCTs were included for qualitative and quantitative synthesis for systemic review and meta-analysis.[30–54]

Study Characteristics

This review included 1619 randomized subjects from five RCTs.[30,31,36–38] The treatment periods in these trials varied from 6 to 8 weeks. In these studies, was compared with placebo for the treatment of ADHD in children and adolescents. The diagnosis of ADHD was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[31] or Fifth Edition (DSM-5).[30,36–38] ADHD symptoms were primarily evaluated using the ADHD Rating Scale (ADHD-RS).

The meta-analysis also observed the use of several standardized rating scales to assess emotional, behavioral, and executive functioning in case of ADHD. Specifically, the Conners 3rd Edition - Parent Short Form (Conners 3-PS), Conners 3rd Edition - Self-Report Short Form (Conners 3-SRS), and Weiss Functional Impairment Rating Scale-Parent Form (WFIRS-P) were employed to evaluate emotional and behavioral problems, as well as executive functioning, in children and adolescents with ADHD. These scales provided comprehensive insights into the impact of ADHD-related

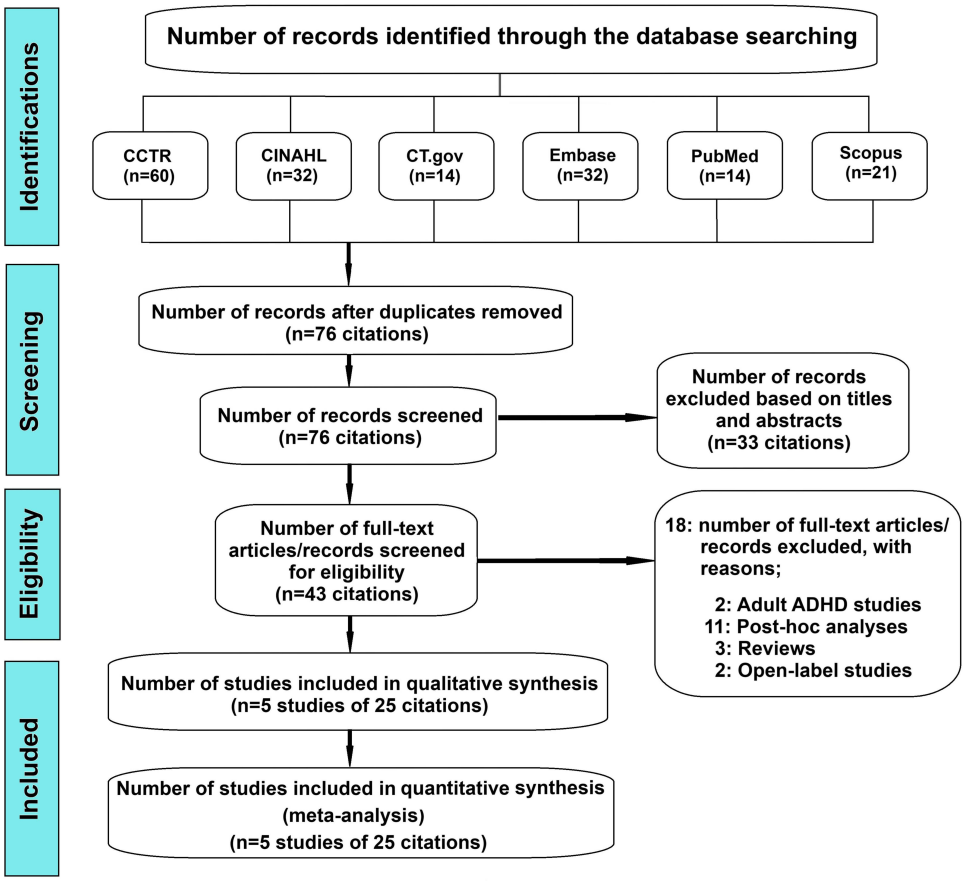

Figure 1 Flow diagram of the study.
Abbreviations: CCTR, Cochrane Controlled Trials Register; CT, Clinical Trials.

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symptoms across various domains of daily life. Additionally, many studies used the CGI-I scale to provide a global assessment of overall treatment outcomes, serving as a subjective, holistic tool that complements the more detailed, standardized rating scales in evaluating treatment efficacy. The characteristic outcomes of included RCTs have been illustrated in Table 1.

Risk of Bias Within Studies

Figure 2 presents the assessment of the risk of bias across different studies, including Johnson 2020,[31] Nasser 2020,[30] and multiple studies authored by Nasser in 2021.[36–38] Each column represents a specific aspect of bias evaluation: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel

Table 1 Characteristics of Randomized Controlled Trials of Viloxazine Versus Placebo in Children and Adolescents With Attention Deficit Hyperactivity Disorder

Study (References)	Number of Randomized Patients	Age of Subjects (years)	Study Duration: (TP+MP) (weeks)	Drug/Dose	Diagnostic Criteria/ DIAGNOSIS	Outcome Measures	Response Criteria
Johnson, 2020[31]	222	6–12	8 (3+5)	-Viloxazine ER/ 100, 200, 300, 400 mg/day - Placebo	DSM-IV	-ADHD-RS-IV -CGI-I -CGI-S	- ≥25% reduction from Baseline in ADHD-RS-IV
Nasser, 2020[30]	477	6–11	6 (1+5)	- Viloxazine ER/ 100, 200 mg/day - Placebo	DSM-5	-ADHD-RS-5 -CGI-I -Conners 3-PS -WFIRS-P	- ≥50% reduction from baseline in ADHD-RS-5 - CGI-I = 1 or 2
Nasser (1), 2021[37]	297	12–17	7 (2+5)	- Viloxazine ER/ 400, 600 mg/day - Placebo	DSM-5	-ADHD-RS-5 -CGI-I -CGI-S -Conners 3-PS -Conners 3-SRS -SIPA -WFIRS-P	≥50% reduction from baseline in ADHD-RS -5
Nasser (2), 2021[38]	313	6–11	8 (3+5)	-Viloxazine ER/ 200, 400 mg/day - Placebo	DSM-5	-ADHD-RS-5 -CGI-I -CGI-S -Conners 3-PS -Conners 3-SRS -PSI-4-SF -WFIRS-P	- ≥50% reduction from baseline in ADHD-RS-5 - CGI-I = 1 or 2
Nasser (3), 2021[36]	310	12–17	6(1+5)	-Viloxazine ER/ 200, 400 mg/day - Placebo	DSM-5	-ADHD-RS-5 -CGI-I -CGI-S -Conners 3-PS -Conners 3-SRS -PSI-4-SF -WFIRS-P	- ≥50% reduction from baseline in ADHD-RS-5 - CGI-I = 1 or 2

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; Conners 3-PS, Conners 3-Parent Short Form; Conners 3-SRS, Conners 3–Self-Report Short Form; ER, extended-release; DSM: Diagnostic and Statistical Manual of mental disorders; MP, Maintenance period; RS, Rating Scale; SIPA, Stress Index for Parents of Adolescents; TP, Titration period; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Form.

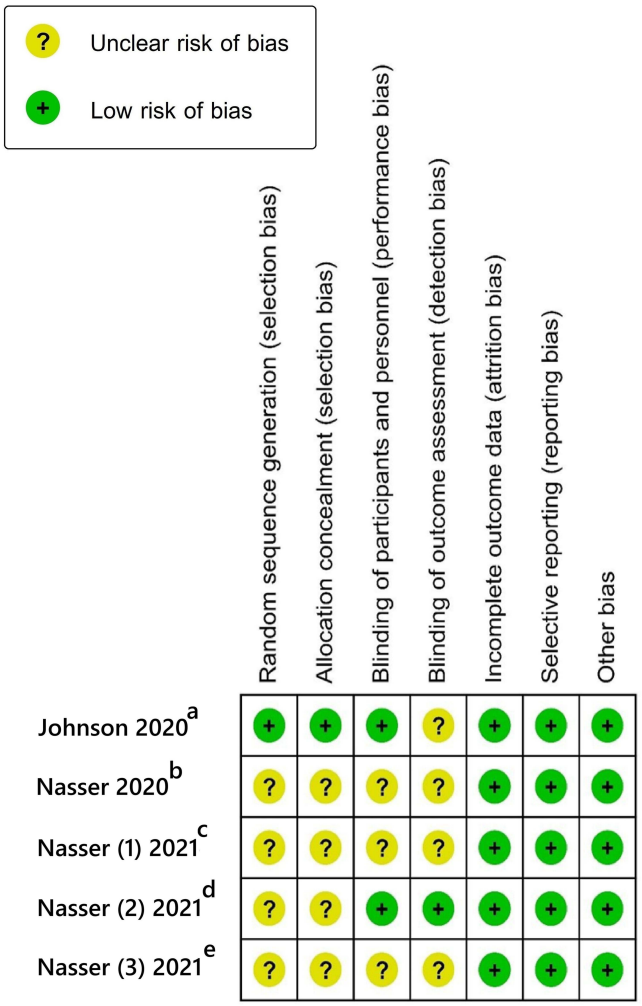

Figure 2 Risk of bias summary in studies of ADHD.

Notes: [a]Johnson JK, Liranso T, Saylor K et al. A Phase II Double-Blind, Placebo-Controlled, Efficacy and Safety Study of SPN-812 (Extended-Release Viloxazine) in Children With ADHD. J Attention Disord 2020;24(2):348–358. doi:10.1177/1087054719836159.[31] [b]Nasser A, Liranso T, Adewole T et al. A Phase III, Randomized, Placebo-controlled Trial to Assess the Efficacy and Safety of Once-daily SPN-812 (Viloxazine Extended-release) in the Treatment of Attention-deficit/Hyperactivity Disorder in School-age Children. Clin Ther. 2020;42(8):1452-1466. doi:10.1016/j.clinthera.2020.05.021.[30] [c]Nasser A, Liranso T, Adewole T, et al. A Phase 3 Placebo-Controlled Trial of Once-Daily 400-mg and 600-mg SPN-812 (Viloxazine Extended-Release) in Adolescents with ADHD. Psychopharmacol Bulletin. 2021;51(2):43–64.[37] [d]Nasser A, Liranso T, Adewole T, et al. Once-Daily SPN-812 200 and 400 mg in the treatment of ADHD in School-aged Children: A Phase III Randomized, Controlled Trial. Clin Ther. 2021;43(4):684–700. doi: 10.1016/j.clinthera.2021.01.027.[38] [e]Nasser A, Liranso T, Adewole T, et al. A Phase 3, Placebo-Controlled Trial of Once-Daily Viloxazine Extended-Release Capsules in Adolescents With Attention-Deficit/Hyperactivity Disorder. J Clin Psychopharmacol. 2021;41(4):370–380. doi: 10.1097/JCP.0000000000001404.[36]

(performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Each cell indicates the associated risk for the specified bias, with "+" signifying a low risk of bias, "?" indicating an unclear risk of bias, and "-" representing a high risk of bias. Overall, all trials demonstrated a low risk of bias in attrition, reporting, and other biases, with intention-to-treat populations utilized for analysis in each trial, ensuring results genuinely reflect initial allocations.

Synthesis of Results

Efficacy

The Conners 3-Parent Short Form (Conners 3-PS)

The Conners 3-PS is a widely used assessment tool that evaluates behavioral functioning, encompassing hyperactivity, impulsivity, and oppositional behaviors, as well as emotional functioning, which includes emotional distress, anxiety,

mood issues, and inattention. While these instruments provide insights into executive functioning through items related to attention and behavior regulation, their primary emphasis focuses on behavioral and emotional symptoms, suggesting the use of additional tools for a comprehensive assessment of executive functioning. The tool assesses multiple domains, including inattention, hyperactivity/impulsivity, learning difficulties, executive functioning, defiance/aggression, and peer relationships. Utilizing a 4-point Likert scale, each item is rated to generate raw scores converted to T-scores, facilitating the determination of symptom severity across diverse areas, thereby assisting clinicians in the pinpointing of areas of concern and the planning of suitable interventions.

Children. The results indicate that there was no significant heterogeneity ($I^2 = 0$) in the pooled mean change for the Conners 3-PS Total score, suggesting that the effects of viloxazine were consistent across studies. Regarding the effectiveness of viloxazine, it was shown to consistently result in beneficial effects in the case of emotional and behavioral problems, as well as executive functioning in children with ADHD, as assessed by the Conners 3-PS. The overall pooled mean change in the Conners 3-PS composite score for children treated with viloxazine was significantly greater than that of the placebo group, with a mean difference of −3.88 (95% CI: −5.12, −2.64). This indicates that children receiving viloxazine had lower scores (better outcomes) compared to those on placebo. In terms of specific areas of improvement, viloxazine significantly reduced scores in several domains, including composite scores, inattention, hyperactivity/impulsivity, learning difficulties, executive functioning, defiance/aggression, and peer relationships (See Table 2 and Figure 3).

Adolescents. The analysis revealed no significant heterogeneity ($I^2 = 0$) in the pooled mean change for the Conners 3-PS Total score, suggesting that the effects of viloxazine were consistent across different studies. Treatment with viloxazine resulted in a significant reduction in ADHD symptoms compared to placebo, as evidenced by the Conners 3-PS Total score. The mean difference for adolescents was −1.69 (95% CI: −3.03, −0.36), indicating that those receiving viloxazine had better outcomes than those on placebo. Additionally, viloxazine was found to significantly reduce scores in specific areas, including inattention, hyperactivity/impulsivity, and executive functioning. The findings support the conclusion that viloxazine is effective in addressing various symptoms of ADHD in adolescents, leading to improved emotional and behavioral

Table 2 Comparative Analysis of Viloxazine vs Placebo on Emotional, Behavioral Problems, and Executive Function in Children and Adolescents With Attention Deficit Hyperactivity Disorder

Component	Children	I^2	Adolescents	I^2
Conners 3-PS Total score, Mean Difference (95% CI)	−3.88 (−5.12, −2.64) *	0	−1.69 (−3.03, −0.36) *	0
Inattention	−4.18 (−5.78, −2.58) *	0	−2.66 (−4.45, −0.88) *	0
Hyperactivity/Impulsivity	−5.38 (−7.01, −3.74) *	0	−2.78 (−4.72, −0.84) *	0
Learning Difficulties	−2.29 (−3.70, −0.88) *	0	−1.43 (−2.93, 0.08)	0
Executive Functioning	−3.97 (−5.52, −2.43) *	5	−1.60 (−3.18, −0.01) *	0
Defiance/Aggression	−2.37 (−4.11, −0.63) *	0	−0.66 (−2.57, 1.25)	0
Peer Relationships	−4.77 (−6.64, −2.90) *	0	−0.43 (−2.42, 1.57)	0
WFIRS-P Total Score, Mean Difference (95% CI)	−0.13 (−0.18, −0.08) *	0	−0.03 (−0.08, 0.02)	39
Family Life	−0.15 (−0.22, −0.07) *	41	−0.08 (−0.15, −0.01) *	0
School Functioning	−0.22 (−0.30, −0.14) *	0	−0.11 (−0.20, −0.02) *	0
Self-Care/ Daily Living Skills	−0.09 (−0.15, −0.03) *	0	−0.08 (−0.15, −0.01) *	0
Social Activities/ Peer Relations	−0.15 (−0.21, −0.08) *	0	−0.02 (−0.09, 0.05)	0
Engagement in Risky Behaviors	−0.05 (−0.12, −0.02) *	57	−0.06 (−0.10, −0.02) *	0
Self-Esteem	−0.03 (−0.10, 0.04)	0	0.06 (−0.03, 0.15)	0
Clinical Global Impression-Improvement				
Pooled Mean Endpoint Score: MD, (95% CI)	−0.49 (−0.62, −0.36) *	0	−0.51 (−0.67, −0.34) *	0
Pooled Response Rate: RR, (95% CI)	0.76 (0.69, 0.85) *	0	0.70 (0.62, 0.80) *	0

Notes: * Significant differences. A negative mean difference indicates that the viloxazine group had lower scores (ie, better outcomes) than the placebo group. The confidence interval (CI) represents the range within which the true mean difference will likely fall. I^2 is a measure of heterogeneity between studies. In this case, all I^2 values are 0, indicating no significant heterogeneity.

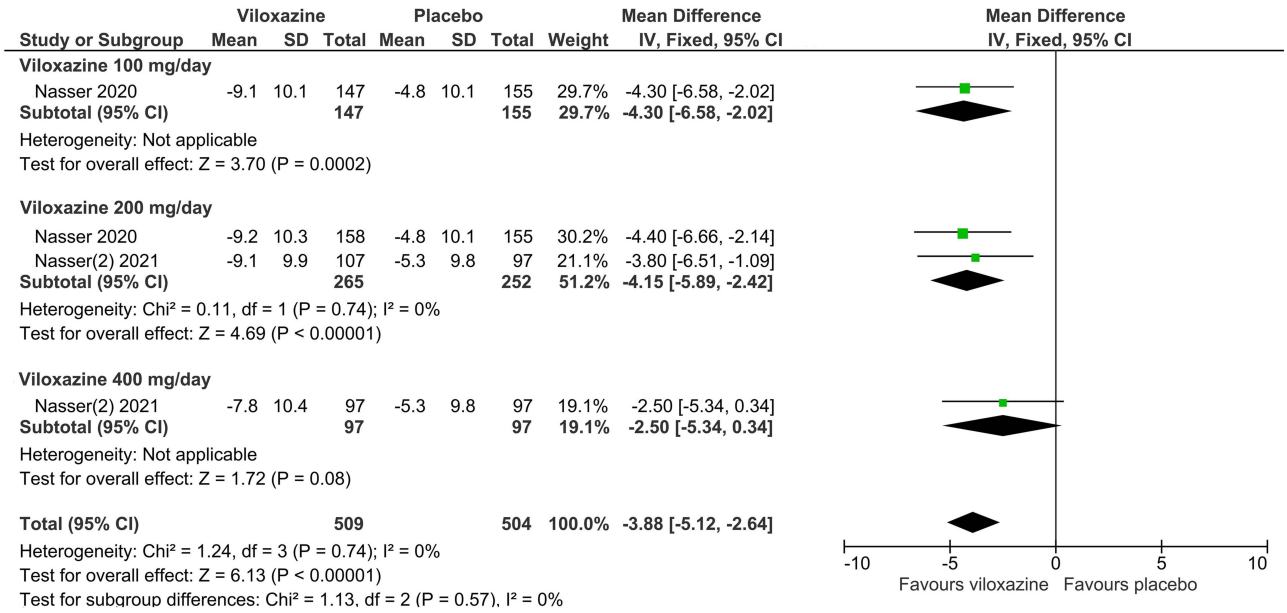

Figure 3 Forest Plot of Pooled Mean Change of vs Placebo on Conners' 3-Parent Short Form in Children with ADHD.

functioning. These results indicate that viloxazine is a beneficial treatment option for adolescents with ADHD, showing significant improvements in multiple domains of ADHD symptoms compared to placebo (See Table 2 and Figure 4).

Weiss Functional Impairment Rating Scale—Parent (WFIRS-P)

The WFIRS-P (Weiss Functional Impairment Rating Scale—Parent) is a tool used to assess the functional impairment experienced by children and adolescents with ADHD across various domains of daily life. Completed by a parent or caregiver, it covers areas such as family life, school functioning, self-care and daily living skills, social activities/ peer relations, engagement in risky behaviors, and self-esteem. Utilizing a Likert-type rating system, higher scores indicate

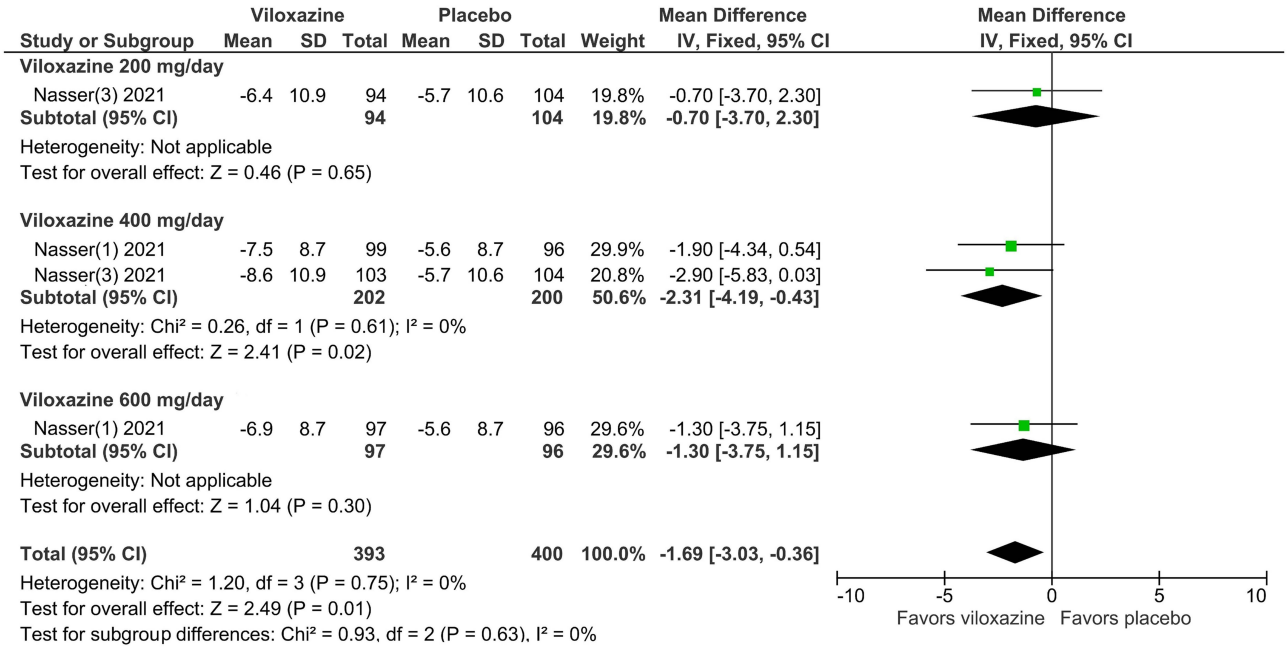

Figure 4 Forest Plot of Pooled Mean Change of vs Placebo on Conners' 3-Parent Short Form in Adolescents with ADHD.

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greater impairment, providing a holistic view of the child's emotional, behavioral, and executive functioning difficulties from the parent's perspective.

Children. The main findings regarding the effectiveness of viloxazine compared to placebo in children with ADHD, specifically using the WFIRS-P Total Score and its related areas of improvement, are that the mean difference for the WFIRS-P Total Score was −0.13 (95% CI: −0.18, −0.08), indicating that children receiving viloxazine had significantly better outcomes in comparison to those on placebo. Regarding specific areas of improvement, the findings indicate that viloxazine is effective in enhancing various aspects of functioning in children with ADHD, including family life, school functioning, self-care/daily living skills, social activities/peer relations, and engagement in risky behaviors compared to placebo. The analysis indicated no significant heterogeneity ($I^2 = 0$) in: school functioning, self-care/daily living skills, social activities/peer relations, and self-esteem, suggesting that the effects of viloxazine were consistent across different studies. However, the analysis indicated moderate heterogeneity for the area of family life, and engagement in risky behaviors with an I^2 value of 41 and 57, suggesting that the effects of viloxazine on family life and engagement in risky behaviors varied across different studies. These results suggest viloxazine is a beneficial treatment option for enhancing overall functioning and well-being in children with ADHD (see Table 2).

Adolescents. The mean difference for the WFIRS-P Total Score in adolescents was −0.03 (95% CI: −0.08, 0.02). This indicates no significant difference in overall outcomes between adolescents receiving viloxazine and those on placebo, as the confidence interval includes zero.

Clinical Global Impression—Improvement

The Clinical Global Impression-Improvement (CGI-I) scale is a 7-point assessment tool used in mental healthcare. It measures the extent to which a patient's mental health condition has changed compared to their initial state. A significantly lower CGI-I score generally indicates substantial improvement. The CGI-I scale can be a valuable tool for evaluating the effectiveness of viloxazine in treating ADHD in children and adolescents when used alongside other measures. It helps clinicians understand how well the medication is working and its impact on the child's overall functioning.

Children. Analysis of the pooled mean endpoint CGI-I scores, and response measures revealed no significant heterogeneity. This suggests that the results are reliable, even when considering variations across different studies. The viloxazine-treated group demonstrated significantly lower CGI-I scores and higher response rates in comparison to the placebo group (See Table 2).

Adolescents. Similar to children, adolescent participants showed no significant heterogeneity in the CGI-I scores or response measures. This indicates that the findings are consistent across studies and groups. The viloxazine-treated group had significantly lower CGI-I scores and higher response rates than the placebo group (See Table 2).

The findings from the Conners 3-PS Total score and WFIRS-P assessments revealed consistent improvements following treatment with viloxazine across most Conners 3-PS subscales in children. In contrast, the WFIRS-P total score in adolescents did not significantly differ from the placebo group, suggesting that viloxazine may have a less pronounced effect on emotional and behavioral problems in this age group. Viloxazine effectively reduced inattention, hyperactivity/impulsivity, and executive dysfunction in both children and adolescents. However, its impact on the WFIRS-P total score in adolescents indicates a need for further investigation into its efficacy in this demographic.

With regarding to the Clinical Global Impression (CGI), both children and adolescents treated with viloxazine demonstrated significant improvements in their overall clinical status compared to those receiving a placebo. However, children showed more pronounced improvements regarding overall emotional and behavioral problems, as measured by testing with Conners 3-PS and WFIRS-P, compared to adolescents. This discrepancy suggests that while viloxazine is beneficial for the management of ADHD symptoms in both age groups, children may experience greater overall clinical benefits than adolescents. Further research is warranted to explore the reasons behind this difference and to optimize treatment strategies for adolescents.

Discontinuation Rates

Overall Discontinuation Rate (Acceptability)

The pooled overall discontinuation rate did not exhibit significant heterogeneity, indicating consistent findings across the studies. For children, the pooled overall discontinuation rate between the viloxazine-treated and placebo-treated groups was not significantly different, with a relative risk (RR) of 1.26 (95% CI: 0.99, 1.60) and $I^2 = 25\%$. In contrast, the pooled overall discontinuation rate for adolescents treated with viloxazine was significantly higher than that of the placebo group, with an RR of 1.58 (95% CI: 1.09, 2.29) and $I^2 = 10\%$. Using the pooled overall discontinuation rate as an indicator of treatment acceptability, the meta-analysis provides valuable insights into the acceptability of viloxazine treatment across different age groups. The findings suggest that overall discontinuation rates remained consistent across studies, indicating a favorable indication of treatment effectiveness and acceptability among the studied population. However, notable differences in acceptability emerge when examining specific age groups. Among children, there was no significant difference in discontinuation rates between those treated with viloxazine and those receiving a placebo, suggesting that viloxazine is generally acceptable in this age group, similar to placebo treatment. In contrast, adolescents treated with viloxazine exhibited a higher rate of discontinuation compared to those receiving a placebo. This finding suggests that adolescents may perceive viloxazine as being less acceptable, potentially leading to a higher likelihood of treatment cessation.

Discontinuation Rate Due to Adverse Events (Tolerability)

There was no significant heterogeneity in the pooled discontinuation rates due to adverse events, indicating consistent results across the studies. In children, the pooled discontinuation rate due to adverse events was significantly higher in the viloxazine-treated group compared to the placebo-treated group, with a relative risk (RR) of 2.02 (95% CI: 1.03, 3.95) and $I^2 = 0$. This suggests that children receiving viloxazine were over twice as likely to discontinue treatment due to adverse events compared to those receiving a placebo. The I^2 value of 0 further confirms the absence of heterogeneity across studies, indicating a consistent finding. Similarly, in adolescents, the discontinuation rate due to adverse events was also significantly higher in the viloxazine-treated group compared to the placebo group, with a relative risk (RR) of 5.26 (95% CI: 1.55, 17.87) and $I^2 = 0$. This indicates a substantially higher likelihood of discontinuation in adolescents receiving viloxazine compared to those on placebo. Again, the I^2 value of 0 suggests no heterogeneity across studies, reinforcing the consistency of this finding.

Adverse Events

In children with ADHD, the pooled rates of common adverse events (occurring in ≥5%) in the viloxazine-treated group were significantly greater than those in the placebo-treated group. The relative risks (RR) with 95% confidence intervals (CIs) for these events were as follows: somnolence (RR = 6.69, 95% CI: 3.85, 11.63, $I^2 = 0\%$), decreased appetite (RR = 4.66, 95% CI: 1.64, 13.25, $I^2 = 50\%$), headache (RR = 2.46, 95% CI: 1.49, 4.07, $I^2 = 0\%$), fatigue (RR = 2.13, 95% CI: 1.10, 4.14, $I^2 = 0\%$), and upper abdominal pain (RR = 5.10, 95% CI: 2.07, 12.55, $I^2 = 0\%$).

In adolescents with ADHD, the pooled rates of common adverse events (occurring in ≥5%) in the viloxazine-treated group were also significantly greater than those in the placebo group. The relative risks (RR) with 95% confidence intervals (CIs) for these events were: somnolence (RR = 2.64, 95% CI: 1.65, 4.24, $I^2 = 21\%$), decreased appetite (RR = 5.34, 95% CI: 2.08, 13.71, $I^2 = 0\%$), fatigue (RR = 3.06, 95% CI: 1.52, 6.12, $I^2 = 0\%$), and nausea (RR = 2.70, 95% CI: 1.32, 5.51, $I^2 = 0\%$). However, the pooled rate of headache was comparable between the two treatment groups, with an RR of 1.51 (95% CI: 0.94, 2.42, $I^2 = 0\%$).

Risk of Bias Across Studies

This systematic review effectively employed the Cochrane Risk of Bias tool to assess the risk of bias across the five randomized controlled trials (RCTs) included in the analysis. The results indicated that most studies had a low or unclear risk of bias, with none showing a high risk. This finding enhances the reliability of the results and supports the credibility of the conclusions regarding viloxazine's efficacy in treating ADHD. Figure 2 provides a detailed visual representation of the risk assessment across various domains, including selection bias, performance bias, detection bias, attrition bias, and

reporting bias. This thorough evaluation ensures that the findings of the systematic review are grounded in robust and methodologically sound evidence, reinforcing the overall conclusions about viloxazine's therapeutic potential in children and adolescents with ADHD. The low risk of bias across the included studies strengthens the argument for viloxazine as a viable treatment option, particularly for patients who may not respond well to traditional stimulant medications. Future research must continue monitoring and assessing the risk of bias in studies evaluating ADHD treatments to maintain the integrity and applicability of the findings in clinical practice. Additionally, due to the inclusion of fewer than ten RCTs in this systematic review, a funnel plot assessment for publication bias was not performed, as it was deemed to have insufficient power to detect real asymmetry. Instead, the review focused on evaluating selective reporting within individual studies. All five RCTs included were found to have a low risk of selective reporting bias, suggesting that these studies reported their findings transparently and comprehensively, thereby minimizing the potential for bias in the extrapolated conclusions of the systematic review. This comprehensive approach to assessment of bias not only enhances the validity of the review's findings but also underscores the importance of transparency in clinical research, which is essential for guiding effective treatment strategies for ADHD.

Discussion

The impact of viloxazine, a non-stimulant medication emerging as a potential treatment option for Attention-Deficit /Hyperactivity Disorder (ADHD) was investigated in this study. Emotional, behavioral, and cognitive aspects were examined using established tools: the Conners 3-Parent Short Form, the Weiss Functional Impairment Rating Scale—Parent (WFIRS-P), and the Clinical Global Impressions-Improvement (CGI-I). These scales are highly regarded for the assessment of various dimensions of functioning, particularly in children and adolescents with ADHD. The Conners 3-Parent Short Form evaluated behavioral, emotional, and academic challenges, including inattention, hyperactivity/impulsivity, learning difficulties, executive function, defiance/aggression, and peer relationships, providing critical insights into the effectiveness of viloxazine in improving these areas. Similarly, the WFIRS-P measured functional impairments across multiple life domains, such as family dynamics, school performance, self-care, daily living, social interactions, risk behaviors, and self-esteem, offering a comprehensive assessment of the impact of viloxazine beyond core ADHD symptoms. Additionally, the CGI-I assessed the overall clinical response compared to placebo, measuring treatment-related improvements. In future research, it could be beneficial to include specific tools designed to assess executive functions, such as the Behavior Rating Inventory of Executive Function (BRIEF) or the Delis-Kaplan Executive Function System (D-KEFS). Including data from these tools could provide a more comprehensive evaluation of executive functioning in children and adolescents treated with viloxazine.

This systematic review revealed significant findings regarding efficacy, acceptability, tolerability, adverse events, and risk of bias. Concerning efficacy, viloxazine consistently yielded positive outcomes in the case of emotional and behavioral challenges, as well as executive functioning in children with ADHD, as supported by Conners 3-PS, the WFIRS-P, and CGI-I assessments. Similar trends were observed in adolescents, although not consistently across all domains. Notable enhancements were shown by the WFIRS-P with regard to family life, school performance, self-care, social engagement, and risk behavior for children compared to placebo. However, these enhancements were not consistent in the case of adolescents. The effectiveness of ADHD treatments in adolescents remains uncertain due to various factors, such as neurodevelopmental changes, symptom presentation, comorbid conditions, and methodological limitations. Firstly, the significant neurodevelopmental changes in adolescents, including brain maturation and hormonal fluctuations, can impact their response to medication. Consequently, these changes can lead to variability in treatment outcomes across studies. Moreover, ADHD symptoms can manifest differently in adolescents compared to younger children, further contributing to variability in treatment outcomes. Furthermore, the presence of comorbid conditions, such as anxiety or depression, can further complicate the clinical picture and make it challenging to assess the true efficacy of a treatment like viloxazine. Additionally, methodological limitations, such as small sample sizes or lack of diversity in participant demographics, can limit the generalizability of findings. Variations in study design, including differences in trial duration, dosages, and assessment tools, can also contribute to inconsistent results. Many studies may not follow participants long enough to capture the full range of treatment effects or side effects, particularly in adolescents requiring longer periods to demonstrate stable responses to treatment. Adolescent populations may also

have lower adherence rates to medication regimens, which can significantly impact the overall effectiveness of the intervention. By considering these factors, researchers can better understand the complexities of ADHD treatment outcomes in adolescents and work towards more consistent and reliable findings in future studies.

The findings regarding treatment for ADHD highlight important distinctions in acceptability, tolerability, and side effects between children and adolescents. In children, the overall discontinuation rate (acceptability) for viloxazine was similar to that of the placebo, suggesting that it is generally well-tolerated in this age group. However, adolescents showed a significantly higher discontinuation rate, indicating lower acceptability and potentially greater challenges in treatment adherence. Both age groups experienced increased rates of discontinuation due to adverse events, with adolescents particularly affected by side effects such as nausea and decreased appetite. In children, viloxazine was associated with a notably higher incidence of somnolence—over six times more likely than the placebo group—which could adversely impact their daily activities, including academic performance and social interactions. The concern over decreased appetite is significant, as it can lead to weight loss and nutritional deficiencies, especially in growing children. Other common adverse events included headaches, fatigue, and upper abdominal pain, which may further diminish the quality of life for children with ADHD. In adolescents, while the risk of somnolence was present, it was less pronounced than in children. Nonetheless, it remains a concern, particularly in contexts requiring alertness, such as driving. The side effects of decreased appetite, fatigue, and nausea in adolescents could similarly hinder their growth and overall well-being. Interestingly, the rate of headaches did not significantly differ between viloxazine and placebo groups in adolescents, contrasting with the findings in children where headaches were more prevalent. These findings underscore the necessity for healthcare providers to closely monitor patients for side effects, especially during the initial phases of treatment. Engagement in discussions about managing these effects with patients and their families is crucial. Clinicians should also ensure that patients and caregivers are well-informed about the potential risks associated with viloxazine, facilitating shared decision-making regarding treatment options. Furthermore, the need for additional research is evident to explore the long-term safety and tolerability of viloxazine, as well as the development of strategies to mitigate adverse effects while preserving its therapeutic benefits.

The limited number of RCT's included precluded a formal funnel plot assessment for publication bias. Although this limitation may hinder a definitive assessment of potential publication bias, the low risk of bias across studies, as indicated by the risk of bias assessment, suggests that selective reporting bias is unlikely. The transparency and comprehensiveness of the included studies further mitigate concerns about overestimating the efficacy of viloxazine. However, it is important to acknowledge that the smaller number of studies may limit the generalizability of the findings and increase the risk of Type II errors. Future research should aim to conduct larger, well-designed RCTs to provide more robust evidence base and address potential limitations.

In addressing the variability in treatment effects of viloxazine for ADHD, our analysis utilized the I^2 statistic to quantify heterogeneity among the included studies, revealing low levels of inconsistency ($I^2 = 0\%$) for several outcomes, yet highlighting the need to consider factors such as age, comorbid conditions, and treatment duration that may contribute to this variability. Specifically, younger children demonstrated more significant improvements in emotional and behavioral symptoms compared to adolescents, suggesting that developmental differences play a crucial role in treatment response. Additionally, the presence of comorbid conditions, such as anxiety or learning disabilities, may further complicate outcomes, emphasizing the necessity for clinicians to tailor treatment approaches based on individual patient profiles, including age and specific symptomatology, to optimize therapeutic efficacy and enhance overall treatment outcomes.

The review recognizes several limitations that impact the interpretation of its findings, in particular with regard to the necessity of including a diverse range of studies from various research groups to enhance the comprehensiveness and reduce potential bias in study selection. Notably, all randomized controlled trials (RCTs) were conducted by specific study groups, raising concerns about potential bias and limiting the generalizability of the results. This limitation suggests that the findings may not fully represent the performance of viloxazine across a broader and more diverse patient population or in real-world settings, necessitating a cautious approach to their application. Additionally, the review includes only five RCTs (three in children and two in adolescents), which restricts the robustness of the conclusions regarding the efficacy of viloxazine. Variability in dosage across studies and the short-term nature of the trials (6–8 weeks) further underscore the need for additional research into the long-term safety and efficacy of viloxazine. The inability to assess publication bias through

a funnel plot due to the limited number of eligible RCTs required reliance on selective reporting assessments, which may not capture all biases. Furthermore, while the review emphasizes the importance of medication in the management of core ADHD symptoms, it acknowledges that medication alone is often insufficient. It advocates combining medication with psychosocial interventions, such as social skills training and behavioral therapy, to address the broader emotional, behavioral, and social challenges associated with ADHD. Lastly, incorporation of comparisons with other non-stimulant treatments, like atomoxetine, would provide a more comprehensive view of the treatment landscape and better contextualize the role and effectiveness of viloxazine relative to established alternatives.

To optimize ADHD management, future research should prioritize head-to-head clinical trials comparing non-stimulant treatments to evaluate their efficacy, safety, and tolerability across diverse populations. Longitudinal studies are essential to track long-term outcomes, including treatment sustainability, side effects, adherence, and quality of life. Meta-analyses and systematic reviews can synthesize existing data to clarify the overall treatment landscape. Prioritization of patient-reported outcomes will help capture subjective experiences that significantly influence treatment adherence and satisfaction. The inclusion of diverse populations such as people from different backgrounds, races, ethnicities, ages, and genders in research and investigating the mechanisms of action will enhance the generalizability of findings and provide insights into which patients may benefit most from specific treatments. Early detection and psychoeducation for caregivers and teachers, along with the combined use of psychosocial treatments and medication, are vital. The application of neurostimulation methods, such as repetitive transcranial magnetic stimulation (rTMS) and theta burst stimulation (TBS), can be used in conjunction with medication and psychosocial treatments to enhance their effects by targeting specific brain regions, especially in the case of the frontal lobe.[55] Assessment of clinical features beyond ADHD symptoms, such as quality of life and behavioral, emotional, and executive functions, is crucial for comprehensive management of ADHD and improve patient outcomes.

Conclusions

This systematic review and meta-analysis demonstrate that viloxazine is a viable non-stimulant alternative for the management of ADHD, showing efficacy in enhancing emotional, behavioral, and executive functioning in children and adolescents, particularly in those who may not tolerate stimulants or have comorbid conditions. However, the findings reveal variability in treatment responses, with viloxazine significantly alleviating emotional and behavioral issues in children but showing more limited effectiveness in adolescents, particularly as regards defiance, aggression, and peer relations. These differences underscore the importance of personalized treatment strategies tailored to developmental stages and specific patient needs, which can improve adherence and long-term outcomes. As viloxazine has the potential to fill a critical gap in ADHD management by providing a non-stimulant option, further research is needed to establish its long-term safety and efficacy, particularly in adolescents, and to compare its effectiveness with other non-stimulant treatments such as atomoxetine. Such efforts could refine therapeutic strategies and ensure effective, individualized care for diverse ADHD patient populations.

Data Sharing Statement

Data sharing is not applicable as no datasets were generated and/or analyzed for this study.

Ethical Approval

The requirement for ethical approval was waived in this study because it did not involve any human subjects, and the data retrieved for synthesis was collected from published studies.

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Author Contributions

All authors made a significant contribution to the work reported, either in the conception, study design, execution, acquisition of data, analysis, interpretation, or in all these areas. All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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