

The Efficacy of Fluoxetine in Treating Depression in Children under 13: A Literature Review

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How to cite this paper: M'Cloud, E. and Azar, R. (2026) The Efficacy of Fluoxetine in Treating Depression in Children under 13: A Literature Review. *Open Journal of Medical Psychology*, 15, 43-51.

<https://doi.org/10.4236/ojmp.2026.154004>

Received: July 19, 2026

Accepted: October 12, 2026

Published: October 15, 2026

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Abstract

Introduction: Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is widely used to treat depression and is FDA-approved for major depressive disorder in children aged 8 - 18 years. However, pediatric regulatory status differs by jurisdiction, and evidence regarding its efficacy and safety specifically in children under 13 remains limited. **Objective:** This review examined fluoxetine's effectiveness and safety for treating depression in children under 13. **Methods:** A literature review was conducted using PsycInfo and PubMed, focusing on studies from 2000-2020. Eight articles met predefined inclusion and exclusion criteria, analyzing fluoxetine's impact on pediatric depression. **Results:** Studies used varied methodologies, complicating direct comparisons. However, key findings emerged: fluoxetine showed modest efficacy in reducing depressive symptoms, although evidence specifically for children under 13 remained limited and inconclusive. Evidence from broader pediatric antidepressant studies also identified an increased risk of suicide-related outcomes, emphasizing the importance of careful monitoring. Reported side effects included behavioural activation and mood instability. Data on long-term remission and safety were insufficient for clear treatment guidelines. **Conclusion:** Fluoxetine may offer short-term benefits for pediatric depression, but evidence specific to children under 13 remains limited. Treatment decisions for younger children should follow applicable clinical guidelines and involve careful assessment and monitoring. Further research is necessary to clarify long-term effects and refine treatment strategies for younger children.

Keywords

Fluoxetine, Pediatric Depression, Selective Serotonin Reuptake Inhibitors, Children, Major Depressive Disorder

1. Introduction

Depression in children and adolescents is a growing concern within the realm of pediatric mental health. While it was once considered rare, there is now an increased recognition of the prevalence and impact of depression in youth. With estimates suggesting that up to 15% of children may experience depressive symptoms at any given time, the issue has garnered significant attention from both clinicians and researchers [1]. Depression in children presents unique challenges, as it often differs in its manifestation compared to adults, making early diagnosis and effective treatment crucial. Furthermore, untreated pediatric depression can lead to long-lasting consequences, including developmental delays, impaired academic performance, strained family dynamics, and an elevated risk of self-harm or suicidal behaviour [1]. As the understanding of pediatric depression evolves, so does the focus on improving treatment options, ensuring that young patients receive the best care to support their emotional and psychological well-being.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) commonly used as an antidepressant medication. It is used to treat major depressive disorder (MDD) and other psychiatric conditions. For pediatric MDD, regulatory status differs by jurisdiction: the U.S. Food and Drug Administration (FDA) has established efficacy for fluoxetine in patients aged 8 - 18 years, whereas current Canadian PRO-ZAC product information states that fluoxetine is not indicated for patients under 18 years of age [2] [3]. Accordingly, regulatory approval should not be generalized across countries. This review focuses on depression-related efficacy and safety outcomes. Some included publications contained mixed diagnostic samples (e.g., MDD with anxiety or obsessive-compulsive disorder); findings from those samples were included only when they provided fluoxetine-related efficacy or safety information relevant to pediatric depression, and evidence from non-depression diagnoses was not treated as direct evidence of antidepressant efficacy for MDD.

The treatment of pediatric depression has advanced with the use of selective serotonin reuptake inhibitors (SSRIs), including fluoxetine. Evidence and recommendations, however, differ substantially by age and illness severity. The FDA indication for pediatric MDD begins at age 8, but this does not mean that efficacy has been established specifically for the narrower under-13 population examined in this review [2]. Current NICE guidance recommends psychological therapy as initial treatment for mild depression and advises that, after multidisciplinary review, fluoxetine may be offered for moderate-to-severe depression that has not responded to psychological therapy; for children aged 5 - 11 years, fluoxetine should be considered cautiously because effectiveness in this age group is not established [4]. Close monitoring for clinical worsening, suicidality, and other adverse effects remains essential.

Fluoxetine is one of the most widely used and studied SSRIs for treating pediatric depression, especially in cases that are moderate to severe. Its proven efficacy has established it as a primary treatment choice for many healthcare providers. However, its use must be approached with caution due to the risk of suicidality,

particularly in children during the early stages of treatment. As a result, it is essential for healthcare providers to monitor young patients closely and involve family members in the treatment process to mitigate these risks. While fluoxetine has shown positive outcomes in managing depressive symptoms, there remain significant gaps in understanding the full scope of its long-term effects, particularly in relation to the emotional, cognitive, and social development of children.

Given the increasing prevalence of pediatric depression, it is more important than ever to ensure that fluoxetine's benefits are maximized while minimizing its risks. This review focused on the existing evidence surrounding fluoxetine's safety and efficacy in treating pediatric (under 13 years of age) depression. Despite its widespread use, ongoing research is necessary to refine treatment guidelines and better understand the long-term impact of fluoxetine on children's overall well-being. Continued investigation into how fluoxetine influences children at different developmental stages is crucial in optimizing its use and ensuring that it remains a safe and effective option for treating pediatric depression. This review aimed to provide a comprehensive evaluation of fluoxetine's role in pediatric depression treatment, contributing to a deeper understanding of how it can best support young patients in managing their mental health.

2. Methods

We conducted a literature review examining the efficacy and safety of fluoxetine for depression in children, with the target population defined as children younger than 13 years. The review was conducted between September and November 2024. We performed title-and-abstract searches in PsycInfo and PubMed using the following keywords: antidepressants, antidepressant medication, fluoxetine, Prozac, child, children, youth, adolescent, childhood depression, pediatric depression, benefits, advantages, pros, disadvantages, cons, risks, effects, depression, depressive disorder, depressive symptoms, major depressive disorder, and depressed. Inclusion criteria were: a) publication between 2000 and 2020, b) English language, c) inclusion of participants younger than 13 years or presentation of evidence directly relevant to that age group, and d) reporting of fluoxetine-related depression efficacy or safety outcomes. Articles exclusively involving participants aged 13 years or older, grey literature, studies without fluoxetine, and non-human studies were excluded. Mixed child-adolescent samples were eligible when they included children younger than 13, but findings from such studies were identified as mixed-age evidence and were not treated as direct estimates specific to children under 13. Studies with comorbid anxiety or other psychiatric conditions were eligible only when depression-related or fluoxetine safety findings relevant to the review question could be extracted. Eligible publication types included randomized or prospective clinical studies, systematic reviews/meta-analyses, and narrative or clinical reviews that reported at least one relevant outcome, such as depressive symptom change, treatment response/remission, suicidality, behavioural activation, other adverse effects, or clinically relevant monitoring/safety findings. The

prospective biomarker cohort was retained because it evaluated suicidality emerging during fluoxetine treatment, a prespecified safety domain of this review. Following title-and-abstract screening, potentially eligible articles were retrieved and assessed in full text against the inclusion and exclusion criteria. Screening and eligibility assessment were conducted by a single reviewer (E.M.). Eight publications were ultimately retained. The article selection process is illustrated in **Figure 1**. Throughout this review, the terms children, child, and youth refer to individuals younger than 13 years unless otherwise specified.

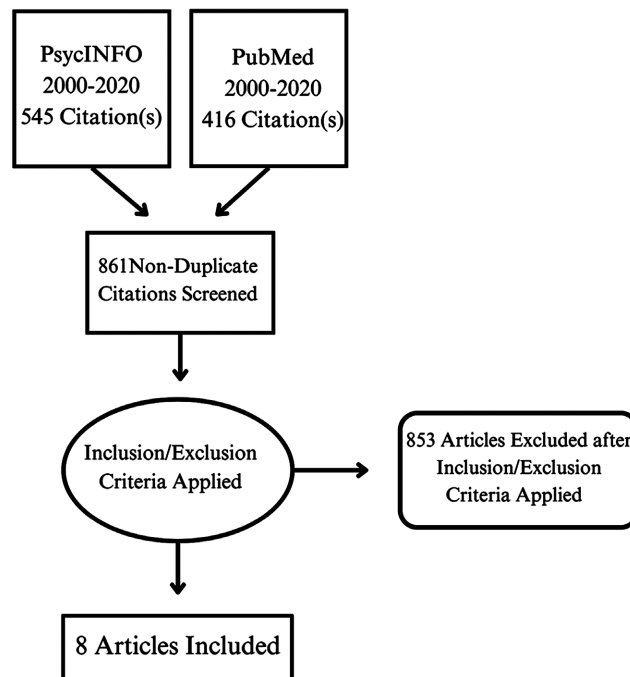


Figure 1. PRISMA flowchart of article selection.

3. Results

The literature review identified several key findings regarding fluoxetine and pediatric depression, but the strength of inference differed by age composition. **Table 1** summarizes the study designs, samples, assessments, key findings, and limitations of the eight included publications. Evidence that included children under 13 was separated conceptually from findings based on mixed samples extending into adolescence. For example, Hetrick *et al.* [8] synthesized 19 randomized controlled trials involving participants aged 6 - 18 years; therefore, its pooled estimates described a broad pediatric population and could not directly establish efficacy or safety specifically in children under 13. By contrast, Bridge *et al.* [11] reported that fluoxetine was among the most effective antidepressant treatments for pediatric MDD and included analyses relevant to younger children, although its overall evidence base also included children and adolescents. Across the included literature, direct age-specific evidence for children under 13 remained limited and inconclusive.

Table 1. Compiled studies analyzing the effects of fluoxetine use in children with depression.

Study	Design	Sample	Assessments	Results	Limitations
Vitiello & Swedo [5]	Review of SSRIs in pediatric depression	Focused on pediatric patients, specifically those diagnosed with major depressive disorder (MDD) and obsessive-compulsive disorder (OCD).	Review mentioned the use of SSRIs in clinical practice and referenced clinical trials on fluoxetine in children with MDD.	Fluoxetine showed response rates of 56% and 65%, higher than placebo (33% and 53%), though one-third of children saw no benefit. No increase in suicidal behaviour was noted, but 10% experienced agitation and manic symptoms, with SSRIs having higher rates of adverse events like mania compared to placebo.	The review highlighted a lack of replication for SSRIs beyond fluoxetine and found no conclusive proof linking fluoxetine (or any SSRI) to suicidal behaviour. It noted potential side effects like agitation, mania, and nervousness, with limited generalizability due to small sample sizes and no long-term safety data.
Amitai <i>et al.</i> [6]	Prospective cohort study	92 children diagnosed with major depressive disorder (MDD) and/or anxiety disorders.	Blood tests for cytokines before and after 8 weeks of fluoxetine. Symptoms and side effects were measured with various clinical scales.	IL-6 levels increased in children who developed suicidality during fluoxetine treatment. TNF α and IL-1 β levels did not change significantly.	Small sample size. The study did not clarify how IL-6 directly contributes to suicidality. The results may not apply to other antidepressants or diverse patient groups.
Du [7]	Review of antidepressant use in childhood depression	Examined various studies on antidepressant use in children and adolescents with depression.	A review of multiple studies on SSRIs (fluoxetine, fluvoxamine, sertraline) and other antidepressants like venlafaxine and duloxetine.	Fluoxetine was effective in treating childhood depression, with effectiveness ranging from 41 to 61% and a remission rate of 23% - 41%. SSRIs like fluvoxamine and sertraline are also effective, though not FDA-approved for depression in children.	The review lacked original clinical data. The use of antidepressants in children is controversial, particularly regarding suicidality risk, and many newer antidepressants have not been adequately tested. Concerns over side effects persist.
Bhatia & Bhatia [1]	Review of childhood and adolescent depression	Reviewed various aspects of depression in children and adolescents, including prevalence, risk factors, and treatments.	A review of epidemiological data, diagnostic criteria, risk factors (biomedical and psychosocial), and treatment options (CBT, antidepressants).	Depressive disorders increased after puberty, especially in girls, and impact growth, development, and relationships. Many children and adolescents remained undiagnosed or untreated. CBT was effective for mild to moderate depression, with antidepressants for severe cases.	Data on antidepressants in children was limited. Tricyclics were ineffective and harmful, while SSRIs, including fluoxetine, have limited effectiveness and a suicidality risk. Regular monitoring is essential, but treatment access may be limited.

Continued

Hetrick <i>et al.</i> [8]	Systematic review and meta-analysis	19 randomized controlled trials (RCTs) with 3335 participants aged 6 to 18 years diagnosed with a depressive disorder.	Randomized controlled trials comparing SSRIs with placebo. Depression severity, response/remission rates, suicide-related outcomes, adverse events.	Antidepressants reduced depression severity slightly (MD-3.51) and increased remission rates—but also raised suicide-related risks by 58% and caused more adverse events compared to placebo.	The trials included had high risk of bias, high dropout rates, and varying definitions of outcomes. Many trials excluded high-risk suicide patients or those with co-morbidities, making results less generalizable. The clinical meaningfulness of the findings was uncertain due to small effect sizes.
Dopheide [9]	Review article	General overview of depression in youth, including risk factors, clinical presentation, and treatment options.	Clinical features, treatment options, antidepressants (specifically fluoxetine), cognitive behavioural therapy, and monitoring for adverse outcomes.	Depression in youth was treatable with antidepressants and CBT, with fluoxetine most effective for ages 13+. Close monitoring was essential for suicide and mania risks.	Very little evidence supported the use of antidepressants for children under 13 years old. The article emphasized the need for close monitoring, especially in the early stages of treatment.
Hayes [10]	Review article	Overview of antidepressant therapy in elderly, children, and patients with unstable angina or acute MI.	A focus on SSRIs, venlafaxine, fluoxetine, tricyclic antidepressants, and treatment in special populations.	SSRIs were effective for elderly with MDD, but increased dosage may be needed for remission maintenance. Fluoxetine was the only SSRI approved for children, though its efficacy was limited. SSRIs may benefit patients with depression and comorbid coronary artery disease.	SSRIs (except fluoxetine) posed a risk in children. The benefits of SSRIs in children and adolescents were debated, with concerns about safety. There was limited evidence supporting antidepressant efficacy in younger populations.
Bridge <i>et al.</i> [11]	Meta-analysis	27 randomized, placebo-controlled trials of second-generation antidepressants in children and adolescents with MDD, OCD, or anxiety disorders.	Defined responder status, suicidal ideation/suicide attempts, efficacy outcomes, and risk differences.	Antidepressants were effective for pediatric MDD (11.0%), OCD (19.8%), and non-OCD anxiety disorders (37.1%), with a small increased risk of suicidal ideation (0.7%) but no completed suicides. Fluoxetine was most effective for children under 13 with MDD.	Risk differences for suicidal ideation were small and not statistically significant for each disorder. Variability in efficacy across age, depression duration, and trial design conditions. Potential bias in reporting and variability in study designs.

4. Discussion

This literature review examined fluoxetine for depression with a specific focus on

children under 13 years of age. The findings revealed a substantial age-specific evidence gap. Although the FDA has established fluoxetine efficacy for pediatric MDD beginning at age 8, many studies synthesized here used mixed child-adolescent samples, meaning their results cannot be assumed to apply specifically to children younger than 13 [2]. In Canada, current PROZAC product information states that fluoxetine is not indicated for patients under 18 years of age [3]. These jurisdictional and age distinctions are important when interpreting the clinical relevance of the evidence.

The evidence surrounding fluoxetine's effectiveness in pediatric depression is mixed and should be interpreted according to treatment approach. Findings involving fluoxetine plus CBT represent evidence for combined treatment, not proof of a fluoxetine-specific effect. A large network meta-analysis found fluoxetine plus CBT more effective than CBT alone, but not clearly more effective than fluoxetine alone, illustrating why monotherapy and combination evidence should be distinguished [12]. More recent systematic review evidence also suggests that antidepressants provide a modest treatment-response benefit in pediatric MDD overall, while most trials remain short in duration and include broad child-adolescent age ranges [13]. Consequently, evidence for sustained benefit specifically among children under 13 remains insufficient.

In terms of safety, the evidence surrounding fluoxetine is similarly complex. The 58% increase in suicide-related outcomes reported by Hetrick *et al.* [8] was a pooled estimate from trials of newer-generation antidepressants across medications and participants aged 6 - 18 years. It should therefore not be attributed specifically to fluoxetine or to children under 13. The broader pediatric antidepressant literature nevertheless supports careful monitoring for clinical worsening, suicidality, behavioural activation, and other adverse effects. Current guidance recommends structured monitoring when antidepressant treatment is used in children and young people [4].

Clinical recommendations should also be distinguished from conclusions that can be drawn directly from this review. NICE guidance recommends psychological therapy as initial treatment for mild depression and, following multidisciplinary review, fluoxetine for moderate-to-severe depression that has not responded to psychological therapy. For children aged 5 - 11 years, NICE advises cautious consideration because evidence for fluoxetine effectiveness is not established in this age group [4]. Thus, rather than concluding from the present review alone that fluoxetine should be "reserved for severe cases," the evidence supports a more limited interpretation: decisions about fluoxetine in younger children should follow applicable clinical guidance, specialist assessment, illness severity, prior response to psychological treatment, and close safety monitoring.

This review's findings underscore the need for research designed specifically for younger children. Existing evidence is dominated by mixed child-adolescent samples, limiting conclusions about children under 13. Future trials should report age-stratified efficacy and safety outcomes, distinguish fluoxetine monotherapy

from combined fluoxetine-CBT treatment, and assess longer-term remission, growth, development, and adverse effects. Until stronger age-specific evidence is available, conclusions for children under 13 should remain narrower than conclusions for pediatric populations as a whole.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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