# Time-to-effect of fluoxetine in children with depression

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## Abstract

**Question** I prescribed fluoxetine to a 16-year-old female patient presenting to my clinic with severe major depressive disorder who did not respond to psychotherapy. Is fluoxetine an effective treatment of depression in this population, and how long should she expect to wait before noticing an effect?

**Answer** For depression in children and adolescents, fluoxetine has the most evidence for efficacy when compared with other selective serotonin reuptake inhibitors; however, it is not approved by Health Canada for this patient population. Available evidence has shown that most of its clinical benefit is seen within the first 2 weeks. Lack of response by week 4 might suggest a need for reevaluation. However, more research is needed to elucidate the optimal length of the initial treatment period. There is conflicting evidence regarding the risk of suicidality in this population, so close patient monitoring is required when using fluoxetine in children and adolescents.


Major depressive disorder (MDD) has become an increasingly challenging and prevalent condition among adolescents.[1] The rate of MDD in childhood is low (<1%) but increases substantially throughout adolescence,[2] with a 12-month prevalence of 6.5% for boys and 9.8% for girls, as reported among more than 17 000 Canadian adolescents in 2005.[3] As MDD is a considerable risk factor for suicide and hence a leading cause of death in this population,[2] treatment of MDD is imperative.

*Major depressive disorder* is defined as a constellation of symptoms, most notably depressed mood or loss of interest in activities for at least 2 weeks with associated functional impairment.[4] In children and adolescents, a core diagnostic symptom can be irritability.[4] Other symptoms include reduced energy, feelings of guilt and worthlessness, reduced self-esteem, pessimistic thoughts, disturbed sleep, changes in appetite, and suicidal thoughts.[5] Severity of MDD, ranging from mild to severe, can be distinguished based on the number of symptoms and extent of functional impairment.[5]

## Use of selective serotonin reuptake inhibitors

For mild to moderate MDD in pediatric patients, psychotherapy such as cognitive-behavioural therapy is the treatment of choice in the 2016 Canadian Network for Mood and Anxiety Treatments guidelines.[6] In a recent systematic review of 31 trials including 4334 children and adolescents with MDD, it was reported that cognitive-behavioural therapy resulted in a 63% reduced risk of having depression at follow-up (no longer meeting the *Diagnostic and Statistical Manual of Mental Disorders* criteria 17 to 39 weeks later).[7] When psychotherapy is inaccessible or ineffective, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is recommended as first-line therapy.[6] Selective serotonin reuptake inhibitors function by blocking the reuptake of serotonin to increase its synaptic availability.[8] This benefits patients with MDD as the depletion of serotonin is thought to contribute to the pathogenesis of this condition.[8]

Among the various SSRIs, only fluoxetine has consistently shown acute efficacy compared with placebo in treating MDD in pediatric patients.[9,10] In a 2002 double-blinded randomized controlled study, 219 children aged 8 to 18 with MDD achieved better remission at the end of 9 weeks with 20 mg of fluoxetine daily (41%) compared with placebo (20%) ($P<.01$).[11] All patients began with a Children's Depression Rating Scale, Revised (CDRS-R) score greater than 40, and remission was defined as a CDRS-R score less than or equal to 28.[11] These findings reconfirmed an earlier study by the same group in the 1990s involving 96 children and adolescents, which was the first to establish the superiority of fluoxetine to placebo in this population.[12]

In a following multicentre network meta-analysis with 5260 participants aged 6 to 20, fluoxetine was the most efficacious (highest reduction in depression symptoms) and was well tolerated (comparatively low discontinuation due to adverse events).[10] The study compared 14 antidepressants within 34 double-blind randomized controlled trials (RCTs),[10] including a sentinel multiclinic trial by the Treatment of Adolescents with Depression Study team.[13] The meta-analysis compared fluoxetine directly with 2 serotonin-norepinephrine reuptake inhibitors (ie, duloxetine and venlafaxine) and a tricyclic antidepressant (ie, nortriptyline), as well as indirectly with 10 other antidepressants including 4 SSRIs (ie, paroxetine, escitalopram, citalopram, sertraline).[10] Of note, 22 (65%) of the trials were funded by pharmaceutical companies, including half of the fluoxetine trials (5 of 10),

which were sponsored by the drug's manufacturer.[10] Based on the available data, fluoxetine has the most evidence supporting its efficacy in treating MDD in pediatric patients when pharmacologic treatment is indicated.[10-13]

## Risks associated with fluoxetine

A black-box warning for fluoxetine was issued by the US Food and Drug Administration (FDA) in 2004 owing to a reported increase in suicidality associated with SSRIs among children and adolescents.[14] However, the evidence behind this decision and its implications remain controversial.[15]

A systematic review of 4 pediatric RCTs comparing fluoxetine with placebo involving more than 700 participants reported that there was no evidence of increased suicide risk.[14] However, in another systematic review of 5 adolescent observational studies, SSRI exposure almost doubled the risk of completed or attempted suicide (odds ratio [OR] of 1.92).[16] The same review also reported that not all SSRIs were associated with the same risk profile; paroxetine (OR = 1.77) and venlafaxine (OR = 2.43) had the highest risk, while fluoxetine (OR = 1.33) had a moderately increased risk overall.[16]

Another consideration when prescribing fluoxetine is its potent inhibition of cytochrome P450 2D6.[17] This can result in serious interactions with drugs such as tricyclic antidepressants, neuroleptics, and antiarrhythmics.[17] Finally, while withdrawal symptoms are a concern with other SSRIs, the long half-life of fluoxetine is correlated with the lowest risk of discontinuation syndrome when compared with other SSRIs.[18]

## Current guidelines for SSRIs

Selective serotonin reuptake inhibitors are currently not approved by Health Canada for children younger than age 18,[19] possibly owing to concerns of increased suicidal behaviour, which has limited the availability of approved pharmacologic options for MDD in this population. In contrast, in the United States, the FDA has approved the use of fluoxetine in patients older than age 8 and escitalopram in patients older than age 12.[19] When fluoxetine is used in children and adolescents, the FDA recommends weekly follow-up for the first 4 weeks to monitor for adverse events and suicide risk.[20] Before considering changes to therapy for nonresponders, the Canadian Network for Mood and Anxiety Treatments guidelines recommend a trial of fluoxetine for at least 4 weeks.[6]

## Time-to-effect of fluoxetine

An optimal drug will have an early onset of effect, especially in the face of adverse events and cost. Among 182 participants aged 16 to 65 receiving 20 mg of fluoxetine daily for 8 weeks, more than half (55.5%) of responders improved within 2 weeks.[21] Response was defined as a 50% decrease in a patient's Hamilton Depression Rating Scale (HAM-D) score.[21] Furthermore, the cumulative response to fluoxetine at weeks 4 and 6 was 80.2% and 89.5% of patients, respectively.[21] Lack of response by 4 to 6 weeks translated to a 73% to 88% chance of not having a response by week 8.[21] In contrast, a 2003 placebo-controlled study of 840 patients concluded that nonresponse to fluoxetine should only be declared after 8 weeks of treatment.[22] This study reported that 51% (63 of 124) of nonresponders (<25% HAM-D score improvement) to fluoxetine by week 4 still achieved remission (≥50% HAM-D score improvement with a total score of ≤7) by week 12.[22]

A subsequent meta-analysis of 28 RCTs with 5872 adult participants reported that 75% of symptomatic improvement from SSRIs was seen within the first week of treatment.[23] A 2015 revision of the British Association of Psychopharmacology guidelines supported these conclusions, noting that most people with sustained responses to SSRIs show onset of improvement in depression rating scales within the first 2 weeks of therapy.[24]

In children and adolescents, the limited evidence available on fluoxetine suggests a time-to-effect phenomenon similar to that in adults.[11,25] Although not primarily evaluating time-to-effect, data from a 2002 RCT of 219 children and adolescents from Texas, comparing fluoxetine (10 mg daily for the first week, then 20 mg daily for 8 weeks) with placebo, demonstrated that most of fluoxetine's effect in reducing the CDRS-R score occurred within the first 2 weeks, with a diminishing rate of improvement thereafter.[11] A 2015 meta-analysis of 13 pediatric trials with a total of 3004 patients with MDD further supported the notion that benefits of SSRIs in this population are observed early in treatment.[25] Notably, a statistically significant benefit of SSRIs as compared with placebo was observed within 2 weeks of treatment onset ($P < .05$).[25] Authors of this study compared the onset of action of fluoxetine, paroxetine, citalopram, escitalopram, and sertraline and reported that these 5 SSRIs followed the same early response time course.[25] Interestingly, the same group conducted a 2016 meta-analysis evaluating SSRI treatment in children with obsessive-compulsive disorder, reporting similarly early treatment gains within the first 2 weeks.[26]

## Conclusion

When psychotherapy is ineffective, fluoxetine is an effective alternative or adjunctive treatment for MDD in children and adolescents. Current guidelines suggest consideration of treatment modification after 4 weeks with no response. Available data support these guidelines, indicating that improvement from fluoxetine treatment largely occurs within the first 2 weeks. More research needs to be done on the exact time-to-effect and risks of fluoxetine in this population, but current evidence suggests it is an appropriate first-line pharmacotherapy.

**Competing interests**
None declared

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