

Fluoxetine Use for Very Young Children with Major Depression Disorder: A Pilot Randomized Clinical Trial

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Abstract

Background: Major depressive disorder (MDD) as one of the disabling mental disorders has turned into one of the significant challenges for health systems worldwide. Although fluoxetine has been successfully applied to over 6-year-old individuals with MDD, its utility for younger patients has not been investigated yet. The current pilot study aims to assess fluoxetine use in 4–6-year-old children diagnosed with MDD.

Materials and Methods: The current double-blinded randomized clinical trial has been conducted on 40 four-to-six-year-old children with MDD who were assigned to one of the treatment groups with 0.7 mg/kg daily fluoxetine ($n = 20$) or placebo ($n = 20$) for 60 days. Preschool Feelings Checklist-Scale (PFC-S) and the antidepressant side effect checklist (ASEC) were assessed at study initiation, within 30 and 60 days after the intervention.

Results: The PFC-S score significantly decreased in the fluoxetine-treated group (P value < 0.001), while those who received placebo revealed no change (P value $= 0.317$). The comparison of fluoxetine versus placebo treatment revealed a remarkable difference between the scores of PFC-S among the groups (P value < 0.001). Besides, the PFC-S scores were statistically lower among those treated with fluoxetine compared with placebo-treated ones in both 30 days (P value < 0.001) and 60 days (P value < 0.001) assessments. None of the patients presented any fluoxetine-related side effect.

Conclusion: Based on the findings of this study, fluoxetine was a safe and efficient agent to manage depression in very young children; however, data in this regard are limited and inconclusive. Further studies are strongly recommended.

Keywords: Antidepressant agents, depression, fluoxetine, major depressive disorder, preschool child

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INTRODUCTION

Major depressive disorder (MDD) as the fourth leading cause of disability has become one of the significant challenges for health systems worldwide. Based on the reports of the Global Burden of Disease Guidelines, it is estimated that depression would become the second by the end of 2020.^[1] Despite all the efforts made to prevent MDD or diagnose it in its early stages, further investigations in 2024 have revealed that an increasing trend of MDD development is going on.^[2,3] Moreover, depression negatively impacts public health with a greater impact than physical disorders such as coronary heart disease.^[4]

Depression diagnosis was made using the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) based on which depression equaled the presence of five (or more) symptoms including depressed mood, loss of interest or pleasure, appetite/weight changes, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, the feeling of worthlessness, diminished ability to concentrate, and recurrent thoughts of death for the least period of two weeks. Furthermore, at least one symptom should meet the criteria for low mood or loss of pleasure.^[5,6]

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Depression diagnosis is challenging in preschoolers, considering the problems of interpersonal relations with children. Irritability is probably the most common symptom for which parents refer to physicians. However, several other medical conditions can cause irritability in children. The absence of developmental delay is a key indicator of depression. Masked symptoms such as aggression, blaming, nagging, dissatisfaction, or somatic complaints are the other frequent presentations. It is noteworthy that caregivers might fail to report some symptoms because they presume them insignificant. For instance, changes in play, social interest, and sleep may not be considered to be associated with a depressed mood.^[7,8]

Evidence in the literature has shown that the prevalence of depression in children is less than any other age span, accounting for about 0.8% in 3–5-year-old children and increasing to 2.8% in under-13-year-old children. Nevertheless, depression can progress with age and increase to 6% in adolescence. Given that, early diagnosis and disease initiation play a critical role in managing depression in children.^[9] Not only does early diagnosis reduce the risk of chronic and treatment-resistant depression, but it can also prevent the incidence of developmental disorders. As neuroplastic development majorly occurs at these ages, and thus critical social and personal development takes place, early diagnosis of depression can help a child have a normal life in the future and also prevent further psychosocial problems in adolescence and adulthood.^[10,11]

Various antidepressants have been successfully administered to manage depression in adults including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs).^[12] Nevertheless, the information on the use of these agents at younger ages is limited and SSRIs are the only studied group.^[5] However, some concerns have been noted regarding the association of SSRIs with suicide commitment in children and adolescents.^[13]

SSRIs have inhibitory properties on the neurotransmitter 5-hydroxytryptamine (serotonin) reuptake into serotonergic neurons, which increases the serotonin level in the synapse. These agents have fewer anticholinergic effects and are safer drugs in cases of overdose.^[12] Besides, they can be applied to psychiatric disorders including anxiety, obsession, or compulsive disorders. Fluoxetine is a well-known SSRI agent with a long-active half-life accounting for one to three days that can increase to six days in cases of chronic use. This agent has mainly a hepatic metabolism via the CYP2D6 pathway, which metabolizes it into the active metabolite norfluoxetine with a half-life of nine days^[14]; however, it might cause side effects including unusual tiredness, sleepiness, weakness, or lack of clearly thinking, nervousness, excitability, irritability, or restlessness, headache, and dizziness; nevertheless, the anticholinergic properties of this agent are less than those of the other antidepressants.^[15–17] Fluoxetine as well as escitalopram,

both SSRIs, are the only antidepressant agents approved to be applied to children and adolescents; however, data in this regard are limited to older than 6-year-old children.^[18,19] Nevertheless, data in the literature are in favor of successful treatment of depression with fluoxetine alone or in combination with cognitive behavioral therapy.^[19,20]

One of the challenging matters in the current study refers to the morality of depriving the control group of treatment with fluoxetine, if it is beneficial.

Although this medication has not been approved for patients in the age range of 4–6 years old, numerous psychiatrists are applying it for these children in this age. The other point was the risk of initiating such medication in these cases; however, it was proposed to cease the drug as soon as facing a new onset symptom that might be associated with the treatment.

Accordingly, the current study aims to investigate the efficacy and safety of this medication among depressed children aged 4–6 years. Furthermore, if the efficacy and safety of fluoxetine were confirmed for the studied subjects, the controls will be treated, as well.

MATERIALS AND METHODS

Study population

The current double-blinded randomized clinical trial included 40 children who suffered from major depression disorder and were referred to outpatient psychiatry clinics affiliated with the Isfahan University of Medical Sciences from October 2022 to September 2023.

The protocol of the study met the tenets of the Helsinki Declaration. It was approved by the Ethics Committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1401.137). Furthermore, the study protocol was confirmed by the Iranian Registry of Clinical Trials (IRCT20220706055386N1). The written informed consent was obtained from the legal guardians of the patients after explaining the study for them.

Four-to-six-year-old children with a documented diagnosis of major depression disorder based on the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5)^[21] whose depression was categorized as severe considering their scores ≥ 3 in the Preschool Feeling Checklist (PFC)^[22] were included in the study. The diagnosis of other major psychiatric disorders other than MDD, concurrent use of other psychotropic medications, the current or history of fluoxetine use or consuming any medication interacting with fluoxetine, being a member of separated families (single-parent child, child of divorce, having a step-father or step-mother, and the parent(s)' death) were determined as unmet criteria. Those who did not adhere to the medications, refused to refer for follow-up visits, presented significant drug-related adverse effects causing drug withdrawal, and had flawed medical data for more than 20% were excluded.

Convenience sampling was applied to select the patients who met the study criteria. Afterward, they were randomly allocated to either the fluoxetine or placebo groups through multistage blocking. Given that, the patients were randomly allocated into 10 blocks, each containing four members using a Random Allocation Software. In the next step, each block randomly received one of the code numbers of one or two, allocating the members to one of the fluoxetine- versus placebo-treatment, respectively.

The patients/their legal guardians as well as the psychiatrist who interviewed the patients/their legal guardians during the follow-up visits were blinded to the medications received.

Intervention

The intervention group was treated with fluoxetine syrup (Abidi Company, Iran) with a dosage of 0.7 mg/kg with a maximal daily dose of 15 mg for a period of 60 days. The latter group received a placebo similar in color and dosage produced by the Pharmacy Faculty of the Isfahan University of Medical Sciences.

Assessments

The preschool feelings checklist

Preschool Feelings Checklist-Scale (PFC-S), a 16-item yes/no question checklist in which yes responses are interpreted as +1 with the exception of the first item, which has a yes-response value of -1. The total summation of +3 or more is suggestive of major depression disorder. The questions are about attending game playing with other children, sense of sadness, obeying the rules, crying, attention trouble, keeping to himself or herself, blaming, confidence, reactions to exciting or upsetting events, level of energy, sense of guilt, weight gain disturbances, developmental regression, and irritability. The current questionnaire has been designed to assess depression in preschool children with favorable psychometrics (Cronbach's alpha = 0.92, test/re-test intraclass correlation coefficient (ICC) = 0.82).^[22]

To apply the Persian version of PFC-S, a panel consisting of two psychiatrists and a psychologist turned the English questionnaire into Persian. Then, it was proposed to an expert person in English to correct the Persian version. In the next step, the revised Persian format was returned to English and given to a native English speaker for further corrections. Afterward, the final version was translated into Persian again.

The antidepressant side effect checklist

Besides, the antidepressant side effect checklist (ASEC) was applied to assess the side effects of treatment with fluoxetine. This checklist has been developed by the Royal College of Psychiatrists for the first time. It consists of all the potential side effects of antidepressant agents and categorizes the side effects into mild, moderate, and severe types.^[23]

Primary outcomes

The response to treatment was evaluated using PFC-S at the study initiation and within 30 and 60 days after the interventions. Besides, the parents were in contact with the

psychiatry assistant responsible for the study, and in case of any drug-related adverse effects, they called the assistant to present their complaint and were visited to assess the adverse effects and complete ASEC. Otherwise, the patients were visited within the fourth and eighth weeks of the intervention and ASEC was evaluated for them.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23. The Smirnov-Kolmogorov test was used to determine the normality of data distribution. The categorical data were compared using the Chi-square test or Fisher's exact test. The continuous data were compared using an independent T-test. A repeated measure analysis of covariance (ANCOVA) test was applied to assess the alterations in the groups and between the groups. A *P* value < 0.05 was considered as the significant level.

RESULTS

In this randomized-clinical trial (RCT), the eligibility of 55 children with documented depression disorder based on the DSM-V was assessed, among whom 10 patients did not enter the study (six unmet study criteria and four refused to participate). The remaining 45 patients were randomly assigned into treatment groups of treatment with placebo (*n* = 23) or fluoxetine (*n* = 22). Three patients in the placebo-treated group (one withdrew from the study and two did not refer for follow-up visits) and two patients in the intervention group with fluoxetine (withdrew from the study due to agitation) left the study. Eventually, 40 patients including 20 in each group fulfilled the protocol [Figure 1].

The studied population consisted of 20 boys (50%) with a mean age of 5 ± 0.50 . The studied groups did not differ in terms of age (*P* value = 0.89) and sex (*P* value = 0.52), as shown in Table 1 in details.

Table 2 shows the patients' PFC-S scores during the study. Based on this table, the baseline depression scores did not differ between the studied groups (*P* value = 0.134); however, significant differences were noted in the scores of the patients in further follow-up assessments performed within 30 days (*P* value < 0.001) and 60 days (*P* value < 0.001) after their interventions. Moreover, a statistically significant decrease was found in the PFC-S scores of the patients in the fluoxetine-treated group (*P* value < 0.001), while those who received placebo revealed no change (*P* value = 0.317).

Table 1: The baseline characteristics of the patients

Variables	Placebo (<i>n</i> = 20)	Fluoxetine (<i>n</i> = 20)	<i>P</i>
Age, mean±standard deviation	5.11±0.51	4.90±0.50	0.89*
Gender, <i>n</i> (%)			
Boy	11 (55)	9 (45)	0.52**
Girl	9 (45)	11 (55)	

*Chi-square test. **Independent *t*-test

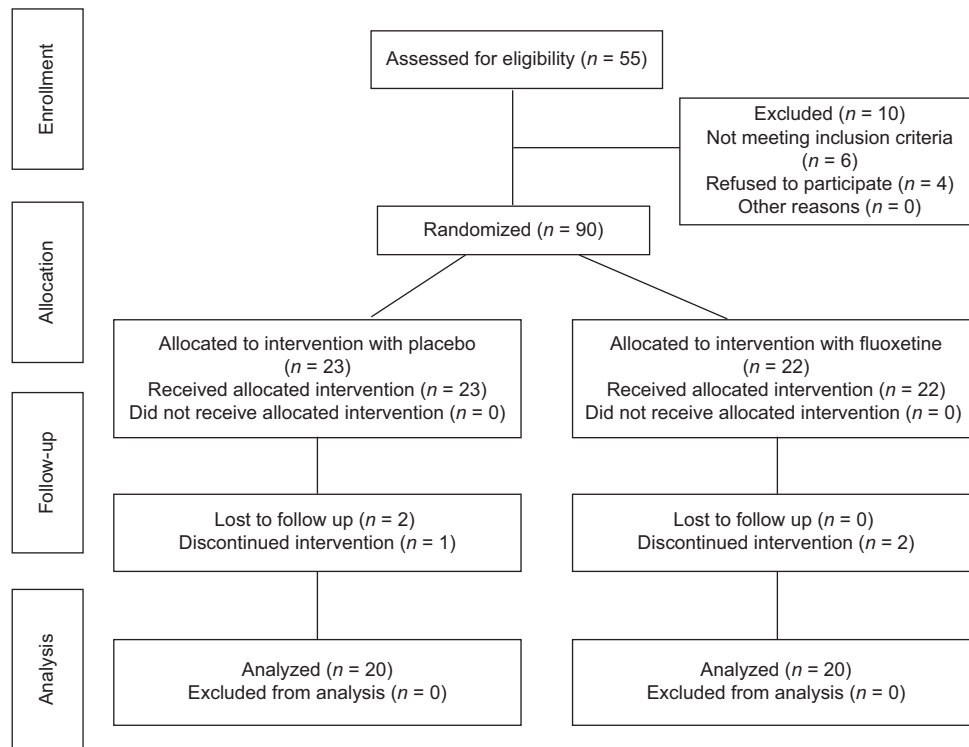


Figure 1: Consort diagram of the studied population

Table 2: The PFC-S scores of the studied groups

Variables	Baseline	Within 30 days	Within 60 days	P-time*	P-intervention*	P-interaction*
Fluoxetine (n=20)	4.90±1.11	3.60±1.04	3.05±1.19	<0.001	<0.001	<0.001
Placebo (n=20)	5.40±0.94	5.20±1.05	5.05±1.14	0.317		
P	0.134**	<0.001 [#]	<0.001 [#]			

*Repeated measure ANCOVA. **Independent *t*-test. [#]ANCOVA

During the follow-up course, based on the ASEC assessments, none of the parents whose children fulfilled the study complained about any adverse effects related to the antidepressant use.

DISCUSSION

Considering the significance of depression diagnosis and management in the early phases, various efforts have been made to treat depression in childhood; however, data regarding the efficacy and safety of agents in children are limited, particularly in very young children. The current study mainly aimed to investigate these two parameters in 4–6-year-old depressed children undergoing treatment with fluoxetine, which revealed promising outcomes considering the patients' response to treatment as well as negligible side effects reported by their legal guardians.

As far as we are concerned, the current RCT is the first one assessing the use of fluoxetine in a context of very young age of less than 6 years old; however, the data on the management of depression in childhood and adolescence are generally in favor of fluoxetine use, but controversial outcomes have been reported as well.

According to the guideline, mild to moderate depression in children can be well managed via cognitive behavioral therapy, and in cases of a lack of response, medications should be applied in which fluoxetine has been considered the first-line.^[15] The claims for fluoxetine use refer to the blockade of serotonin reuptake and increasing synaptic availability, as serotonin depletion contributes to the pathogenesis of depression.^[24]

Surfing the literature shows consistent data for our findings. The first efforts to assess fluoxetine use for children and adolescents with MDD were made by Emslie *et al.*^[25] assessed 96 patients who were assigned into treatment groups of fluoxetine versus placebo and found considerable symptom relief among those who were intervened by fluoxetine. The assessments continued in a double-blinded RCT on 219 children with MDD that revealed significant symptom relief among those receiving fluoxetine at a 20 mg daily dose compared with placebo for a period of nine weeks.^[26] These outcomes were confirmed in a meta-analysis assessing 14 antidepressants on 6–20-year-old individuals with MDD in which fluoxetine was the most efficacious and well-tolerated considering better symptom relief as well as the least rate of drug discontinuation due to side effects.^[16] Another investigation by Reyad and colleagues

on 1259 patients revealed that fluoxetine use significantly improved symptom intensity in very young patients suffering from MDD and was considered well tolerated.^[13] Nevertheless, Göttsche *et al.*^[27] contradicted the previous studies, which showed that fluoxetine use for children with depression was not only ineffective but also not safe. This conclusion has been made based on the findings, including that being prone to commit suicide or increased violence occurred more often on fluoxetine than on placebo as well as an insignificant reduction in height and weight after 19 weeks of fluoxetine use and prolonged the QT interval. However, they mentioned their biased data.

Despite the benefits of fluoxetine use for depression management at an early age, the increased risk of suicidality is the most concerning adversity of fluoxetine; however, the implications behind the increased probability of suicide following fluoxetine use remain controversial.^[28] In this regard, one study represented no association between fluoxetine use and suicidality,^[29] while the other presented a moderately increased risk of completing or attempting suicide after fluoxetine use that was remarkably less than that of paroxetine or venlafaxine.^[30]

However, along with increased suicidality as the most considerable potential adverse effect of fluoxetine, this agent might have other negligible with lower significance adverse effects attributed to its anticholinergic properties including unusual tiredness, drowsiness, weakness, or cognitive problems, nervousness, excitability, irritability, or restlessness, headaches, and dizziness.^[15,16,18,19] Nevertheless, none of the parents complained of any of the mentioned side effects presumably due to the low applied dose.

The other consideration for fluoxetine refers to its metabolism pathway, which might interact with other antidepressants or antiarrhythmic agents. Moreover, the long half-life of fluoxetine limits withdrawal syndrome following its abrupt discontinuation, which is one of the superiorities of this agent over other antidepressants.^[31]

Given what is mentioned above, Canadian guidelines have not approved fluoxetine in under 18-year-old individuals, probably due to the increased risk of suicide commitment, while this age decreases to 8 years old in American guidelines. Furthermore, close weekly follow-ups have been recommended in the first four weeks of fluoxetine initiation in children.^[32,33]

The primary response to treatment following fluoxetine use is achieved within two weeks after drug initiation, which can reach its pinnacle within 4–6 weeks after fluoxetine use. Response to treatment might differ based on the definitions in various studies; however, in cases of irresponsiveness after six weeks, it seems not to respond to further use.^[15] However, Quitkin and colleagues represented that a response to treatment might be achieved until the 12th week of treatment.^[34] However, data on children are limited, but the response to treatment seems similar to that of adults.^[35–37]

Limitations

The short period of follow-up was the most significant limitation of the current study.

CONCLUSION

Based on the findings of this study, fluoxetine was a safe and efficient agent to manage depression in very young children; however, data in this regard are limited and inconclusive. Further studies are strongly recommended.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Isfahan University of Medical Sciences, Iran (IR.MUI.MED.REC.1401.137). Furthermore, the study protocol was confirmed by the Iranian Registry of Clinical Trials (IRCT20220706055386N1). The study protocol was explained to the patients; they were reassured regarding the confidentiality of their personal information and signed written consent for participation in the study.

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Gutiérrez-Rojas L, Porras-Segovia A, Dunne H, Andrade-González N, Cervilla JA. Prevalence and correlates of major depressive disorder: A systematic review. *Brazilian J Psychiatry* 2020;42:657-72.
- Wang L, Zhang D, Wu J, Wang M, Zhang C, Gao J, *et al.* Global, regional, and national burdens of major depressive disorder and dysthymia in adolescents and young adults aged 10–24 years from 1990 to 2019: A trend analysis based on the global burden of disease study 2019. *International Journal of Mental Health and Addiction* 2025;23:3154-83.
- Luo J, Tang L, Kong X, Li Y. Global, regional, and national burdens of depressive disorders in adolescents and young adults aged 10–24 years from 1990 to 2019: A trend analysis based on the Global Burden of Disease Study 2019. *Asian J Psychiatr* 2024;92:103905.
- Egede LE. Depression: Greater effect on overall health than angina, arthritis, asthma or diabetes. *Evid Based Ment Health* 2008;11:57.
- Luxton R, Kyriakopoulos M. Depression in children and young people: Identification and management NICE guidelines. *Arch Dis Childh Educ Pract* 2022;107:36-8.
- Shelton J. Definition D. DSM-5 Diagnostic Criteria. 2022. Available from: <https://www.psychom.net/depression-definition-dsm-5-diagnostic-criteria>.
- Luby JL. Early childhood depression. *Am J Psychiatry* 2009;166:974-9.
- Luby JL, Whalen D, Zeanah C. Depression in early childhood. *Handbook of Infant Mental Health*. The Guilford Press; 2019. p. 426-37.
- Juul EML, Hjemdal O, Aune T. Prevalence of depressive symptoms

- among older children and young adolescents: A longitudinal population-based study. *Scand J Child Adolesc Psychiatr Psychol* 2021;9:64-72.
10. Luby JL. Preschool depression: The importance of identification of depression early in development. *Curr Direct Psychol Sci* 2010;19:91-5.
 11. Tavormina MGM, Tavormina R. Depression in early childhood. *Psychiatr Danub* 2022;34:64-70.
 12. Rang H, Ritter J, Flower R, Henderson G. Rang and Dales Pharmacology. 8th ed. Elsevier Churchill Livingstone; 2016.
 13. Reyad AA, Plaha K, Girgis E, Mishriky R. Fluoxetine in the management of major depressive disorder in children and adolescents: A meta-analysis of randomized controlled trials. *Hosp Pharm* 2021;56:525-31.
 14. Organization WH. World Health Organization Model List of Essential Medicines: 22nd list (2021). World Health Organization; 2021.
 15. Yan T, Goldman RD. Time-to-effect of fluoxetine in children with depression. *Can Fam Phys* 2019;65:549-51.
 16. Cipriani A, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, *et al.* Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: A network meta-analysis. *Lancet* 2016;388:881-90.
 17. Shakibaei F, Gholamrezaei A, Alikhani M, Talaeizadeh K. Serum sodium changes in fluoxetine users at different age groups. *Iran J Psychiatr* 2010;5:113-6.
 18. Selph SS, McDonagh MS. Depression in children and adolescents: Evaluation and treatment. *Am Fam Phys* 2019;100:609-17.
 19. Viswanathan M, Kennedy SM, McKeeman J, Christian R, Coker-Schwimmer M, Bann C, *et al.* Treatment of Depression in Children and Adolescents: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.
 20. Shakibai F, Esmacili M, Basiri N. Differential responses to cognitive behavioral therapy and pharmacotherapy versus combined therapy in young adolescents with depression. *J Dis* 2018;5:33-42.
 21. Nuckols CC, Nuckols CC. The Diagnostic and Statistical Manual of Mental Disorders, (DSM-5). Philadelphia: American Psychiatric Association; 2013.
 22. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behav Res Ther* 2000;38:835-55.
 23. Uher R, Farmer A, Henigsberg N, Rietschel M, Mors O, Maier W, *et al.* Adverse reactions to antidepressants. *Br J Psychiatr* 2009;195:202-10.
 24. Artigas F. Serotonin receptors involved in antidepressant effects. *Pharmacol Ther* 2013;137:119-31.
 25. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, *et al.* A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatr* 1997;54:1031-7.
 26. Emslie G, Heiligenstein J, Hoog S, Ernest D, VanHooy B, Brown E, *et al.* Fluoxetine for maintenance of recovery from depression in children and adolescents: A placebo-controlled, randomized clinical trial. *Eur Neuropsychopharmacol* 2001;11:S192-S3.
 27. Göttsche PC, Healy D. Restoring the two pivotal fluoxetine trials in children and adolescents with depression. *Int J Risk Saf Med* 2022;33:385-408.
 28. Fornaro M, Anastasia A, Valchera A, Carano A, Orsolini L, Vellante F, *et al.* The FDA “black box” warning on antidepressant suicide risk in young adults: More harm than benefits? *Front Psychiatr* 2019;10:294.
 29. Gibbons RD, Brown CH, Hur K, Davis JM, Mann JJ. Suicidal thoughts and behavior with antidepressant treatment: Reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Arch Gen Psychiatr* 2012;69:580-7.
 30. Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: A systematic review of observational studies. *CMAJ* 2009;180:291-7.
 31. Zito JM, Pennap D, Safer DJ. Antidepressant use in Medicaid-insured youth: Trends, covariates, and future research needs. *Front Psychiatr* 2020;11:113.
 32. Garland EJ, Kutcher S, Virani A, Elbe D. Update on the use of SSRIs and SNRIs with children and adolescents in clinical practice. *J Can Acad Child Adolesc Psychiatr* 2016;25:4-10.
 33. Aydin V, Kirmizi N, Isli F, Aksoy M, Akici A. Comparison of drugs prescribed by psychiatrists and child/adolescent psychiatrists. *Psychiatr Clin Psychopharmacol* 2020;30:175-81.
 34. Quitkin FM, Petkova E, McGrath PJ, Taylor B, Beasley C, Stewart J, *et al.* When should a trial of fluoxetine for major depression be declared failed? *Am J Psychiatr* 2003;160:734-40.
 35. Lukmanji A, Pringsheim T, Bulloch AG, Stewart DG, Chan P, Tehrani A, *et al.* Antidepressant prescriptions, including tricyclics, continue to increase in Canadian children. *J Child Adolesc Psychopharmacol* 2020;30:381-8.
 36. Varigonda AL, Jakubovski E, Bloch MH. Systematic review and meta-analysis: Early treatment responses of selective serotonin reuptake inhibitors and clomipramine in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatr* 2016;55:851-9.e2.
 37. Mendez EM, Dahlsgaard KK, Hjelmgren JM, Mills JA, Suresh V, Strawn JR. What is the added benefit of combining cognitive behavioral therapy and selective serotonin reuptake inhibitors in youth with obsessive compulsive disorder? A Bayesian hierarchical modeling meta-analysis. *J Child Adolesc Psychopharmacol* 2023;33:203-11.