

# Use of selective serotonin reuptake inhibitor medications for the treatment of child and adolescent mental illness

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Paediatr Child Health 2013;18(9):487-91

## Abstract

Comprehensive clinical management plans for treating depression or anxiety disorders in children and adolescents frequently include the use of selective serotonin reuptake inhibitor (SSRI) medications. This statement reviews empirical data regarding the effectiveness of specific SSRI medications, monitoring guidelines, and potential adverse effects of SSRI use including risk of suicidality. SSRI medications can be effective in treating child and adolescent depression and anxiety disorders. Untreated depressive illness may be more harmful than appropriate use of SSRI medication. Physicians should ensure careful elicitation and documentation of baseline depressive and anxious symptoms before initiating SSRI medication. Following medication initiation, patients should also be closely monitored for potential adverse effects, including suicidal ideation and behaviour.

**Key Words:** Adolescent; Antidepressant; Anxiety; Depression; Psychopharmacology; SSRI

Mental illness is increasingly recognized as an important public health concern among children and adolescents, and is closely associated with poor social, psychological and physical health outcomes. Early identification of mental illness is critical to facilitate appropriate intervention and timely treatment for affected children and youth. However, despite the recognized need for earlier diagnoses and management, the limited availability of child and adolescent psychiatrists has led to long waiting periods for services in many regions of Canada. Paediatricians play an important role in the assessment and management of depression and anxiety disorders. However, many paediatricians report the field of psychiatry to be an area of their own relative discomfort within their scope of practice.<sup>[1]</sup>

This statement will summarize recent literature on the efficacy of selective serotonin reuptake inhibitor (SSRI) medications in the treatment of depression and anxiety among children and youth, discuss common and potentially serious adverse effects associated with SSRI medications in this population, and present monitoring guidelines for children and youth being treated with SSRIs for depression or anxiety disorders.

## SSRI medications: An overview

Antidepressant medications are classified on the basis of their specificity in relation to brain neurotransmitters. SSRIs are a class of medications that include fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine and paroxetine. SSRIs inhibit serotonin transporters, blocking reuptake and increasing concentration of the neurotransmitter serotonin within the synapse. However, within the broader SSRI class, specific medications may also influence other neurotransmitter systems (eg, dopamine, norepinephrine), leading to differences in both effectiveness and adverse effects of various SSRIs. Pharmacokinetically, SSRIs are rapidly absorbed and metabolized by the liver. Absorption of SSRIs is largely unaffected by ingestion of food, making the coadministration of food and SSRI medication a potentially useful strategy to reduce the gastrointestinal effects associated with SSRI use.

SSRIs are long-acting drugs that can be given in a single daily dose, usually in the morning. However, there are differences in half-life duration among SSRI medications that are clinically relevant (Table 1). The propensity for a specific SSRI medication to result in withdrawal symptoms (discontinuation syndrome) on abrupt cessation has been generally related to half-life. Paroxetine has been reported to have the highest incidence of withdrawal symptoms on abrupt discontinuation.<sup>[2]</sup> Fluoxetine is associated with the fewest reports of discontinuation symptoms. It has also been suggested that the half-lives of some SSRIs may be shorter in children than in adults, leading to increased propensity to result in withdrawal symptoms following abrupt cessation of these medications among children.<sup>[3]</sup> While laboratory investigations may be in-

licated to rule out alternative underlying etiologies of the presenting symptoms (eg, hypothyroidism), to assess comorbid medical conditions (eg, hepatic impairment) or to monitor therapeutic drug levels of medications used in combination with SSRI medications (eg, valproic acid), laboratory investigations are not routinely required before initiating or maintaining SSRI medication use. In the presence of comorbid chronic medical illness or requirement for SSRI use in combination with other medications, child and adolescent psychiatry consultation should be considered.

**TABLE 1**  
**Selective serotonin reuptake inhibitor medications: Half-life and dosing schedules**

Medication (trade name; manufacturer, country)	Mean half-life, h	Dosing frequency
Fluoxetine (Prozac; Eli Lilly, USA)	96	Daily
Sertraline (Zoloft; Pfizer, USA)	26	Daily
Fluvoxamine (Luvox; Abbott Laboratories, USA)	15	Daily
Citalopram (Celexa; Forest Laboratories, USA)	35	Daily
Escitalopram (Cipralext; Lundbeck, Denmark)	30	Daily
Paroxetine (Paxil; GlaxoSmithKline, USA)	21	Daily

## SSRI use in the treatment of child and adolescent depression

While treatment of depression in children and adolescents may include multiple modalities of therapy, this statement is focused on SSRI medications, the primary class of antidepressant medications used in this population. Antidepressants (including SSRIs) have not been approved by Health Canada for the treatment of depression in children and adolescents. As such, it is important that physicians carefully document relevant issues when prescribing SSRIs for patients in this age group. In the United States, the Food and Drug Administration (FDA) has approved fluoxetine for the treatment of depression in children and adolescents, and escitalopram for the treatment of depression in adolescents.

Evidence from randomized double-blinded placebo-controlled trials and systematic reviews suggest that SSRIs are effective in the treatment of adolescent depression, with response rates ranging from 40% to 70%.<sup>[4][5]</sup> Response rates for patients receiving placebo are also considerable at 30% to 60%, indicating that study design and methodology are of key importance in evaluating the efficacy of antidepressant

medications among youth. Of the SSRI medications, data are most supportive for the efficacy of fluoxetine, with clinical trials of fluoxetine demonstrating the greatest difference between active drug and placebo. Data addressing the efficacy of SSRI medications for treating paediatric depression found that for children younger than 12 years of age, only fluoxetine has demonstrated benefit over placebo.<sup>[4]</sup> Among adolescents, two randomized controlled trials (RCTs) have demonstrated the efficacy of escitalopram for the treatment of depression.<sup>[6][7]</sup> Both citalopram and sertraline have shown some efficacy for the treatment of adolescent depression, with a single positive RCT each reporting greater benefits for these medications over placebo.<sup>[8][9]</sup> A second RCT of citalopram demonstrated negative results in the treatment of adolescent depression.<sup>[10]</sup> In contrast, examination of paroxetine's efficacy in the treatment of child and adolescent depression has yielded negative results in three RCTs.<sup>[11][13]</sup> Current evidence also suggests that the medication-placebo difference may be larger among more severely depressed adolescents compared with individuals experiencing mild depression. Research suggests, for example, that milder depressive symptoms may be more highly responsive to the supportive nonpharmacological management elements inherent in clinical trials, which may account for the high placebo response rates reported in some studies.<sup>[3]</sup>

The largest randomized placebo-controlled study to date, the Treatment for Adolescents with Depression Study (TADS), compared placebo, cognitive behavioural therapy (CBT) alone, fluoxetine alone and combination fluoxetine + CBT.<sup>[14]</sup> Adolescent participants in the medication arms demonstrated significantly greater improvement in their depressive symptoms compared with those in either the CBT alone or placebo arms. In this investigator-initiated study, patients with more severe and persistent depression benefited equally from medication alone or combined medication and CBT.<sup>[14]</sup>

SSRIs are generally well tolerated by children and adolescents. Common short-term side effects include gastrointestinal symptoms, sleep changes (either insomnia or somnolence, and sleep disturbances, including vivid dreams), restlessness, headaches, appetite changes and sexual dysfunction. Research suggests that these side effects are dose-dependant and decrease over time.<sup>[15][17]</sup> An increase in agitation or impulsivity (behavioural activation) may occur. Should children or adolescents experience behavioural activation, early signs of hypomania in children at risk of bipolar disorder must be eliminated in the differential diagnosis.<sup>[18]</sup> Rarely, SSRIs have been associated with increased risk of bleeding, syndrome of inappropriate secretion of antidiuretic hormone, and serotonin syndrome/toxicity (mental status changes, myoclonus, ataxia, diaphoresis, fever and autonomic dysregulation).<sup>[19][21]</sup> Recently, both Health Canada and the FDA have issued a health advisory/drug safety communication regarding dose-dependent QT-interval prolongation and risk of arrhythmia with citalopram dosages >40 mg/day and, furthermore, rec-

ommending that clinicians not exceed this dose. Moreover, children and adolescents with congenital long QT syndrome should not be treated with citalopram. Patients with underlying congenital heart disease or hepatic impairment (affecting citalopram metabolism), including a predisposition to cardiac arrhythmia due to electrolyte disturbances, should be treated with caution if receiving citalopram and monitored closely for cardiac adverse effects, including *torsades de pointes*.<sup>[22][23]</sup>

The association of SSRI medications with suicidality has been the focus of recent reviews by the FDA and others.<sup>[4][24][25]</sup> Studies reviewed generally examined occurrences of suicidal ideation and behaviour; there were few suicide attempts and no completed suicides across any of the RCTs included in these systematic reviews. The FDA analyses of suicidal adverse events among participants treated with an SSRI for depression revealed an overall RR of 1.66 (95% CI 1.02 to 2.68).<sup>[24]</sup> A more recent meta-analysis included unpublished RCT data along with the studies reviewed by the FDA, but did not find significant risk differences between drug and placebo in the SSRI treatment of depression in children and adolescents.<sup>[4]</sup> The same study also noted that the overall number needed to harm for active treatment was 112. This number compares with an overall number needed to treat of 10 for SSRIs in depression,<sup>[4]</sup> indicating that >10 times more children and adolescents with depression may benefit from SSRIs than may report suicidality. The clinical significance of these findings is considered together with the epidemiological observation that during the period of increased SSRI use, a concomitant decrease in adolescent suicide has occurred.<sup>[3]</sup> Clinical studies also confirm that suicidality lessens with effective treatment and the improvement of depressive symptoms.<sup>[15]</sup>

Collectively, research suggests:

- The potential benefits of SSRI use outweigh the potential harms for the treatment of depression in children and adolescents.
- Untreated depression is more likely to result in harm than appropriate SSRI use.
- Close initial monitoring, along with careful documentation of symptoms and adverse effects, are required.

For patients who begin a course of SSRI treatment, initiation of the starting dose should commence with a goal of achieving the minimum effective dosage over the following one to two weeks. That is, children and adolescents should not be allowed to remain on starting doses of medication for a prolonged period of time in the face of ongoing symptomatic distress. Generally, the effective doses for children and adolescents are similar or slightly lower than those found in adult guidelines.<sup>[16]</sup>

The FDA has suggested that clinical monitoring of patients occur at least:

- weekly for the first four weeks following initiation of SSRI medication;
- every two weeks for the next four weeks;
- at 12 weeks;
- then as clinically indicated beyond the 12-week point.<sup>[26]</sup>

The FDA notes that additional contact by telephone may be appropriate between face-to-face visits. Guidelines from the American Academy of Child and Adolescent Psychiatry have also encouraged providers to follow the FDA monitoring schedule, while highlighting the lack of evidence supporting an association between weekly face-to-face visits and suicide risk.<sup>[3]</sup> Monitoring assessments should include evaluation of suicidal thoughts and behaviours as well as the potential adverse medication effects described above. Overall medication adherence should also be assessed over time because an abrupt discontinuation of SSRI medications (except fluoxetine) may lead to withdrawal symptoms and an abrupt worsening of depressive symptoms, including suicidality.

The goal of treatment is to achieve full remission of depression symptoms. Once an effective dose of the medication is reached, symptoms should be reassessed at four-week intervals to evaluate both the effectiveness and tolerability of the current dosage, and to determine whether there is a need for dose increase. Once complete response is achieved, the medication should be continued for a minimum of six to 12 months to decrease the risk of depressive relapse.<sup>[3]</sup> Discontinuing an SSRI should consist of a slow taper of medication and occur during a relatively stress-free time (eg, the summer months). For children and adolescents with a history of multiple depressive episodes, comorbid psychiatric illnesses or complicated depressive episode (eg, with psychotic features), psychiatric consultation may be warranted before medication discontinuation.

The presence of psychiatric comorbidity, including substance use disorders, may warrant further psychiatric assessment before embarking on a treatment plan. The relationship between ongoing substance use and depressive/anxious symptoms is frequently bidirectional. The presence of a substance use disorder should not necessarily exclude patients from receiving appropriate treatment for comorbid depression or anxiety disorders.

## Key messages

- Of the SSRI medications, fluoxetine has the most data supporting its use for treating depression in children and adolescents.

- Citalopram should not be used in dosages >40 mg/day.
- Citalopram should be prescribed with caution in certain individuals (described above), and should not be prescribed for children and adolescents with congenital long QT syndrome.
- The risk of suicidality associated with untreated depression is likely greater than that associated with appropriate SSRI use.

## SSRIs in the treatment of child and adolescent anxiety disorders

Treatment planning for anxiety disorders should occur following a comprehensive clinical assessment to determine the nature, severity and level of impairment associated with the anxiety disorder. The assessment should explore potential comorbidities and rule out other illnesses that may present similarly to anxiety disorders symptoms (eg, attention-deficit hyperactivity disorder, depression, bipolar disorder, autistic spectrum disorder). Although the overall management plan for children and youth with anxiety disorders includes a multimodal approach that may involve psychoeducation, psychotherapy and family interventions, this statement focuses on the role and use of medication.

Guidelines endorsed by the American Academy of Child and Adolescent Psychiatry have confirmed that SSRIs are the medication of choice for the treatment of childhood anxiety disorders.<sup>[27]</sup> SSRIs may be considered early in the course of treatment if anxiety symptoms are severe or significantly impairing, or if other impairments preclude the child or adolescent's ability to benefit from psychotherapy. Medication may also be considered for children or youth who have had a suboptimal response to psychotherapy. Before starting SSRIs, the clinician should explore and document the presence of physical (somatic) symptoms of anxiety to ensure these do not become erroneously attributed to adverse medication effects following medication initiation. Clinicians should also screen for bipolar disorder and family history of bipolar disorder before initiating SSRI medications. Individuals with a personal or family history of bipolar disorder should be referred for psychiatric consultation before embarking on a course of SSRI medication for treatment of a depressive or anxiety disorder.

Data from randomized placebo-controlled trials (Table 2) confirm that SSRIs are efficacious for the treatment of anxiety disorders in children and adolescents. In contrast to the results of depression research, however, the anxiety treatment data have not demonstrated superiority of one SSRI over another. Fluoxetine, sertraline and fluvoxamine have all demonstrated effectiveness compared with placebo in the treatment of generalized anxiety disorder.<sup>[28][30]</sup> Fluoxetine, fluvoxamine and paroxetine have also been reported to be effective in the treatment of social phobia.<sup>[8], [28], [30]</sup> Although one study re-

ported that children and youth with separation anxiety disorder showed greater improvement when treated with fluvoxamine compared with placebo,<sup>[30]</sup> another study did not find any benefit of fluoxetine over placebo for separation anxiety disorder.<sup>[28]</sup> While data from open-label studies have been positive,<sup>[31][32]</sup> there are no controlled studies investigating citalopram or escitalopram for the treatment of childhood anxiety disorders. As a result, the selection of an SSRI in the treatment of childhood anxiety is based less on empirical evidence of efficacy and more on tolerability and family history of SSRI responsiveness among first-degree relatives with anxiety disorders.<sup>[33]</sup> SSRI medications used to treat anxiety disorders in children are generally well tolerated, and demonstrate a similar adverse effect profile as that described above in the treatment of depression. The cautions with respect to worsening suicidality associated with SSRI treatment are based on studies of children and youth with depression, not anxiety, as the primary treatment target. However, monitoring for suicidality among children and youth who have started on SSRI medication for an anxiety disorder may still be prudent. Children and youth treated with SSRI medication for anxiety disorders should be started at low initial doses with close monitoring for adverse effects and tolerability. Dosage can then be adjusted to achieve optimal treatment response while maintaining overall medication tolerability. Clinical experience suggests that anxious children and families may be very sensitive to adverse effects or changes in somatic symptoms. Addressing the potential for this sensitivity proactively, by providing psychoeducation regarding the potential for these adverse effects and their often transient nature, and by starting young patients at lower initial dosages, may help to increase overall tolerability for children and families.

## Key messages

- SSRIs may be considered early in the course of treatment for anxiety disorders if anxiety is severe or causing significant functional impairment, or if the child is unable to benefit from psychotherapy.
- Careful elicitation and documentation of physical symptoms of anxiety should be completed before initiating medication.
- To improve tolerability of medication for anxious patients, clinicians should include the following in their overall approach:
  - Psychoeducation
  - Lower starting dosages
  - Gradual titration to therapeutic dosages.

## Summary and recommendations

- When undertaken following an appropriate clinical assessment, and within the context of a comprehensive management plan, SSRI medications may be effective in the treatment of child and adolescent depression and anxiety disorders.
- Because depression in particular is associated with high rates of suicidal ideation, behaviour and completed suicide, untreated illness may be more harmful than appropriate use of SSRI medication.
- Before initiating pharmacotherapy, physicians should carefully elicit and document baseline depressive and anxious symptoms.
- Following medication initiation, patients should be closely monitored for potential adverse effects, including suicidal ideation and behaviour.

**TABLE 2**  
Use of selective serotonin reuptake inhibitors in the treatment of child and adolescent anxiety: Summary of randomized controlled trial data

Diagnosis	Medication	Author [reference], year	Participant age, years	Outcome
Generalized anxiety disorder	Fluoxetine	Birmaher et al [28], 2003	7–17	+
	Sertraline	Rynn et al [29], 2001	5–17	+
	Fluvoxamine	Research Unit on Pediatric Psychopharmacology Anxiety Study Group [30], 2001	6–17	+
Selective mutism	Fluoxetine	Black and Uhde [34], 1994	6–11	+
Social phobia	Fluvoxamine	Birmaher et al [28], 2003	7–17	+
		Research Unit on Pediatric Psychopharmacology Anxiety Study Group [30], 2001	6–17	+
	Paroxetine	Wagner et al [8], 2004	8–17	+
Separation anxiety disorder	Fluoxetine	Birmaher et al [28], 2003	7–17	Ns
	Fluvoxamine	Research Unit on Pediatric Psychopharmacology Anxiety Study Group [30], 2001	6–17	+

+ Positive outcome versus placebo; Ns No significant benefit of medication versus placebo

## Acknowledgements

This position statement has been reviewed by the Adolescent Health, Community Paediatrics, and Drug Therapy and Hazardous Substances Committees of the Canadian Paediatric Society, as well as by the Canadian Academy of Child and Adolescent Psychiatry.

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