



Michael Gordon
Glenn Melvin

Selective serotonin re-uptake inhibitors

A review of the side effects in adolescents

Background

Selective serotonin re-uptake inhibitors (SSRIs) are prescribed by general practitioners (GPs) for adolescents. GPs' prescribing patterns for SSRIs changed following warnings issued by United Kingdom and United States drug advisory bodies on the use of antidepressants in children and adolescents in 2003 and 2004, respectively. Recent studies shed further light on the safety profile of SSRIs with adolescents.

Objective

To provide a narrative review of the physical and psychiatric side effects of SSRIs as reported by adolescents. To provide GPs with practical advice regarding the prevalence and nature of side effects of SSRIs when prescribed for adolescents.

Discussion

The research literature suggests that adolescents taking SSRIs are at a small, but increased, risk of suicidal thoughts and behaviours. The prescribing GP needs to be aware of a number of potential side effects and interactions. Monitoring for common physical side effects and possible emerging suicidal ideas and behaviours, especially early in treatment, is recommended.

Keywords

adolescent psychiatry; selective serotonin re-uptake inhibitors; adolescent; adverse drug events; mental health



Selective serotonin re-uptake inhibitors (SSRIs) are a class of antidepressants that have been available since the late 1980s. The SSRIs act by selectively blocking the presynaptic serotonin transport proteins in the presynaptic neural membrane.¹ Monitoring of drug side effects is an important task, given they may be serious and also may be the reason for discontinuation.

It cannot be assumed that the side effects of SSRIs in adolescents will be the same as in adults. Adolescents have developmentally different pharmacodynamics and pharmacokinetics to adults. For example, tricyclic antidepressants are efficacious in adult depression, but do not work for adolescent depression.² Further, age has been shown to be a modifier in the expression of some side effects of antidepressants.³

General practitioners (GPs) are the predominant prescribers of SSRIs in Australia.⁴ Discussion of SSRI side effects specifically in adolescents is warranted given antidepressants are widely prescribed by child psychiatrists and paediatricians for adolescents.⁵ GPs may choose to initiate antidepressants or may be monitoring SSRI side effects when the SSRI has been initiated by a child psychiatrist or a paediatrician. A discussion on the efficacy or effectiveness of SSRIs in adolescents is outside the scope of this paper. This paper reviews the side effects of SSRIs from the published studies on adolescents treated for anxiety and depressive disorders.

Side effects

The reported side effects can vary between studies and individual SSRIs. Individual SSRIs differ from one another in their secondary binding to non-serotonergic receptors (eg. pronounced anticholinergic effect of paroxetine), active metabolites, excretion half-lives and inhibition of the hepatic cytochrome system.⁶

Many adolescent drug studies do not systematically collect information on side effects, instead, they offer open-ended enquiry into side effects.⁷ Most drug studies in adolescent populations are studies of medication efficacy and are not primarily designed to report side effects systematically,⁷ which limits the available data.

Non-psychiatric side effects

The most commonly reported SSRI side effects are physical rather than psychiatric, as shown in *Table 1*. Common physical side effects of fluoxetine detected within the large 'Treatment of Adolescent Depression Study' (TADS) were headache, nausea, vomiting, abdominal pain, insomnia and sedation.⁷



Table 1. Selective serotonin re-uptake inhibitor side effects in adolescents^{7,9,10,28,38,42}

Non-psychiatric side effects		Psychiatric side effects	Rare side effects
Most common	Other		
<ul style="list-style-type: none"> • Headache • Nausea • Vomiting • Abdominal pain • Dry mouth • Discontinuation syndrome 	<ul style="list-style-type: none"> • Sweating • Flushing • Weight changes • Sexual side effects • Flu-like symptoms • Aches • Rash and itchy skin • Epistaxis • Amotivation syndrome • Decreased projected growth 	<ul style="list-style-type: none"> • Insomnia • Sedation • Suicidal ideas and behaviours • Hypomania or mania (manic switching) • Akathisia • Agitation • Increased anxiety • Irritability • Hypersensitivity • Anger • Worsening of depression • Tremor • Crying 	<ul style="list-style-type: none"> • Serotonin syndrome • Hyponatraemia (probably more of an issue in the elderly) • Lowered seizure threshold

In studies of sertraline, the most common side effects were fatigue, impaired concentration, insomnia, drowsiness, restlessness, headache, gastric distress, sore throat and yawning.^{8,9}

In treatment of adolescent depressive disorder, 60% of participants experienced mild-to-severe side effects associated with the use of an SSRI.¹⁰ The high proportion of adolescents experiencing side effects contrasts with the modest discontinuation rate due to side effects for SSRIs, which is 5–10%.¹¹ Self-reported physical symptoms were found to decline over time across 3 months of treatment.⁷

In the TADS study, commonly reported side effects of SSRI such as insomnia (54%), headache (34%) and stomach pains (27%) were present before starting treatment.⁷ GPs should be alert to somatic baseline symptoms prior to starting an SSRI and consider whether somatic side effects differ significantly from baseline symptoms.

A potentially important side effect of SSRIs in adolescents is reduction in expected growth.¹² However, there is a lack of research to comment on this possible association.¹³ As a course of treatment for SSRIs usually lasts many months or longer, GPs are encouraged to monitor growth commencing with a baseline measurement prior to treatment initiation.

The rates of sexual side effects of SSRIs, including erectile dysfunction, anorgasmia, delayed ejaculation and decreased libido, are poorly described in the adolescent literature.¹⁴ The rates of sexual side effects of SSRIs, based on the adult literature, may be as high as 60%.¹⁵

Psychiatric side effects

Psychiatric side effects of SSRIs have been grouped into the mania spectrum (mania, hypomania, elevated mood), depression spectrum (aggravation of depression, crying, irritability, anger, hypersensitivity), agitation spectrum (agitation, akathisia, restlessness, nervousness, hyperactivity), anxiety and panic symptoms, tremor and ‘feeling spacy’.⁷

Antidepressant-induced manic switching is a single manic swing that is temporally related to antidepressant use, involving ‘the transition from depression into mania’.³ Manic switching is distinguished from rapid cycling, in which a patient with bipolar affective disorder has four or more distinct mood swings in a given year.¹⁶ Martin et al. report the rate of antidepressant-related manic switching to be 5.4%, with adolescents being particularly vulnerable.³ Evidence from randomised controlled trials (RCTs) in children and adolescents have suggested that the risk is $\leq 2\%$, at least in the short-to-medium term.¹¹

Mania spectrum symptoms are relatively common, although mild symptoms are much more prevalent than manic switching.⁷ It has been found from retrospective chart reviews that fluoxetine can cause irritability and ‘hypomania-like effects’,¹⁷ and sertraline has been reported to cause behavioural activation.¹⁸ The presence of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), manic symptoms requires the cessation of the antidepressant and urgent psychiatric review. The GP should be particularly alert to this possibility of antidepressant-induced manic switching if there is a family history of bipolar affective disorder or the presence of psychotic depression.¹⁹

Increased suicidal ideation, suicidal behaviour and suicide

Increased suicidal behaviours have been reported in case studies with fluoxetine in adolescents since 1991,²⁰ although systematic investigation of this association has only been reported since 2004.²¹

In 2004, the United States Food and Drug Administration (FDA) commissioned an assessment of the manufacturers’ data from antidepressant trials involving five SSRIs.^{21,22} These trials were RCTs for the treatment of children and adolescents with major depressive disorder, obsessive compulsive disorder, generalised anxiety disorder, social anxiety disorder and attention-deficit hyperactivity disorder.^{21,22}



Hammad reported to the FDA that for patients less than 18 years of age, there is an increased risk of suicidal thoughts or behaviours of 4% with an antidepressant (SSRI or another newer antidepressant) compared with 2% with placebo.²¹ There were no suicides across the 4 582 children or adolescents.^{21,22} On the basis of Hammad's findings, the FDA instructed the drug manufacturers to put a black-box warning on all antidepressants.²³ Hammad's findings have been challenged,^{24,25} with other authors finding lower levels of risk with antidepressants,²⁶ or no risk in the case of fluoxetine.²⁷

The most recent Cochrane review of this topic, published in 2012, found that across 17 RCTs of newer antidepressants for child and adolescent psychiatric disorder (N = 3 229), the risk ratio of a suicide-related outcome (using the Columbia Classification Algorithm of Suicide Assessment) was 1.58.²⁸ That is, there was an increased risk of suicide event by 58% in adolescents taking newer antidepressants, as compared with placebo.²⁸ There was no significant increase in suicide-related outcomes for individual SSRIs (paroxetine, fluoxetine, sertraline, citalopram or escitalopram).²⁸ Where suicidal ideation was measured, two RCTs showed no difference between antidepressant (where fluoxetine and escitalopram were examined) and placebo.²⁸

Epidemiological studies have been used to explore the link between antidepressant prescription rates and suicide rates using large population samples. The consensus from these studies is that the suicide rate is inversely associated with the SSRI prescription rate.^{24,29} One interpretation is that at a population level, antidepressant prescriptions for adolescents are associated with a lower suicide rate. However, epidemiological studies inherently have many confounding factors, and are a weaker level of evidence for causality than RCTs. It has been argued that the interpretation of epidemiological studies may confuse correlation with causation, and further do not address the heterogeneous reasons for prescribing antidepressants.³⁰

Toxicological assays, which assessed for the presence of any antidepressant, have been conducted in samples from adolescents who died by suicide. In toxicological studies the presence of antidepressants varied from 3% to 10%.^{31,32} While this suggests that antidepressants are uncommonly prescribed for, or at least taken by, adolescents in the days and weeks prior to suicide, it has been also argued that suicide may have been triggered by antidepressant withdrawal, and so was not detected by toxicological screening.³⁰ This argument may not hold for fluoxetine, which has a long half-life.

Observational studies are another way of linking antidepressants and adolescent suicidal behaviours and suicide. Observational studies have used prescription databases and joined them with clinical databases. Collectively, observational studies have reported an intriguing finding. The highest risk of suicide attempt across all ages may be in the month before starting the antidepressant³³ and in the first 9 days of starting treatment,³⁴ with the risk in adolescents declining over 6 months of continued treatment.³⁵

Taken together, these findings suggest that adolescents taking SSRIs are at small, but increased, risk of suicidal thoughts and behaviours, at least in the short-term. This finding speaks to the importance of close monitoring of the adolescent for emerging suicidal thought and behaviours

after starting an antidepressant. This is in keeping with the recommendation of the combined statement from the colleges of general practitioners, psychiatrists and physicians response to the black-box warning from 2005.³⁶

Other side effects

Serotonin syndrome (SS) – a rare, but potentially fatal condition of excess serotonin – has been described in adolescents.³⁷ SS arises from serotonergic toxicity in the brainstem and spinal cord.^{38,39} SS presents acutely with serious cardiovascular, gastrointestinal, psychiatric and/or neurological symptoms including tremor, hyper-reflexia, clonus, autonomic instability, agitation, diaphoresis, mydriasis and agitation, progressing onto delirium and, if untreated, death.³⁸ Drugs that can interact with SSRIs to cause SS include other antidepressants, sumatriptan, St John's Wort, ginseng, tramadol, metoclopramide and dextromethorphan.³⁸ Switching SSRIs necessitates a gradual withdrawal of the first agent and may require a drug-free period before initiating the next antidepressant to reduce the risk of SS.⁴⁰ The treatment of SS requires the abrupt cessation of the serotonergic agents and urgent referral to the Emergency Department for supportive measures such as paralysis and active cooling, and, as clinically determined, oral cyproheptadine (a serotonergic receptor blocker).³⁹

Withdrawal reactions

Serotonin discontinuation syndrome has been described in children.⁴¹ Serotonin discontinuation syndrome is a condition in which the patient experiences unpleasant physical withdrawal symptoms if the SSRI is stopped abruptly. Symptoms include dizziness, nausea, vomiting, tiredness, headache, gait and sleep disturbance.⁴² These are reported to occur within 1–3 days after stopping the SSRI in those antidepressants with a short half-life.⁴² Gradual tapering of SSRIs, rather than abrupt cessation, is recommended.⁴³ It should be noted, however, that a small minority of young people stopping SSRIs require a very extensive period of weaning over many weeks or even months.

Key points

- SSRIs have been shown to increase suicidal thoughts and behaviours in adolescents. Parents and the adolescents should be warned to look out for these symptoms. Adolescents should be monitored, initially at least weekly, to inquire about the possible side effects.
- GPs should be alert to the risk of manic switching. Those at increased risk have psychotic depression or a family history of bipolar affective disorder.
- The GP should be aware of potential drugs that could lead to serotonin syndrome when co-prescribed with an SSRI.
- Should the GP be prescribing SSRIs for many months or longer, monitoring the growth of their patient is advised.

Authors

Michael Gordon MBBS, MPM, MD, is Consultant Psychiatrist, Unit Head Early in Life, Monash Health Early in Life and Adjunct Senior Lecturer, Monash University, Melbourne, VIC. Michael.Gordon@southernhealth.org.au

Glenn Melvin MPsych, PhD, is Senior Lecturer, Centre for Developmental Psychiatry & Psychology, School of Psychology & Psychiatry, Monash University, Melbourne, VIC

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correspondence afp@racgp.org.au