Management of Side-Effects of Selective-Serotonin Re-Uptake Inhibitors in Children and Adolescents

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Abstract: Background: Selective serotonin reuptake inhibitors are the recommended and most commonly used antidepressant medications for children and adolescents. This class of medications has been considered generally safe with few significant treatment emergent adverse reactions that generally abate over time. All antidepressants carry the precautionary warning for potential increase in suicidal ideation and close monitoring is recommended. Management of side effects of this widely used class of drugs is an important aspect of any medical practice that cares for children and adolescents.

Objective: To provide a succinct and clinically relevant review of side effects of SSRIs and their management in clinical practice.

Method: A literature search was done of relevant published articles in English language in the Medline database.

Results and Conclusion: Gastrointestinal side effects are most common with the use of SSRIs and generally are tolerable and do not need discontinuation of the medication. Cardiovascular side effects are uncommon; however, prolonged QT syndrome has been reported. In utero exposure results in a constellation of signs and symptoms in the newborn called poor neonatal adaptation syndrome. In utero exposure also is associated with teratogenicity. Although less frequent, symptoms suggesting behavioral activation, switching, serotonin syndrome and discontinuation or withdrawal syndrome need careful evaluation and management.

Keywords: Selective serotonin reuptake inhibitors, behavioral activation, bipolar switching, serotonin syndrome, discontinuation syndrome, suicide ideation.

1. INTRODUCTION

Depression is prevalent in the pediatric population, with reported rate of 8% of all teenagers, who meet diagnostic criteria for depression [1]. Recently, there has also been an increase in children and adolescents presenting to their pediatricians with concerns of mental health disorders and visits resulting in a prescription for an antidepressant [2]. For patients with mild depression, close follow up and support by the primary care physician is recommended [3, 4]. Cognitive behavioral therapy [CBT] can also be initiated for mild forms of depression. Combined therapy with CBT and an antidepressant medication is recommended for patients with moderate to severe depression [3-6]. Selective Serotonin Reuptake Inhibitors SSRIs are the most commonly prescribed drugs for the treatment of depressive disorders in children and adolescents due to their proven efficacy and tolerability. Fluoxetine and escitalopram are specifically approved to treat major depressive disorder while sertraline, fluvoxamine and fluoxetine are approved to treat obsessive compulsive disorder [7]. Tricyclic antidepressants are rarely used in the pediatric population due to their unfavorable side
effect profile. Bupropion, mirtazapine, and buspirone have been studied in childhood depressive disorders but have not shown to be effective [6, 7].

SSRIs are the drugs of choice when treating pediatric patients with depression. Fluoxetine is the most researched and tends to be the SSRI of choice when initiating treatment with SSRIs due to high efficacy and tolerability [3-8]. For patients with poor response to fluoxetine, sertraline, escitalopram, and citalopram have all been shown to be effective in pediatric depression [8]. SSRIs act by blocking the reuptake of serotonin into pre-synaptic neurons and enhance serotonergic neurotransmission [9-15].

2. SIDE EFFECTS

Several side-effects of SSRI medications [such as nausea] are dose related, and likely due to serotonergic effects [5-HT3 receptor stimulation] and can usually be alleviated by reducing the dose of the SSRI [11-14]. Some other side-effects such as skin reactions are not dose related and are likely idiosyncratic. Similarly, certain system side-effects are noted with certain SSRI agents; fluvoxamine is associated with the highest frequency of GI disturbances, while sertraline and fluoxetine are more often associated with anxiety, agitation, and insomnia [11-14].

2.1. Gastrointestinal Side Effects

Treatment emergent gastrointestinal side effects are common with the use of SSRIs, including nausea, vomiting, diarrhea, flatulence, decreased appetite, dry mouth and heartburn [11, 13, 16, 17]. These side effects predominantly emerge when the treatment is initiated and whenever dosage is increased, are mostly transient and resolve over a period of few weeks. Although weight loss is often seen as a side effect of SSRIs, in a small subset of patients, weight gain is noted. Such weight gain may be difficult to manage by decreased caloric intake and increased physical activity [10, 11, 18, 19]. In some instances, persistent weight gain may necessitate discontinuation of the drug.

2.2. Behavioral Activation

It is important to recognize signs and symptoms of behavioral activation in patients on SSRIs and other classes of antidepressant drugs [20-25]. Treatment emergent behavioral activation is relatively more common in children and adolescents when compared to adults, incidence ranges from 20% to 50% [13, 26, 27]. Like most other side effects associated with the use of SSRIs, it is also seen most commonly during the first few days to weeks of initiation of the SSRIs and when the dose is increased [11, 13]. The signs and symptoms of behavioral activation include, dysphoria, cognitive difficulty, nervousness, agitation, and akathisia [11-13, 16, 20]. Akathisia is characterized by an uncomfortable feeling of restlessness. In a few cases, the use of SSRIs has been associated with the emergence of hypomania, mania or psychotic reactions [9, 21, 26]. Although, such symptoms may suggest possibility of a bipolar disorder, behavioral activation is neither an indication nor predictive of a bipolar disorder [9, 21, 26]. Symptoms of behavioral activation may depend on the degree of severity of symptoms; in those with persistent and severe symptoms, it may be necessary to gradually taper and discontinue the SSRI [18, 26, 28].

2.3. Switching (or Bipolar Switching)

Switching or bipolar switching, although infrequent, is a significant treatment emergent adverse reaction seen in patient on SSRIs, characterized by a change in the mood state from depressed mood to hypomania or mania [12-14, 25]. This is in contrast to behavioral activation, in which, the mood state remains the same; in other words, in switching, the caregivers or patient recognize the symptoms as new, not present prior to the initiation of the SSRI agent [26]. Another differentiating feature between behavioral activation and switching is the temporal course of symptom emergence. The symptoms of switching emerge several days to weeks after initiation of SSRIs and may not resolve after the SSRI agent is discontinued [9, 13, 29]. Switching is not yet well studied in the pediatric population but some studies in adults suggest that the risk of switching is similar in those patients treated with SSRIs and those who are not [30-34]. One such study found that certain clinical features of bipolar disorder, such as younger age of onset, are associated with a greater risk of switching [32]. The emergence of symptoms suggestive of a bipolar disorders necessitates further diagnostic evaluation, and discontinuation of
the SSRI agent [26, 27, 30, 31]. In addition to the emergence of symptoms suggestive of a bipolar disorder, children and adolescents when effectively treated with SSRIs for depression or anxiety, may also manifest symptoms of other underlying comorbid behavioral disorders. This will indicate need for further diagnostic evaluation for the comorbid condition.

2.4. Serotonin Syndrome

Serotonin Syndrome [SS], a serious adverse event associated with SSRI use, is a manifestation of excessive serotonergic activity in the central nervous system [13, 14, 23, 25, 35]. The risk for emergence of SS is relatively higher when the dose of an SSRI agent is high or when multiple serotonergic drugs are used together [11, 13, 17, 26, 36, 37]. Although infrequent, it is important to recognize the emergence of signs or symptoms of SS (Table 1) because early and prompt treatment is critical to prevent serious complications (Table 2) and possible death [13, 23]. Proper management of SS includes immediate discontinuation of serotonergic medications, supportive care and sedation with benzodiazepines. More severe cases may require the use of cyproheptadine [38]. With proper care SS usually resolves in 24 hours. However, in SS caused by medications with long half-lives, like fluoxetine, symptoms may persist beyond this time frame [38].

Table 1. Signs and symptoms of serotonin syndrome.

<table>
<thead>
<tr>
<th>Agitation</th>
<th>Confusion</th>
<th>Diaphoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated blood pressure</td>
<td>Excessive sweating</td>
<td>Fever</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Incoordination</td>
<td>Muscle rigidity</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Seizures</td>
<td>Shivering</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Tremors</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Complications and potentially adverse outcomes of serotonin syndrome.

<table>
<thead>
<tr>
<th>Coma</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Seizures</td>
</tr>
</tbody>
</table>

2.5. Withdrawal or Discontinuation Syndrome

Abrupt discontinuation after several weeks of use of an SSRI agent may result in signs and symptoms of drug withdrawal (Table 3) [9, 11, 26, 36, 39]. Discontinuation syndrome tends to occur more often with SSRIs with a shorter half-life when compared to those with a long half-life [11, 18, 23, 40, 42]. It is also more likely to occur after a longer duration of use of an SSRI agent [11, 18, 23, 40]. Discontinuation syndrome should be differentiated from behavioral activation. In most instances, the symptoms of withdrawal from an SSRI agent are seen within 2-5 days of lowering the dose or discontinuation [10, 11, 26, 30]. In case of fluoxetine, with a long half-life, the symptoms of withdrawal may not be apparent until after 7-10 days of discontinuing the drug [10, 11]. In most cases, no active intervention is indicated other than observation and reassurance of the patient. Most symptoms generally resolve within 1-2 weeks [13]. In a few cases, when symptoms persist or are severe, it may be necessary to re-start the SSRI agent at a lower dose and continue for a short period, followed by gradual tapering and discontinuation [13, 28, 41-43]. Some patients may develop suicidal ideation with discontinuation of treatment. In order to avoid or lessen the symptoms of discontinuation syndrome, SSRI dosages are tapered over 2-4 weeks [44, 45]. There are no controlled data to recommend a pattern of dose reduction or the actual dose to which SSRIs be reduced [11-14]; instead it is left to the judgment of the clinician, the dose at which symptoms occur, the availability of dosing options, availability of monitoring procedures among other factors.
Table 3. Signs and symptoms of SSRI discontinuation syndrome.

<table>
<thead>
<tr>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Dysphoric mood</td>
</tr>
<tr>
<td>Electric shock like sensations</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Increased sweating</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Sleep difficulty</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

2.6. Suicide Ideation

The issue of suicidality with the use of SSRIs and other antidepressants in the treatment of depression is a subject of much debate. In 2004, the United States Food and Drug Administration (FDA) conducted a pooled analysis of placebo-controlled trials in children and adolescents with major depressive disorder, obsessive compulsive disorder or other systematic psychiatric disorders. The analysis comprised a total of 24 short-term trials of 9 antidepressant drugs [including SSRIs] in over 4400 patients. Based on the findings of the analysis, the FDA issued a warning for all antidepressants regarding increased risk of suicidality among children and adolescents being treated with antidepressants. The FDA recommended that patients placed on antidepressants be monitored closely, especially during the first few days to week for any signs of increased suicidality. Further studies have shown that the risk of increased suicidality is similar in all [SSRIs [46, 47]. One study found that rates of deliberate self-harm was twice as large in patients who started with high-dose therapy versus those who started at lower initial doses [48, 49].

Multiple subsequent studies have not been able to conclusively show that antidepressant use in children and adolescents is associated with increased risk for suicidality [10, 11, 16, 17, 26, 28, 37, 50, 51]. Specifically, the Treatment for Adolescents with Depression Study (TADS) showed decreased suicidality in all treatment groups: fluoxetine alone, CBT alone, and combined fluoxetine-CBT treatment [52]. It should also be noted that untreated depression is a risk for suicidal behavior and providers should weight the risks and benefits of antidepressant therapy carefully before initiating treatment.

More recently, a systematic review of double-blinded, placebo controlled trials looked at the effects of SSRIs and SNRIs on healthy adult volunteers [53]. The study was done to quantify the risk of harms related to suicidality and violence when administering SSRI or SNRIs to healthy people. The study concluded that usage of SSRIs and SNRIs double the occurrence of events related suicide and violence in healthy adults. In another recent study, Sharma et al. [2016] conducted a systematic review and meta-analyses on 23 different studies of how 5 different antidepressants, duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine, were associated with mortality, suicidality, akathisia, and aggression [54]. The authors concluded that all four outcomes were not significantly increased in adults. However, in children and adolescents, the risk of suicidality and aggression doubled.

2.7. Cardiovascular Side Effects

Cardiovascular side effects associated with SSRIs are uncommon; however, prolonged QT syndrome has been reported with higher doses and in cases of SSRI overdose [9, 10, 13, 18, 30]. Adverse cardiac events, including ventricular arrhythmias, cardiac arrest and sudden death were found to be three to four times higher in those patients on citalopram and escitalopram than fluoxetine [55]. Polypharmacy of psychotropic medications including antidepressants, ADHD medications, and antipsychotics is becoming more common in pediatric patients. QT prolongation is a known side effect of many of these medications and the risk of adverse cardiac events may be compounded with the use of more than one of these medications [55, 56]. It is important to keep in mind that children with psychiatric disorders have been shown to have greater sympathetic activity, heart rate, and QT variability than those without psychiatric diagnoses, potentially increas-
Side-Effects of Selective-Serotonin Re-Uptake Inhibitors

2.8. Effects of In Utero Exposure to SSRIs

Numerous studies provide evidence that the use of SSRIs by mothers during late pregnancy is associated with signs and symptoms affecting multiple systems [59]. These include respiratory difficulties, cyanosis during feeding, and jitteriness. Other self-limited signs and symptoms include irritability, persistent crying, shivering, increased muscle tone, sleep difficulties, and sometimes seizures. This collection of signs and symptoms has been termed poor neonatal adaptation syndrome. In addition to the acute effects seen in neonatal period in utero exposure to SSRIs has also been associated with teratogenicity.

Reefhuis et al. [2015], used a Bayesian analysis on previous studies that assessed the association between maternal prenatal use of specific SSRIs and birth defects that were reported to the US National Birth Defects Prevention Study [60]. Based on the analysis, sertraline, which was the most commonly used SSRI in the study was not significantly associated with birth defects. Fluoxetine and paroxetine, however, were associated with multiple types of birth defects. Some birth defects occur 2-3.5 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy.

The evidence supporting or refuting adverse neurobehavioral or neuromotor outcomes in infants and children with in utero exposure to SSRIs is equivocal, with most studies suggesting no short term or long term adverse outcomes [59]. Handal, et al. [2015] conducted a population-based prospective pregnancy cohort study that aimed to elucidate if there is an association between prenatal exposure to SSRI and motor development in children. Result was measured by maternal assessment of gross and fine motor development through ASQ questionnaires when the child reached 3 years of age. Prolonged prenatal exposure to SSRIs was weakly associated with delay in fine and gross motor development in children at 3 years of age [61]. A prospective study found that infants born to a euthymic mother who took serotonin reuptake inhibitors [SRIs] in the third trimester had poorer motor development, lower 5- minute APGAR scores, and shorter mean gestational age compared to infants born to a euthymic mother who did not take SRI in the third trimester [62].

2.9. Sexual Side Effects

Sexual side effects of SSRIs are poorly studied in adolescents. One small chart review study found that 23% of adolescents experienced sexual dysfunction secondary to SSRI use but it is hypothesized that this number may actually be closer to the rate of sexual dysfunction seen in adult patients on SSRIs which may be greater than fifty percent [63]. Sexual side effects include delayed orgasm, anorgasmia, and decreased libido [14, 15, 21-23]. Most of these non-life threatening side effects tend to diminish with time. SSRIs have been used to treat premature ejaculation in some cases because it delays orgasm.

2.10. Sleep Disturbance

The use of SSRIs has been shown to reduce the total duration of sleep as well as the duration of sleep in the rapid-eye-movement phase [10, 16, 18, 23, 40]. Difficulty with sleep is a relatively common treatment emergent side effect of SSRIs. The major symptoms of sleep disturbance include difficulty initiating or falling asleep, vivid dreams and daytime drowsiness [10, 16, 18]. In most cases the symptoms improve with time. In those with persistent symptoms, administration of the SSRI in the morning along with improved sleep hygiene has been shown to be effective. In a few cases, use of a sleep aid such as melatonin is indicated.

2.11. Other Side Effects and Precautions

Other less frequently reported side effects with the use of SSRIs include increased yawning, in-
creased sweating, gynecomastia, and bleeding tendencies (Table 4) [10-13, 16, 17, 27, 28].

Table 4. Other side effects of SSRIs.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased yawning</td>
<td>Improves with time</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>May be severe and necessitate changing to a different SSRI, use of terazosin, or rarely discontinuation of all SSRIs is needed</td>
</tr>
<tr>
<td>Mammoplasia in girls</td>
<td>May take several months to resolve after discontinuation the SSRI</td>
</tr>
<tr>
<td>Gynecomastia in boys</td>
<td></td>
</tr>
<tr>
<td>Syndrome of inappropriate antidiuretic hormone secretion</td>
<td>Discontinue the SSRI</td>
</tr>
<tr>
<td>Increased bleeding tendency</td>
<td>Discontinue the SSRI</td>
</tr>
</tbody>
</table>

There is an increased risk of adverse events with the use of SSRIs in some patients (Table 5) that requires careful consideration of benefits versus risk before considering the use of an SSRI [11, 13]. SSRIs should not be used concomitantly with monoamine oxidase inhibitors [MAOIs] and should be used with extreme caution if other serotonergic agents are also being used. Since SSRIs are metabolized by cytochrome P450, interactions with concurrent medications should be assessed prior to initiation [11, 13].

Table 5. Increased risk of adverse events with the use of SSRIs.

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese or significantly overweight patients</td>
</tr>
<tr>
<td>Underlying liver disease</td>
</tr>
<tr>
<td>Underlying kidney disease</td>
</tr>
<tr>
<td>History of atrial tachycardia</td>
</tr>
<tr>
<td>History of cardiac conduction disorders</td>
</tr>
<tr>
<td>History of excessive daytime sleepiness</td>
</tr>
</tbody>
</table>

CONCLUSION

SSRIs are the drugs of choice and most widely used medications for the treatment of depressive disorders in children and adolescents. SSRIs have shown to be generally safe and have a favorable side effects profile. Although most common treatment emergent adverse reactions improve within the first few weeks of use, some side effects, although less frequent deserve specific consideration. These include behavioral activation, bipolar switching, and the potential for increased suicidal ideation, all of which may necessitate discontinuation of SSRIs.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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All authors have contributed substantially to the design, performance, analysis, drafting of the manuscript, revisions of the manuscript and final approval of the manuscript.

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