SSRI adverse events: How to monitor and manage

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Abstract
Antidepressants are efficacious for pediatric major depressive disorder, obsessive compulsive disorder (OCD), and non-OCD anxiety disorders. Antidepressants should be used in an evidence-based fashion, with frequent monitoring for side effects, especially when initiating treatment and adjusting dosage. With diligence to appropriate prescribing and monitoring, the benefits of therapy outweigh the potential of treatment related risk.

Introduction

Although children and adolescents tolerate selective serotonin reuptake inhibitors (SSRIs) well, many parents and clinicians are hesitant to prescribe them, given concerns, both realistic and not, about possible side effects. There is a clear need for effective and safe medications to treat disabling disorders such as depression, given that suicide (often associated with depression) represents the third leading cause of death in adolescents (National Center for Health Statistics, 2001). Although the methodology and terminology for addressing adverse effects has not been standardized among clinical trials, consistent rates of 3–12% of those youths on active drug discontinue treatment due to adverse events (Cheung, Emslie, & Mayes, 2005). Further, the recent controversies about SSRI use point to a clear need to assess risks versus benefits of SSRI use.

Neuropsychiatric side effects
Adverse effects that most often result in medication changes are the neuropsychiatric side effects such as behavioural activation, enuresis (Herguner, Kilincasla, Gorker, & Tuzun, 2007), tremor, tics, apathy and sedation.

Behavioural activation is the most concerning of all adverse effects for most clinicians. Behavioural activation may present at any time during treatment but is most common in the initial two weeks and is often dose-dependent, warranting use of the lowest possible starting dose. Connotations of behavioural activation (Goodman, Murphy, & Storch, 2007) differ among clinicians, but mainly the children are described as having a worsening of their clinical presentation, and/or being more hyperactive, impulsive, talkative, or ‘mean’ (Carlson, 2005; Go, Malley, Birmaher, & Rosenberg, 1998; Guile, 1996; Riddle et al., 1991). This activation syndrome implies (at least transient) behavioural toxicity, whereas the energizing effects following initiation of antidepressant therapy suggests that patients are along the path toward recovery but their mood has yet to respond.

Akathisia is often difficult to distinguish from activation syndrome. In this instance, clinical parallels between antipsychotic-induced akathisia and antidepressant-induced activation exist, with SSRIs having been implicated in akathisia on occasion. In this instance, motor restlessness must not be mistaken for worsening of the underlying disease and treated with an increased dose when the correct response is to lower the dose or switch to a different medication.

Mania can be induced by any antidepressant in susceptible individuals (Faedda, Baldessarini, Glovinsky, & Austin, 2004); compared to the adult literature, however, the evidence for antidepressant-induced mania among children is less consistent (Craney & Geller, 2003). State-shifts into mania may be recognizable by qualitatively distinct features that include euphoria, grandiosity and hypersexuality (Kowatch, Youngstrom, Danielyan, & Findling, 2005). This type of ‘behavioural activation’, which can include behaviours that lead the child to harm himself or others, may be more likely in those with personal or family history of bipolar disorder as well as those children with comorbid anxiety disorders (Faedda et al., 2004). During this period of behavioural activation, youths are at greatest risk.
of acting on impulsive urges that may result in harm of self or others. Close monitoring for these symptoms is important throughout therapy but especially critical during the first weeks after initiation of medication treatment or subsequent dosage increases (Goodman et al., 2007). Fortunately, upon detection, activation symptoms usually abate after decreasing or discontinuing the medication.

**Frontal lobe amotivational syndrome** is characterized by apathy, affective blunting, and forgetfulness and is more likely to be found in cases of SSRI therapy of several months’ duration. It is more commonly seen with higher dosages and unfortunately does not seem to dissipate with time. Clinicians may mistake this presentation as a return of depressive symptoms and increase the dose, whereas the best treatment is to lower the dose. Generally, depressive symptoms, such as irritability and sadness, are absent. It is therefore critical to differentiate apathy from depression or sedation (Garland & Baerg, 2001; Reinblatt & Riddle, 2006). If one is uncertain about the apathy being attributed to either the SSRI or simply being part of the clinical depression, increasing the SSRI dose to assess for either improvement or worsening of the symptoms is one option. If symptoms worsen, then apathy was likely a side effect of the SSRI and not part of the depression. The next logical step would be to decrease the SSRI to a dose lower than the original dose. A lower dose, however, sometimes may not be feasible because it may lead to a sub-therapeutic range to target the depression or anxiety. In those cases, augmentation with another antidepressant that has noradrenergic or dopaminergic reuptake inhibition properties may be an alternative, although not studied in pediatric populations. On the other hand, one may opt to cross-taper the SSRI with another antidepressant.

**Suicidal ideations or behaviours as adverse effects**

*The path to the black box warning*

The observation of mild increase risk of suicidal ideation on antidepressants in large clinical trials has resulted in intense debate about the role of antidepressant medication-induced activation in the initiation or worsening of suicidal ideation or behaviours. In 2003, the Medicines and Healthcare Products Regulatory Agency, the British counterpart of the FDA, banned the use of antidepressants, except fluoxetine, in children and adolescents (MHRA, 2003). In the first meta-analysis that included 23 placebo-controlled trials evaluating the effectiveness of antidepressants in depressed youth, Hammad, Laughren and Racooisin (2006) found a modest, but statistically significant increased risk of suicidality. The finding of elevated suicidality was independent of the underlying psychiatric diagnosis. Because of this possibility of increased suicidal behaviour, the FDA issued a black box warning in 2004 regarding suicidality for all antidepressant medications in the pediatric (<18 years) population. None of the approximately 4,000 pediatric subjects in these trials committed suicide although 4% of these individuals exhibited an increase in suicidal-like behaviours compared to 2% on placebo (Hammad et al., 2006). A recent FDA report also found an increase in suicidality among young adults up to 25 years of age. Although the increased risk was relatively small in magnitude, this should be kept in mind when starting an antidepressant.

Jick and colleagues conducted a matched case control study in a base population of nearly 160,000 individuals in the practices of general practice physicians in the UK (Jick, Kaye, & Jick, 2004). The relative risk for suicidal behaviour and completed suicides was significantly higher for the first 1–9 days of antidepressant treatment compared to after 90 days on medication. The FDA analysis of the extant pediatric clinical data did not reveal similar differences in rates of suicidality when early and late phases of treatment were compared. Some data suggest that suicidality may increase during the period of decreased usage, as post-mortem data have shown that the majority of youth suicide victims have no detectable antidepressant levels in their bodies (Leon et al., 2006). There is more concern with paroxetine and venlafaxine (those with shorter half-lives) in regard to treatment of emergent suicidality, and these medications should be used with caution in youths. The FDA has recommended that those started on antidepressants should be monitored appropriately and observed closely for worsening of symptoms, suicidality and unusual behaviours. In addition, patients and families should be informed of the need for monitoring and that medication and/or dose adjustments should be only made by the physician. In 2004, the prescription of antidepressants in the population changed from a moderately increasing trend in a 10-year period to a steep decline within a six-month period, reaching its lowest point July of 2004 (two months before the black box warning for SSRIs was established) (Nemeroff et al., 2007; Libby et al., 2007). In parallel to this prescribing trend, suicide trend data documented a decline in youth suicide rates in the USA following the introduction of SSRIs (Olson, Shaffer, Marcus, & Greenberg, 2003) with a subsequent increase following decreased prescribing rates after antidepressant labelling changes (Gibbons et al., 2007).

*Risk related to diagnosis.* In a subsequent analysis, Bridge and colleagues identified 27 randomized
placebo-controlled trials (including the 23 in the Hammad study) comparing second generation antidepressants versus placebo in children and adolescents meeting DSM-IV criteria for either MDD \((n = 3430)\), OCD \((n = 718)\) or non-OCD anxiety disorders \((n = 1162)\). They concluded that efficacy appears greater for non-OCD anxiety disorders (number needed to treat \((\text{NNT}) = 10\)) and for OCD \((\text{NNT} = 6)\) and more modest for MDD \((\text{NNT} = 3)\), whereas the NNH (number needed to harm based on suicidal risk) was 143, 200, and 112, respectively. They concluded that the balance is in favour of benefit over harm (Bridge et al., 2007). Others have reported that antidepressant-induced mania was much higher in those youths with bipolar risk factors (44–50%) (Baumer et al., 2006; Faedda et al., 2004), than those with depressive disorders or OCD (22%) (Wilens et al., 2003). Those with bipolar diathesis (diagnosis, subsyndromal or family history) were also reported to have a higher risk for suicidality (14–25%), (Baumer et al., 2006; Faedda et al., 2004). Of note, these studies were not RCTs and secondly, many of the studies analysed by the FDA excluded bipolar disorder for study inclusion. Nonetheless, screening for bipolar risk is recommended and increased monitoring for self harm behaviours is prudent. Although there are risks related to antidepressant use in the context of inadequate monitoring or aggressive dosing, greater risks exist for not treating youth depression.

**Risk related to antidepressant choice.** With respect to efficacy, only three of 15 antidepressant trials submitted to the FDA for pediatric depression demonstrated superiority of drug over placebo (Hammad et al., 2006). Fluoxetine showed the most consistent superiority over placebo in studies of pediatric depression and is the only one to receive FDA labelling for pediatric depression. One trial of citalopram was positive in pediatric depression. When the data from two separate sertraline trials were pooled, drug was superior to placebo in pediatric depression. In age-stratified analysis of children, only fluoxetine showed benefit over placebo younger than 12 years old with MDD (Bridge et al., 2007). In contrast to outcome in pediatric depression, trials in pediatric OCD with fluoxetine, sertraline and fluvoxamine were all positive. The suicidality signal was not limited to a particular chemical class of antidepressants: it occurred with SSRIs, the SNRI venlafaxine and atypical antidepressants. It should be noted that meaningful statistical inferences could not be drawn from individual trials because their sample sizes and corresponding number of adverse behavioural events were not large enough. The majority, 13 studies, showed an elevated suicidal risk ratio ranging as high as 10.1 times placebo for one venlafaxine trial and 6.6 times placebo for one paroxetine trial (Hammad et al., 2006). Notably, venlafaxine may have a higher tendency to cause behavioural activation in some children, particularly those with comorbid ADHD (Manassis, 2007).

**Comorbid disorder and/or evolving psychopathology** may become more apparent after successful SSRI treatment, yet this aspect may confound the therapeutic approach if not given adequate attention. Given the myriad, albeit uncommon list of adverse effects associated with SSRIs, one could easily confuse a comorbid symptom with an adverse effect. A child may have been so depressed or anxious that these symptoms could mask symptoms related to other comorbid disorders, such as ADHD or conduct problems. This evolving psychopathology (Walkup & Labellarte, 2001) refers to the evolution of psychological states that is probably related to the child’s innate psychiatric vulnerability. An open discussion with the family about this potential for new or comorbid psychopathology to emerge during the course of treatment should instill greater confidence in the treatment plan and consequently improve compliance.

**Maturation.** Susceptibility to, and nature of, SSRI-induced behavioural side effects may be a function of brain maturation and vary according to the age of the patient (Gross et al., 2002) with younger patients being at highest risk.

**Pharmacogenomics.** Individual susceptibility to SSRI side effects may reflect genea drug interactions. A study in adults found that a polymorphism in the serotonin transporter gene confers a greater risk of side effects to SSRI therapy (Perlis et al., 2003). More recently, a team has examined 68 genes in 1915 adults meeting DSM-IV MDD criteria. They identified two markers in two genes, GRIA3 and GRIK2 that corresponded to a significant increased risk of developing suicidal thoughts while taking citalopram. Participants with the GRIA3 variation had nearly double the risk of developing suicidal thoughts, and participants with the GRIK2 variation showed an eight-fold increase in risk. In the rare cases of participants carrying both markers there was a 15-fold increase in risk of developing suicidal ideations. These findings, if replicated, may shed light on the biological basis of this potentially dangerous adverse event and help identify patients at increased risk in the future (Laje et al., 2007).

PSYCHOTHERAPY AS A POWERFUL TOOL WHEN USED IN CONJUNCTION WITH ANTIDEPRESSANTS. In addition to specific approaches regarding medication management, psychotherapy in the management of depression may reduce the incidence and attenuate the magnitude of behavioural side effects that could
lead to suicidality. Recently, the NIMH-funded TADS study evaluated the effectiveness of fluoxetine alone, cognitive behavioural therapy (CBT) alone, CBT and fluoxetine together and clinical management with placebo, in 439 patients between the ages of 12 and 17 years meeting DSM-IV criteria for mild-to-severe MDD. Despite the fact that suicidality improved markedly across all the treatment conditions, suicide events were twice as common in patients treated with fluoxetine alone than with the combination treatment or CBT alone. The authors concluded that CBT may provide a protective effect against suicidal events given that combination treatment appeared to accelerate recovery relative to CBT alone and (for some outcomes) fluoxetine alone (March, Klee, & Kremer, 2006).

**Adverse effects related to pharmacodynamics and pharmacokinetics**

Patients who are slow metabolizers at the cytochrome P450 2D6 isoenzyme might have reduced clearance of drug (e.g., paroxetine or fluoxetine), resulting in higher plasma (and brain) levels with a given administered dose (Brosen, 2004). Variants in either pharmacodynamic (e.g. serotonin transporter polymorphisms) or pharmacokinetic (e.g. slow hepatic biotransformation) handling of an antidepressant may contribute to idiosyncratic reactions to antidepressants. The pharmacokinetic factors can be dealt with by lowering the dose or selecting a different agent.

*Serotonin syndrome* is possible when multiple serotonergic agents are combined. Symptoms may range from mild to severe and consist of any combination of agitation, nausea, vomiting, diarrhoea, chills, muscle twitching, fever, confusion, dizziness, and diaphoresis. Symptoms usually abate with discontinuation of the medications. Severe presentations of delirium, coma, and seizures are possible but rare.

The *half-life of a medication influences the risk of adverse effects*. Abrupt withdrawal from a SSRI can lead to a discontinuation syndrome which is characterized by flu-like symptoms and, rarely, sexual side effects. This is more common in antidepressants with a short half-life and non-linear kinetics (e.g. paroxetine). Patients should be advised of the possibility of this reaction, and care should be taken to avoid missing medication doses. Discontinuation symptoms can be managed by very slowly tapering these medications, or by switching to a medication with a longer half-life (e.g. fluoxetine) and then tapering. Paroxetine is the most anticholinergic of the SSRIs with more sedation and weight gain. The shorter half-lives of paroxetine and venlafaxine may also contribute to a higher incidence of treatment-emergent suicidality. Whereas fluoxetine’s very long half-life may be beneficial when treating patients with poor compliance, it can be detrimental if an adverse side effect or need to switch medication occurs.

**Somatic side effects**

The associated somatic side effect profile is generally favourable with the most common side effects being initial mild headache and gastrointestinal (GI) symptoms upset.

*Gastrointestinal symptoms* affect approximately 15% of youths and may be related to the large number of serotonin receptors in the GI tract. Nausea and stomach pain are the most common GI complaints followed by diarrhoea or reflux-type symptoms (Safer & Zito, 2006). Gastrointestinal symptoms are usually transient and respond quickly to dosage lowering or taking the medication with meals. Some children will complain of chest or stomach pain that may be due to direct oesophageal or gastric irritation that is often alleviated by consuming more fluids when taking the medication. Children tend to have fewer side effects when doses are started as low as possible and, when feasible, given in divided doses (e.g. paroxetine, and fluvoxamine). With greater tolerance, larger and daily dosing regimens may be possible.

*Sexual dysfunction* is commonly induced by SSRIs with an estimated 30–40% incidence in all age groups. A lower incidence in youths may be related to reluctance to self-report sexual symptoms, particularly among adolescents (Scharoko, 2004). The most commonly reported sexual adverse effects are: loss of interest, anorgasmia and loss of physical arousal (erectile dysfunction in males and lubrication in females). The presentation of sexual dysfunction may result in decreased treatment compliance; unfortunately, treatment for this class of SSRI-associated symptoms is still limited.

**Overall endocrine adverse effects are infrequent with SSRIs**

*Changes in appetite* are not uncommonly reported with SSRIs although most are weight neutral with occasional reports of weight loss or gain. A small case series suggest SSRI-induced changes in growth velocity (Weintrob, Cohen, Klipper-Aurbach, Zadik, & Dickerman, 2002). In this report on four patients with a decrease in growth rate while on SSRI therapy, two resumed normal growth after SSRI discontinuation. Further study is warranted to delineate better if alterations in growth patterns...
are related to a neuropsychiatric condition or to the therapy (Weller et al., 2007). Regardless, careful monitoring for height and weight during long-term SSRI therapy is essential.

Abnormal bleeding associated with SSRIs, although uncommon, has been reported in youths (Lake et al., 2000) and led to investigation of the influence of antidepressants on haemostasis markers. Drugs with the highest degree of serotonin reuptake inhibition – fluoxetine, paroxetine and sertraline – are more frequently associated with abnormal bleeding and modification of haemostasis markers. The most frequent haemostatic abnormalities are decreased platelet aggregability and activity and prolongation of bleeding time. Patients with a history of coagulation disorder, especially those with suspected or documented thrombocytopenia or platelet disorders, should be monitored in case of prescription of any serotonin reuptake inhibitor (SRI). A non-SSRI antidepressant should be favoured over an SSRI or an SRI in such a context (Halperin & Reber, 2007). The most sensitive tests to detect SRI-associated bleeding disorder are platelet aggregation tests and are difficult to perform. Haemostasis tests have a low sensitivity when performed in cases of uncomplicated bleeding in the general population.

Conclusion and future directions

Overall, benefits from antidepressants appear to be much greater than risks such as suicide ideation and attempts across indications, although comparison of the risk-to-benefit ratio varies as a function of indication, age, chronicity and treatment conditions. Additional research in areas such as pharmacogenomics, adverse effects assessment (e.g. to differentiate symptoms of activation from mania), and SSRIs impact on long term growth and development are needed to investigate these individual susceptibilities in children and adolescents.

References


