Selective serotonin reuptake inhibitors are the most commonly prescribed medications for pediatric anxiety and depression. Despite widespread use, providers who primarily work with adults can vary widely in their knowledge base about use of this class of medication for children. This article therefore reviews the child-specific indications, side effects, and recommended monitoring parameters that prescribers should know when prescribing this class of medication to young people.

Selective serotonin reuptake inhibitors (SSRIs) are once-a-day medications that selectively inhibit the reuptake of serotonin from neuronal synapses in the brain. This selectivity distinguishes them from the older tricyclic antidepressants (TCAs) and certain newer antidepressants such as the serotonin-norepinephrine reuptake inhibitors (SNRIs), both of which are less selective and impact both the serotonin and norepinephrine systems.

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Disclosure: The authors have no relevant financial relationships to disclose.

doi: 10.3928/00485713-20130306-06
rine systems. Although less selectivity may contribute to unique benefits in certain circumstances (eg, neuropathic pain, treatment-resistant obsessive-compulsive disorder), this characteristic is also responsible for a higher side effect burden that has limited the use of these other agents in children.

SSRIs are also generally preferred over TCAs and the SNRIs because they have generally been found to be more clinically beneficial for children. For instance, every published randomized controlled trial using TCAs to treat childhood depression found that they had no treatment benefits. And despite SNRIs such as venlafaxine being shown to be a valid treatment option for adolescents who fail to respond to SSRI treatment, venlafaxine poses a higher risk of treatment-emergent suicidal ideation and more discomfort on discontinuation. As a result, SSRIs are more widely used than other agents for pediatric depression and anxiety due to better overall tolerability, less severe adverse side effects, and greater treatment effectiveness.

Despite their fairly widespread use, there are relatively few US FDA-approved indications for SSRIs in children. Fluoxetine, fluvoxamine, and sertraline are approved for the treatment of pediatric obsessive-compulsive disorder (OCD), and fluoxetine and escitalopram are approved for the treatment of adolescent depression. This limited number of specific FDA approvals means that SSRIs are commonly being used off-label, despite a significant amount of randomized controlled trial evidence that demonstrates benefits for children.

SSRI use should ideally not occur in isolation, but rather in conjunction with evidence-based psychotherapy such as cognitive-behavior therapy (CBT). For instance, one study of different types of childhood anxiety found 55% of sertraline-only patients improved, whereas 81% of sertraline plus CBT patients improved. In a different study of adolescent major depression, 61% of the fluoxetine-only group improved and 71% of the fluoxetine plus CBT group improved as well as having a lower incidence of suicidal thinking. Using an SSRI medication along with CBT is therefore preferred because of greater overall clinical effectiveness and because a psychotherapist can help support treatment plans and monitoring.

ANXIETY TREATMENT
Common anxiety disorders in childhood include OCD, generalized anxiety, social anxiety, and panic disorder. They are a potentially very disabling group of problems, and collectively occur in approximately 20% of children under the age of 18. In addition to discomfort and suffering, anxiety disorders can significantly impact social success, emotional development, and academic performance. Family functioning can also be greatly impacted as anxiety takes a toll on caregivers and siblings. Increasing recognition of the early onset of anxiety disorders has driven the need to identify effective treatments in younger and younger populations.

A systematic review of pharmacotherapy for pediatric anxiety disorders in 2010 identified that the pediatric anxiety treatment response to SSRIs was significantly greater (58.1%) than with placebo (31.5%). Relatively greater treatment effects were seen in studies of pediatric OCD, but benefits were demonstrated across the range of anxiety disorders. It should be noted that among randomized controlled trials, there have been a total of four fluoxetine studies, four sertraline studies, two paroxetine studies, and two fluvoxamine studies that demonstrated a treatment response over placebo. Because of this data, FDA approvals, and certain additional side-effect issues that exist for paroxetine and fluvoxamine, we recommend that fluoxetine and sertraline be considered as the first-line agents to try for childhood anxiety disorders.

DEPRESSION TREATMENT
Like the anxiety disorders, major depression is both disabling and commonly occurs in children. Point prevalence of depression is about 2% in prepubertal children and 8% in adolescents. During adolescence, approximately 20% of teenagers experience clinically significant depression, with girls being diagnosed twice as often as boys. As with the anxiety disorders, depression causes discomfort and suffering and can impact social success, emotional development, and academic performance. Left untreated, episodes of moderate to severe childhood depression are likely to take 6 to 12 months to resolve on their own, and future relapse is more the rule than the exception.

The seminal nonindustry-sponsored research studies in pediatric depression demonstrate that there is a role for SSRIs in the treatment of adolescent depression, and that they are safe and generally well tolerated. For instance the Treatment for Adolescents with Depression Study (TADS) demonstrated that 60% to 70% of teens with moderate to severe depression will respond to fluoxetine alone or fluoxetine plus CBT. The Treatment of Resistant Depression in Adolescents (TORDIA) study demonstrated that 40% of depressed adolescents who did not respond to their initial SSRI trial will respond to a second SSRI, with or without receiving adjunctive CBT. Clinically, this means it is best to try at least two different SSRIs before trialing a non-SSRI or concluding that usual medication treatment is ineffective.

First-line options for pediatric depression treatment are fluoxetine and escitalopram, which are the only two that carry FDA approvals for pediatric depression. Other second-line SSRI options that have at least one randomized control trial demonstrating efficacy over placebo are citalopram, sertraline, and paroxetine. Most child psychiatric spe-
cialists prefer not to use paroxetine to treat depression due to the fact that only one of three controlled trials with children had a positive outcome. As a class, SSRIs have been reported to be roughly twice as effective for pediatric anxiety disorders as they are for pediatric major depression, so although we commonly refer to the SSRIs as “antidepressants,” in the case of children they might more accurately be thought of first as “anxiolytics” that also work for depression.

**SELECTION OF CORRECT SSRI**

Although the SSRIs have similar side effect profiles overall, individual patients can vary greatly in their response to particular agents, both in terms of clinical benefits and tolerability. Unfortunately, there are limited data to guide decisions about which particular SSRI will be best for a particular patient. There are no head-to-head studies that compare response rates to different SSRIs, nor are there head-to-head side effect comparisons. Response can sometimes be predicted based on the experience of a first-degree relative (a familial biological response) or influenced by patient/parent preference for a particular medication (influencing observed placebo effects), so it is reasonable to take into consideration family history of response to specific SSRIs and to some extent, patient/caregiver preference. Unless there are specific family reasons against it, the aggregate of research supports that fluoxetine or escitalopram/citalopram should be the first-line options for depression, and sertraline or fluoxetine should be the first-line option for anxiety.

**SIDE EFFECTS**

Common SSRI side effects include headaches, mild gastrointestinal discomfort (nausea, diarrhea, constipation), and a change in level of alertness. Despite being fairly innocuous and typically transient, these common side effects can contribute to discontinuation, and discussing them beforehand as part of informed consent can reduce the likelihood of premature discontinuation. Nontransient behavioral activation or mood irritability occurs at a rate of around 5%. Although these are reversible with discontinuation, this occurrence might be related to the rare but potentially serious treatment-emergent suicidal ideation (discussed further below). The intensity of behavioral activation can range from trouble falling asleep and feeling restless, to the less common disinhibition or full hypomanic symptoms (mood elevation, talkativeness, accelerated thinking, increased energy). The development of a full manic episode — “mood flipping” — is a rare but potentially serious side effect. Although the development of manic symptoms may indicate an underlying bipolar diathesis, most children who experience manic symptoms from an SSRI do not go on to develop bipolar disorder.

Insomnia is common, and it can be addressed by giving medication in the morning or by adding melatonin at night. Temporary sexual dysfunction also occurs, but the frequency in adolescent populations is not clear. The potential for sexual side effects should be discussed but not overemphasized as it can pose a barrier to treatment. Increased bleeding and bruising is a very rare side effect in children, presumably related to altered platelet serotonin function. This is typically only clinically relevant in the context of an underlying clotting disorder (eg, hemophilia) or major surgery while receiving an SSRI.

All SSRIs with the exception of paroxetine are pregnancy risk category C (some animal studies show adverse effects; no controlled studies in humans). Paroxetine is risk category D (positive evidence of risk to human fetus; potential benefits may justify use during pregnancy), so alternatives should be used instead. Mothers using SSRIs at the end of pregnancy may be at increased risk of bleeding during delivery, and their infants may experience transient irritability perinatally. Neonatal exposure to SSRIs has also been associated with prolonged hospitalizations, breathing difficulties, poor feeding, and pulmonary hypertension. Although there was one report that maternal antidepressant use in the year before delivery is associated with autism spectrum disorder, epidemiologic data do not suggest this is a clear causal factor. Despite these concerns, maternal depression itself negatively impacts developing neonates, so the use of SSRIs during pregnancy is often recommended for mothers failing to respond to nonpharmacological strategies.

Other rare but potentially serious SSRI side effects include hyponatremia, prolonged QT interval, and serotonin syndrome. Serotonin syndrome symptoms include agitation, ataxia, diarrhea, diaphoresis, hyperreflexia, mental status changes, tremor, and hyperthermia. It is usually only seen in the context of either very high SSRI doses or the concomitant use of other serotonergic medications such as include trazodone, tricyclic antidepressants, meperidine, St. John’s Wort, melatonin, and some atypical antipsychotics.

**SSRIs AND SUICIDALITY**

There is a small but increased risk of suicidal thoughts in adolescents treated with SSRIs. There is a small but increased risk of suicidal ideation during the first 12 weeks of treatment. The FDA’s warning on suicidal ideation was
based on a review of 24 short-term randomized controlled trials with SSRIs in children for any indication, which found there was a twofold (2% in placebo versus 4%) increased risk of suicidal thoughts or behaviors while taking an SSRI versus taking a placebo.21 Since that time, subsequent research looking specifically at this issue has found different results. At the case series level, such as youth suicide autopsies, there is little signal of SSRI use triggering suicide (ie, a large series found only 1.6% of adolescent suicides had recent exposure to SSRIs).22 At the broader population level, repeated analyses of data from Western countries show that more use of SSRIs is associated with fewer completed youth suicides.23,24

Despite this discrepancy, it is prudent to inform all families prior to initiating use of an SSRI that their child may experience irritability, agitation, or suicidal thinking after starting the medication and to document that this discussion occurred. Typically when these problems appear, it is within the first month of initiation or following a dose increase. If new suicidal thoughts occur that are attributable to the SSRI, it is usually advised to stop administering the medication and reevaluate your treatment strategy.

Right after the black box warning was issued, the FDA made a monitoring suggestion that children starting an SSRI should be seen weekly for the first 4 weeks, and then seen every other week over the next 4 weeks. This specific monitoring recommendation was later changed to the more generic recommendation that patients be “monitored appropriately and observed closely” during the initial few months of treatment.25 To most child psychiatric specialists, “appropriate” monitoring of SSRI initiation means screening for the rapidly emergent side effects of concern like irritability, agitation, or suicidality 1 to 2 weeks after starting treatment in the office or over the phone, and then having another appointment 4 to 6 weeks after the SSRI was started.

SSRIs IN COMBINATION WITH PSYCHOThERAPY

As stated earlier, the added benefit of psychotherapy and medication is most clear for the treatment of anxiety disorders and for moderate to severe depression. In situations where suicidality is a concern, psychotherapy provides a very practical means of treatment monitoring and it may be the most effective intervention for reducing the risk of suicide. Despite professional consensus that combined treatment is generally preferable, it is not uncommon to encounter patient or caregiver resistance to using either medications or psychotherapy. Respecting this patient treatment preference in the initial treatment plan may increase the chance of a positive response (for instance, even placebo effects are “real” responses) and supports your therapeutic alliance.

The good news is that the literature does support medication-only and therapy-only approaches, depending on the circumstances. For adolescents and parents who want to use medication alone, the results of the Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT)26 suggest that the addition of psychotherapy to medication sometimes does not substantially change outcomes. For those who want to use psychotherapy alone, TADS13 demonstrated that CBT alone for mild depression produced similar outcomes as CBT plus medication. Even with the use of either medication or psychotherapy alone to treat depression or anxiety, it is generally recommended that if no improvement is seen after 8 to 12 weeks of an evidence-supported therapy, there should be a reconsideration of using combined treatment. However, for more severely depressed adolescents, the evidence does not support using CBT as monotherapy treatment.27

TREATMENT RESPONSE

Periodically monitoring response to treatment for depression or anxiety is a good idea regardless of the treatment approach. Both anxiety and depression can be chronic conditions, and as such benefit from surveillance and support. With medication starts, a check-in should ideally occur in 1 to 2 weeks to screen for side effects, and from there re-screening for side effects, assessing response, and considering dose increases should occur at roughly 4-week intervals (as it takes 4 to 6 weeks to see a treatment response from a given SSRI dosage). Given some evidence that more rapid titration leads to quicker response in some patients, patients with severe symptoms may benefit from more rapid initial titration to reduce the chance that a child will have a long duration of inadequately treated symptoms.28

Prior to starting an SSRI, the child’s weight should be checked for the purpose of tracking any weight loss or gain associated with the medication or the depression. It is also important to establish if there is any current or past suicidal thinking or behavior. This can help reduce the chance that you, the parents, or your patient will unnecessarily implicate medication as the cause of subsequently reported suicidal thoughts. At follow-up appointments, patients should be weighed, asked about new onset of easy bruising (until bruising is demonstrated not to be a concern), asked about any emergence of suicidal thoughts, irritabilit-
CONCLUSION

It is important to identify and to treat both anxiety and depression early in children. Although initial treatment may or may not include medication, early treatment does minimize morbidity and can prevent progression to more serious and persistent dysfunction. If either anxiety or depression progresses to the point that medications are considered, co-treatment with psychotherapy is recommended both for the purposes of maximizing response to treatment and increasing monitoring. Although other SSRIs may be equally effective, the research evidence base and FDA approvals support that fluoxetine, escitalopram/citalopram, and sertraline are first-line choices that should serve most pediatric anxiety and depression patients very well, and as such should be the agents to become familiar with using in children.

REFERENCES


