Review Article

Pharmacological treatment of anxiety disorders in children and adolescents: a review for practitioners

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Abstract: Anxiety disorders are common in children and adolescents with reported prevalence rates between 10% and 30%. A combined approach to treatment has been found to be the most effective for optimal outcomes and is typically comprised of psychotherapy (especially exposure-based cognitive behavior therapy), family and patient education, and use of medication if indicated. In children and adolescents who might benefit from use of medications, selective serotonin reuptake inhibitors (SSRIs) are the drugs of choice. The safety and efficacy of medications other than SSRIs in the treatment of children and adolescents with anxiety disorders are not fully established. Most children and adolescents respond well to treatment with long lasting resolution of symptoms, although, recurrence of the same, or development of a different type of anxiety disorder, is not uncommon. In most children and adolescents, anxiety disorders tend to persist into adulthood requiring long-term treatment planning. This paper reviews the pharmacological agents used in the treatment of anxiety disorders in children and adolescents.

Keywords: Anxiety disorders; selective serotonin reuptake inhibitors (SSRIs); behavioral activation; serotonin syndrome (SS); bipolar switching

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Introduction

The key feature of anxiety is fear or apprehension by the child or adolescent of a future event (1-4). Feelings of anxiety are typically accompanied by emotional stress or tension, and somatic signs and symptoms (1-4). The main feature of an anxiety disorder is functional impairment from persistent fear or worry (1-6). Such impairment may affect functioning in school, play, work or interpersonal relationships (1-6). The symptoms of an anxiety disorder take up a significant amount of daily time of the child or the adolescent and such symptoms last over a period of several months, typically six or more (1). Different types of anxiety disorders are recognized based on their clinical presentation, acuity, and type of stimuli associated with anxiety (*Table 1*) (1).

Epidemiology

Anxiety disorders are common in children and adolescents with a reported prevalence between 10% and 30%, and a higher prevalence in females (1,3,5). A combination of genetic factors, temperamental characteristics of the child, and environmental risk factors play a role in the development of anxiety disorders (2,3,6). Although the age of onset varies depending on the specific disorder, most

Table 1 Anxiety disorders

Acute stress disorder
Agoraphobia without history of panic disorder
Anxiety disorder due to a general medical condition
Anxiety disorder not otherwise specified
Generalized anxiety disorder
Obsessive-compulsive disorder
Panic disorder without agoraphobia
Post-traumatic stress disorder
Separation anxiety disorder
Social phobia
Specific phobia
Substance-induced anxiety disorder

Table 2 Mental health conditions co-morbid with anxiety disorders

Major depressive disorder (most common)
Other mood disorders
Attention-deficit/hyperactivity disorder
Oppositional defiant disorder
Conduct disorder
Learning disorders
Language disorders

anxiety disorders are first recognized in late childhood to early adolescent years (1-4). While long term outcomes of childhood anxiety disorders have not been clearly elucidated, it is generally recognized that most tend to persist into adulthood (1-4). The long term impact of anxiety disorders on the psychosocial development of the child or adolescent is significant (1-4). Anxiety disorders also have a high rate of other comorbid mental health disorders (see *Table 2*) (1).

Clinical features

Normal developmental fears vary depending up on the age and developmental stage of the child and these should not be confused with anxiety disorders (4-6). Infants may be fearful of sudden loud noises and strangers; the preschool child may have fear of animals, the dark, imaginary creatures or the storms (3,6). Anticipatory anxiety may first manifest during preschool age (6). The school age child may have fears related to attending school that involve acceptance by peers at school or concern about a particular subject or even a specific teacher (2,3,6). During the adolescent years, fears may be regarding the future events, about one's physical appearance, and sexuality (1-3). Conditions that should be considered in the differential diagnoses of anxiety disorders are listed in *Table 3* (1-4).

Approach to treatment

In children and adolescents, a multimodal treatment approach is found to be the most effective approach. The multimodal approach comprises exposure-based cognitive behavior therapy, family therapy, patient and family education and the use of medications (3,5,7-22).

Selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in children and adolescents; whereas, the safety and efficacy of other drugs in the treatment of anxiety disorders in children and adolescents is not fully established (2,3,5,7-22). Our understanding of the safety, efficacy, and use of specific treatment modalities is informed by several key clinical trials: the Treatment of Adolescents with Depression Study (TADS) (23-30), the Child/Adolescent Anxiety Multimodal Study (CAMS) (31,32), the Research Unit on Pediatric Psychopharmacology (RUPP) Anxiety Study Group (33), the Pediatric Obsessive-Compulsive Disorder Treatment Study (POTS) (34), and the Treatment of Resistant Depression in Adolescents (TORDIA) (35-37). Our focus in this clinical review is on the use of medications in pediatric anxiety disorders, the key characteristics of which are summarized in *Tables 4*, *5* and *6* (16,38-45).

SSRIs

SSRIs are the recommended drugs of choice for pediatric anxiety disorders and found to be effective alone or in combination with cognitive behavior therapy (5,9,12,18). SSRIs act by blocking the reuptake of serotonin into pre-synaptic neurons and enhance serotonergic neurotransmission (6,14,18-20,46,47).

Side effects

Gastrointestinal side effects

Gastrointestinal side effects are common with SSRI use. Nausea, vomiting, diarrhea, flatulence, decreased appetite, dry mouth and heartburn are the most commonly

Table 3 Differential diagnoses of anxiety disorders

Mental health conditions
Agoraphobia
Anxiety disorder due to general medical condition
Anxiety disorder not otherwise specified
Acute stress disorder
Adjustment disorder with anxious mood
Attention deficit hyperactivity disorder
Childhood developmental fears and phobias
Competitive anxiety in athletes
Depression
Generalized anxiety disorder
Hyperventilation
Hypochondriasis
Obsessive compulsive disorder
Panic attacks and panic disorder
Post-traumatic stress disorder
Selective mutism
Separation anxiety disorder
Social phobia
Somatization disorder
Specific phobia
Substance-induced anxiety disorder
Medical conditions
Asthma
Epilepsy
Fetal alcohol syndrome
Fragile X syndrome
Hyperthyroidism
Hyperparathyroidism
Hyperadrenocorticism
Hyperventilation syndrome
Hypoglycemia
Mitral valve prolapse
Pheochromocytoma
Porphyria
Vestibular dysfunction

reported side effects (12,15,18,20). Most are transient and resolve over a period of few weeks. In a few children and adolescents, weight gain may be a problem rather than weight loss and may not respond well to decreased caloric intake and increased physical activity (8,14,16,18).

Behavioral activation

Behavioral activation is much more common in children and adolescents than in adults and reported incidence ranges from 20% to 50% (3,13,20,21,48-52). Activation is more common during the initial days and weeks of starting the SSRI and after an increase in dose (18,20). Behavioral activation is characterized by alteration in mood, dysphoria, altered cognition, nervousness, agitation, irritability and in severe cases by akathisia (uncomfortable sensation of restlessness that can be physical or psychological or both) (12,18-21). Although hypomania, mania, and acute psychotic reactions have also been reported, behavioral activation is neither an indication of nor predictive of bipolar disorder (3,6,20). Many symptoms of behavioral activation and discontinuation syndrome are similar. A careful documentation of adherence to taking SSRIs will favor the diagnosis of behavioral activation (3,8,11).

Switching (or bipolar switching)

In switching, the patient's mood state changes from depressed or anxious mood to that of manic or hypomanic state. This clinical feature differentiates bipolar switching from behavioral activation. In behavioral activation the mood state does not change (19,20,46,52).

The patient and the family recognize these as new symptoms not present before the treatment was started with an SSRI agent (3). Switching is a less common but significant side effect of SSRIs in children and adolescents. Bipolar switching should be differentiated from behavioral activation. Symptoms of switching tend to occur later in the course of the treatment and may not abate even after discontinuation of the SSRI agent (4,6,20). Development of symptoms suggestive of bipolar disorder requires discontinuation of SSRIs and starting appropriate treatment for bipolar disorder after further evaluation (3,5,13,22). Children and adolescents when effectively treated with an SSRI agent for anxiety or depression may also then manifest symptoms of comorbid mental health disorders more clearly (e.g., symptoms of attention deficit hyperactivity disorder or conduct disorder) and require further evaluation and

Table 4 Characteristics of SSRIs/SNRIs used in anxiety disorders

Drug	Initial & maximum dose	Metabolism	Half-life	Comments
Citalopram	Initial: 10 mg daily; maximum: 40 mg daily	Hepatic via CYP 3A4, 2C19 & 2D6 to multiple metabolites	24–48 hours	Off label indication for OCD; available in oral solution
Escitalopram	≥12 years: 10 mg daily; maximum 20 mg daily	Hepatic via CYP 3A4 & 2C19; S-desmethylcitalopram metabolized via CYP 2D6	~27–32 hours	S-enantiomer of citalopram; FDA approval: MDD; available in oral solution
Fluoxetine	≥7 years: 10 mg daily initially; maximum (lower weight): 20–30 mg daily; maximum (adolescents & higher weight): 20–60 mg daily	Hepatic via CYP 2C19 & 2D6 to norfluoxetine; norfluoxetine has equal activity of fluoxetine	Fluoxetine: 4–6 days; norfluoxetine: 4–16 days	FDA approval: OCD; available in oral solution
Fluvoxamine IR	8–17 years: initial 25 mg daily; 8–11 years: maximum 200 mg daily; ≥12 years: maximum 300 mg daily	Hepatic via oxidative demethylation & deamination	~14–16 hours	FDA approval: OCD; doses >50 mg daily; divide into 2 doses with larger portion at bedtime
Paroxetine	OCD 7–17 years: initial 10 mg daily; maximum 60 mg daily; SAD 8–17 years: initial 10 mg daily; maximum 50 mg daily	Hepatic via CYP 2D6	21 hours	Off label indication for OCD & SAD; available in oral suspension & ER tablet
Sertraline	6–12 years: initial 25 mg daily; maximum 200 mg daily; 13–17 years: initial 50 mg daily; maximum 200 mg daily	Hepatic via CYP 2C19 & 2D6; extensive first pass metabolism	26 hours	FDA approval: OCD; available in oral concentrate solution
Venlafaxine ER	6–17 years: initial 37.5 mg daily; 25–39 kg: maximum 112.5 mg daily; ≥40 kg: maximum 225 mg daily	Hepatic via CYP 2D6 to ODV (active metabolite) & 2 other metabolites	Venlafaxine: 5±2 hours; ODV: 11±2 hours	Not FDA approved in children or adolescents; dosing based on data by Rynn *et al.*
Duloxetine	7–17 years: initial 30 mg daily; maximum 120 mg daily	Hepatic via CYP 1A2 & 2D6; multiple inactive metabolites	~12 hours	FDA approval: GAD
Mirtazapine	8–17 years: initial 15 mg daily; maximum 45 mg daily	Hepatic via CYP 1A2, 2D6 & 3A4 as well as demethylation & hydroxylation	20–40 hours	Antagonizes histamine & muscarinic receptors; off label: dosing based on pilot trial in 18 patients with social phobia (Mrakotksy *et al.*); available in dispersible tablet
Nefazodone	1 case (15 years): initial 50 mg daily; titrated to 350–400 mg daily (2 divided doses)	Hepatic by n-dealkylation & hydroxylation to a minimum 3 metabolites; 2 active metabolites	Nefazodone: 2–4 hours; active metabolites: 1.4–8 hours	Off-label; dosing based on case series by Mancini *et al.*

MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SAD, social anxiety disorder; CYP, cytochrome; ODV, O-desmethylvenlafaxine; GAD, generalized anxiety disorder; FDA, Food and Drug Administration; IR, immediate-release; ER, extended-release.

treatment for the specific comorbid disorder.

Serotonin syndrome (SS)

Although infrequent, SS is a serious treatment emergent adverse event associated with the use of SSRIs (20,46,50,52,53). SS is caused by excessive serotonergic neuronal activation. The likelihood of SS increases when the dose of a SSRI is high and when a patient is also taking multiple drugs with serotonergic activity (3,9,15,18,20). The clinical features of SS include agitation, confusion, tachycardia, hypertension, tremors, incoordination, muscular rigidity, myoclonus, hyperreflexia, fever, shivering, excessive

Table 5 Characteristics of benzodiazepines

Drug	Initial & maximum dose	Time to peak	Metabolism	Half-life	Comments
Alprazolam	Initial: 0.125 mg 3×/day; Max: 0.06 mg/kg/day	1–2 hours	Hepatic oxidation via CYP 3A4; 2 active metabolites (less potent & lower concentrations)	11.2 hours	Available in dispersible and extended-release formulations
Chlordiazepoxide	<6 years: not recommended; ≥6 years: 5 mg 2–4 times daily; up to 10 mg 2–3 times daily	0.5–2 hours	Hepatic to multiple metabolites; produces desmethyldiazepam which is active & long-acting	Chlordiazepoxide: 6.8–28 hours; demoxepam: 14–95 hours	
Clonazepam	>10 years or ≥30 kg: 0.25 mg twice daily; target dose: 0.5 mg twice daily	1–4 hours	Hepatic via glucuronide & sulfate conjugation	22–33 hours	Available in a dispersible tablet
Diazepam	0.12–0.8 mg/kg/day divided in 3–4 doses	15 min–2.5 hours	Demethylated by CYP3A4 & 2C19 to N-desmethyldiazepam; hydroxylated by CYP3A4 to temazepam; active metabolites;	Diazepam: 44–48 hours; desmethyldiazepam: 100 hours	Active metabolites are further metabolized to oxazepam; available in oral solution & oral concentrate
Oxazepam	>12 years (mild to moderate): 10–15 mg 3–4 times daily; >12 years (severe or associated with depression): 15–30 mg 3–4 times daily	~3 hours	Hepatic via glucuronide conjugation; inactive metabolite	~8 hours	No cytochrome P450 associated drug interactions

CYP, cytochrome.

sweating, diaphoresis, and diarrhea (20). The complications of SS include seizures, metabolic acidosis, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure, coma, and death (20,42). As soon as any clinical symptoms or signs of SS is recognized, all serotonergic drugs must be immediately discontinued, and appropriate emergent general medical care must be initiated (3,11,17-19).

Withdrawal or discontinuation syndrome

The symptoms of SSRI drug withdrawal may be seen in some children and adolescents when the SSRI is abruptly stopped following a period of regular use (3,6,7,9,18). It is more likely to occur with the use of shorter half-life SSRIs, longer duration of use and abrupt discontinuation (8,10,18,50). Withdrawal symptoms include gastrointestinal disturbances, dysphoric mood, irritability, headache, sweating, chills, fatigue, agitation, dizziness, sensory disturbances (e.g., electric shock like sensations), anxiety, confusion, and sleep disturbances (13,20,50,54,55). For most SSRIs, symptoms are seen within 2–5 days of reducing the dose or discontinuation of the medication; in the case of fluoxetine, because of its longer half-life, symptoms of discontinuation may not be seen until after 7–10 days of stopping the medication (14,16,18,20,46,50). Most symptoms associated with discontinuation of SSRI agents generally resolve within 1–2 weeks (20). Sometimes severe symptoms associated with discontinuation of an SSRI agent may require restarting the patient on an SSRI at a lower dose for a short period and gradually tapering the medication (2,11,20). Symptoms of discontinuation syndrome should be differentiated from those of anxiety disorder recurrence or relapse.

Suicide ideation

The potential risk for suicidality associated with the use of antidepressants continues to be a subject of much

Table 6 Characteristics of other drugs used in anxiety disorders

Drug	Initial & maximum dose	Metabolism	Half-life (hours)	Comments
Buspirone	5–7.5 mg twice daily; Max: 15 mg twice daily	Hepatic oxidation via CYP 3A4; active metabolite	1.99–3.44	Extensive first pass metabolism; not FDA approved in children/ adolescents; evaluated in children ranging in age from 6–17 years
Hydroxyzine	<6 years: 50 mg daily in 3–4 divided doses; ≥6 years: 50–100 mg daily in 3–4 divided doses	Hepatic to multiple metabolites; active metabolite (cetirizine)	~7	Available in oral syrup & solution
Propranolol	Initial: 10–20 mg per day; target: 20–40 mg per day divided twice daily	Hepatic oxidation via CYP 2D6 and 1A2; active metabolite	3.9–6.4	Extensive first pass metabolism; available in oral solution & ER capsule

ER, extended-release; CYP, cytochrome; FDA, Food and Drug Administration.

debate. In 2004, the U.S. Federal Drug Administration (FDA) conducted a pooled analysis of placebo-controlled trials in children and adolescent with major depressive disorder, obsessive compulsive disorder or other systematic psychiatric disorders. The analyses comprised of a total of 24 short-term trials of 9 antidepressant drugs (including SSRIs) in over 4,400 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 children and adolescents placed on antidepressants be monitored closely, especially during the first few days to week for any signs of increased suicidality. Multiple subsequent studies have not been able to conclusively show that antidepressant use in children and adolescents is associated with increased risk for suicidality (2,3,11-15,17,18,28,31).

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 (5,6,8,12,14,20). In practice, a routine electrocardiogram is not recommended before starting SSRI agent, unless otherwise indicated based on history and physical examination findings.

Sexual side effects

Some individuals report delayed orgasm, decreased sexual desire, and ineffective orgasm while taking SSRIs (46-50). Most of such sexual side effects decrease in frequency or resolve over time with continued use of SSRIs (46-50). SSRIs have been used to treat premature ejaculation in some cases because it delays orgasm.

Sleep disturbance

Disturbance in sleep pattern is a common side effect of SSRIs. Such sleep disturbances include delayed onset of sleep, frequent waking up, shortened duration of sleep, and abnormal dream states (8,10,12,14,50). Because of poor quality of sleep, children and adolescents often may experience daytime drowsiness. Administration of the medication in the morning, improved sleep hygiene or use of melatonin should be considered if sleep disturbance is significant.

Other side effects

Other less frequently reported side effects with the use of SSRIs include increased yawning, increased sweating, mammoplasia, gynecomastia, and bleeding tendencies (11-15,18). Some children and adolescents may experience significant increased sweating. Nighttime sweating may be severe enough to drench the bed sheets. A different SSRI agent may be tried in these cases; also terazosin has been shown to be effective in the treatment of increased sweating in such cases (18,19).

Mammoplasia in girls and gynecomastia in boys have also been reported (19). SSRI induced increase in prolactin can cause galactorrhea in both men and women. It may take several months to resolve following discontinuation of the SSRI agent.

Apathy or amotivational syndrome, syndrome of inappropriate antidiuretic hormone secretion, and increased bleeding tendencies including gastrointestinal bleeding have been reported in children and adolescents on SSRIs (18,20). Increased bleeding is due to functional impairment of platelet aggregation and requires discontinuation of the SSRI (18,20).

Precautions

There is an increased risk of adverse events with the use of SSRIs in children and adolescents who are significantly underweight, have underlying hepatic or renal disease, have a history of atrial tachycardia or conduction disorders, and those who have a history of excessive daytime sleepiness (18,20). 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 (18,20).

Use in practice

Behavioral treatment modalities are the mainstay of treatment of anxiety disorders in children and adolescents, which requires effective participation by the patient and family in behavioral treatment. However, for many children and adolescents the symptoms of anxiety are severe enough to preclude effective participation in behavioral treatment. In these children and adolescents, SSRIs are indicated in order to first ameliorate anxiety symptoms to a sufficient level to allow for effective participation in behavioral treatment (3). Also, when symptoms of anxiety are severe, SSRIs should be continued along with behavioral treatment.

Comorbid disorders must be recognized and appropriately treated at the same time. The response to pharmacotherapy varies depending upon the severity and specific type of the anxiety disorder and the efficacy ranges from 50% to more than 70% (2,3,5,22).

SSRIs are the drugs of choice for the treatment for treatment of anxiety disorders in children and adolescents (2,5,46-50). Numerous studies provide evidence for the safety and effectiveness of SSRIs for the treatment of anxiety disorders in children and adolescents (23-37). Studies suggest that treatment of anxiety disorders may require dosages that are relatively higher than those used in the treatment of depression and the response may take longer (2,16,20). There is no conclusive evidence that suggests superiority of one SSRI over another, and no long term studies are available to guide the decision for duration of treatment (8,54,55). SSRIs should be continued for initial period of at least 1 year. If the patient is stable for a year, SSRI agent may be discontinued and patient monitored for re-emergence of anxiety symptoms (2-5,9,14,20). If symptoms of anxiety recur, the SSRI should be re-started. (2-5,9,14,20).

Once started, the SSRI agent should be continued for a period of 4 weeks before considering an increase in the dose or changing to a different SSRI agent (4,20,49,50). Subsequent increase in SSRI dose should not occur less than every 4 weeks (5,8,18,19). The dose is titrated higher until symptoms of anxiety resolve, intolerable side effects emerge, or a maximum recommended dose is reached without improvement in symptoms (3,5,8).

Due to higher rates of drug metabolism in children and adolescents, dosing of certain medications that are typically given once daily in adults may have to be divided into twice daily dosing to prevent withdrawal effects (2,3,6,20).

In children and adolescents on SSRIs, no specific laboratory monitoring is indicated (8,18,19,50). Children and adolescents taking SSRIs should be monitored clinically for an increased risk for suicidal behaviors. According to the U.S. FDA, a patient taking SSRIs should be clinically followed every week for the first month of treatment, every 2 weeks during the second month of treatment, and at the end of the third month of treatment. Because multiple factors play a role in the effective treatment and emergence of side effects, most medical practitioners individualize their approach to such clinical follow up.

Serotonin norepinephrine reuptake inhibitors

Venlafaxine and duloxetine

Multiple studies have shown serotonin and norepinephrine reuptake inhibitors (SNRIs), venlafaxine and duloxetine, to be effective in anxiety disorders in children and adolescents (12-15,18,35). SNRIs block both the serotonin and norepinephrine reuptake and weakly inhibit dopamine reuptake leading to increased serotonergic, noradrenergic, and dopaminergic neurotransmission (6,18,19,20). Venlafaxine acts like an SSRI at low doses and provides dual mechanism at higher doses (1,18,20).

Side effects

Side effects of SNRIs are similar to those of SSRIs but also includes an increase in systemic blood pressure, especially dose-dependent increase in supine systolic and diastolic blood pressure has been reported (9,15,18,19). Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion are uncommon but have been reported with SSRIs and SNRIs (5,20). Nervousness, somnolence, nausea, decreased appetite, weight loss, constipation,

increased sweating, dry mouth, dizziness, difficulty sleeping and sexual dysfunction are the most commonly reported side effects of venlafaxine and duloxetine (12,15,16,18,20).

Precautions

SNRIs have similar precautions and contraindications as those for SSRIs including risk for SS (especially when combined with other serotonergic drugs) and a warning for increased suicidality. If there is a history of hypertension, it should be controlled prior to initiating an SNRI. Recent cardiovascular or cerebrovascular events may preclude use of SNRIs, and these agents should be used with great caution in children and adolescents with a history of seizures (19). Venlafaxine dose should be reduced in significant renal impairment while duloxetine should be avoided.

Use in practice

Venlafaxine and duloxetine are not considered the initial drugs of choice for the treatment of anxiety disorders in children and adolescents (2,5). Duloxetine is approved by the U.S. FDA for use in the treatment of generalized anxiety disorder in the age group from 7 to 17 years. Venlafaxine is not FDA approved for use in children and adolescents; however, it has been used when a SSRI is found to be ineffective. Extended release venlafaxine has been reported to be effective for generalized anxiety disorder and social phobia (5,7,18).

In addition to the monitoring guidelines noted for SSRIs, blood pressure should be routinely monitored in children and adolescents on SNRIs while a fasting lipid profile should be checked periodically (3,7,18,19). The initial starting dose of venlafaxine ER is 37.5 mg daily and maximum dose varies based on weight (see *Table 4*). The starting dose of duloxetine is 30 mg daily and maximum dose is 120 mg daily in children and adolescents (4,19).

Mirtazapine and nefazodone

Rarely, mirtazapine and nefazodone may be considered for the treatment of pediatric anxiety disorders when first line drugs of choice have been ineffective. These drugs are not approved by U.S. FDA for anxiety disorders, and data and clinical experience are limited to provide meaningful guidance for their use in children and adolescents.

Mechanism of action

Nefazodone is a SARI (serotonin antagonist/reuptake inhibitor) antidepressant and works via antagonism at the post-synaptic serotonin 5-HT2 receptor; it also blocks pre-synaptic serotonin and norepinephrine reuptake (4,9,19,20). Mirtazapine is an antagonist of the pre-synaptic norepinephrine alpha-2 receptor contributing to a release of norepinephrine and serotonin. It also blocks post-synaptic 5-HT2 and 5-HT3 receptors (19).

Side-effects

Mirtazapine is quite sedating (especially at lower doses), frequently causes weight gain, may elevate serum cholesterol, triglycerides and transaminases (9,18,20). Other side effects of mirtazapine include dry mouth, constipation, dizziness, abnormal dreams, increased appetite, nausea, weakness, abdominal pain, and flu-like symptoms (9,18-20). A potentially serious side effect of nefazodone is unpredictable acute hepatic failure. Other side effects of nefazodone include nausea, dry mouth, constipation, dyspepsia, increased appetite and weight gain, headaches, dizziness, insomnia, agitation, confusion, blurred vision, decreased libido and postural hypotension (9,18-20).

Use in practice

Although no specific laboratory tests are recommended for mirtazapine and nefazodone use, in practice, it is prudent to periodically check a fasting lipid profile, complete blood count, liver function tests and closely monitor weight gain, body mass index, and blood glucose (3,4,19,20). In adults the initial dose for mirtazapine is 7.5–15 mg per day with target dose of 15–45 mg given before bedtime. The initial dose for nefazodone is 100 mg twice daily day with usual dosage range of 150–600 mg daily divided into 2 doses (4).

Buspirone

Mechanism of action

Buspirone is an azapirone with a high affinity for 5-HT1A and 5-HT2 serotonin receptors. Buspirone is a serotonin 1A partial agonist. The effectiveness of buspirone in ameliorating the symptoms of anxiety is attributed to its post-synaptic partial agonist actions (19-21,56).

Buspirone is rapidly absorbed after oral ingestion. Peak plasma level is reached between 40 and 90 minutes after oral dose and has an average elimination half-life of 2 to 3 hours (21,56).

Side effects

Side effects of buspirone are generally mild and include headache, dizziness, nervousness, drowsiness, nausea, weakness, blurred vision, and excitement (56). Buspirone use has not been associated with physical or psychological dependence and no significant withdrawal symptoms occur when stopped (20,21,56).

Precautions

Buspirone should not be used with MAOIs; certain SSRIs used concomitantly with buspirone may reduce its clearance and raise its plasma levels (20,21).

Use in practice

No serious side-effects have been reported with the use of buspirone in children and adolescents. Therefore, buspirone is sometimes used as an initial drug for the treatment of anxiety disorders in children and adolescents. It has also been used as an adjunctive agent along with SSRI (21,56). No specific laboratory monitoring is indicated with the use of buspirone. Buspirone is not FDA approved in children, but studies in the package insert indicate a starting dose of 5 mg twice daily and range of 10–30 mg daily divided in 2 doses (21,56). It can take up to 3 weeks for its optimal effects and improvement in the psychic symptoms precedes improvement in somatic symptoms of anxiety.

Propranolol

Propranolol reduces the neuronal sympathetic outflow by blocking the beta-adrenergic receptors (19). Beta-blockers differ in their degree of selectivity for beta 1 (cardiac) and beta 2 (non-cardiac) receptors (57). Beta-blockers also have different degrees of lipophilicity (57). The exact mechanism of action of beta-blockers on the central nervous system had not been clearly elucidated (4,19,20). Propranolol is non-selective beta-adrenergic receptor blocker and reduces peripheral autonomic tone, which is believed to result in amelioration of somatic symptoms of anxiety, its effect on reducing emotional symptoms of anxiety is not well established (4,19,20).

Side effects

Dizziness, fatigue, bradycardia, hypotension, gastrointestinal upset, and rashes are commonly reported side effects of propranolol (19,57,58). Bronchospasm and heart failure, although less frequent, are more serious side effects of propranolol (57,58). In some children and adolescents, propranolol use has been associated with the emergence of Raynaud phenomenon (57,58).

Precautions

The beta blockers are contraindicated in children and adolescents with sinus bradycardia and greater than first degree heart block, uncompensated heart failure, asthma, and sick sinus syndrome (57,58). Beta-blockers should be used with caution in patients with significant peripheral arterial disease, pheochromocytoma, diabetes mellitus, hyperthyroidism, myasthenia gravis and compensated heart failure due to risk for disease exacerbation (57). Propranolol can exacerbate depression in children and adolescents (3,20,57).

Use in practice

Evidence is insufficient to support the use of propranolol in the treatment of anxiety disorders in children and adolescents. Propranolol has been found to be effective when used in certain specific circumstances that provoke anxiety, such as performance anxiety or in athletes to ameliorate anxiety associated with competition (3-5). The initial dose is 10–20 mg daily with a target of 20–40 mg daily divided twice (58).

Because propranolol lowers systemic blood pressure and heart rate, both should be monitored periodically (57,58). Before initiating propranolol, a baseline electrocardiogram is recommended to detect asymptomatic cardiac conduction abnormalities (57,58). It is also recommended to obtain a fasting blood glucose level prior to initiating treatment with propranolol (57,58). Propranolol can sometimes cause elevations in serum potassium, aspartate aminotransferase, alanine aminotransferase, triglycerides and alkaline phosphatase as well as reduce high-density-lipoprotein (HDL) cholesterol (57,58). Because of the potential for a rebound increase in systemic blood pressure, propranolol should be gradually tapered over a 2-week period when no longer indicated (57,58).

Hydroxyzine

Mechanism of action

Hydroxyzine is an antihistamine and it acts by blocking the

histamine-1 receptors. It also antagonizes the muscarinic receptors and 5-HT2a receptors which is thought to mediate is anxiolytic properties (59,60).

Side effects

Hydroxyzine may cause dry mouth, sedation, tremor, increased appetite, fatigue, dizziness and constipation (59,60).

Use in practice

Hydroxyzine is not recommended for use in the treatment of anxiety disorders in children and adolescents. The use of hydroxyzine is limited to special circumstances in children and adolescents with symptoms of anxiety associated with organic diseases, and medical procedures (59,60). It is sometimes used in allergic conditions associated with pruritus and anxiety, acute hysteria, and anxiety associated with alcohol withdrawal (59,60). See *Table 4* for dosing guidelines.

Benzodiazepines (BDZs)

BDZs bind to the benzodiazepine receptors in the central nervous system at the gamma aminobutyric acid-A (GABA-A) ligand-gated chloride channel complex and enhance the inhibitory effects of GABA (19,21,57). BDZs facilitate the chloride conductance through GABA-regulated channels. Their therapeutic effects in reducing anxiety symptoms are believed to be due to inhibition of amygdala-centered neuronal circuits (59,60).

Side effects

Side effects of BZDs include sedation, cognitive blunting, dizziness, ataxia, nystagmus, depression, transitory hallucinations, memory impairment (typically anterograde amnesia), constipation, diplopia, hypotension, urinary incontinence or retention, fatigue, slurred speech, paradoxical hyperexcitability, and nervousness (19,21,47,59,60). Paradoxical reactions are a significant concern in children and adolescents. Such episodes are characterized by behavioral disinhibition, loss of control, increased anxiety, increased aggressiveness, rage reaction, nightmares and hallucinations.

Respiratory depression, liver toxicity, and blood dyscrasias are less frequent but serious adverse reactions associated with the use of BDZs (21,47,59,60). Drug accumulation can occur in those with hepatic or renal impairment (21,59,60).

Precautions

The risk for abuse and dependence is increased with higher dosages and long-term use of BDZs. They are classified as class IV controlled substances within the U.S. Tolerance can be seen with the hypnotic and sedative effects but not the anxiolytic properties of BZDs. To prevent withdrawal or rebound symptoms, BDZs should be tapered when discontinued.

BZDs are contraindicated in children and adolescents with narrow angle glaucoma (21,60). Caution should be exercised in those with a history of depression or respiratory disorders.

BDZs should not be used in adolescents with potential for drug abuse or drug dependence. When individuals are on BDZs for long-term, periodic complete blood count and liver function tests are indicated (2,4,19,21,47,59,60).

Use in practice

The evidence is insufficient to support the use of BDZs in the treatment of anxiety disorders in children and adolescents (59,60). Rarely, BDZs are used for short-term treatment to control of severe anxiety (4,19,21,59,60). BZDs are more commonly used for procedure related anxiety. For adults, clonazepam is approved by the U.S. FDA for panic disorder, lorazepam for generalized anxiety disorder, and alprazolam for panic disorder as well as generalized anxiety disorder (2,19,21,59,60). Diazepam, chlordiazepoxide, and oxazepam have FDA-approved dosing for generalized anxiety disorder in children and adolescents (see *Table 4* for details).

Conclusions

Children and adolescents with symptoms of anxiety or anxiety disorders commonly present in the primary care setting. Signs and symptoms of anxiety include cognitive, physiological, and behavioral manifestations. Other mental health conditions that can be co-morbidities with anxiety disorders should be recognized. Behavioral treatment, especially various cognitive behavioral therapy approaches, has been shown to be efficacious in the treatment of anxiety disorders in children and adolescents. Some children and

adolescents may need pharmacotherapy at the same time behavioral treatment is initiated to allow for more effective participation in the therapy. Generally, a multimodal approach that includes behavioral and pharmacotherapy has been shown to be the most effective. SSRIs are the drugs of choice in treating anxiety in children and adolescents. Data are insufficient to recommend any other class of anti-anxiety drugs in children for long term treatment. Most children and adolescents respond well to treatment with long lasting resolution of symptoms. Recurrence of the same, or development of a different type of anxiety disorder, is not uncommon and in most individuals, anxiety disorders tend to persist into adulthood requiring long-term treatment planning.

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Footnote

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