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Therapeutic Options

FOCUS ON ANXIETY AND DEPRESSION IN CHILDREN AND ADOLESCENTS

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Mental health is a recognized and accepted part of health care, but one portion of our population is often overlooked. Children and adolescents commonly experience emotional, behavioural, and psychosocial issues but only a small fraction of these patients receive appropriate treatment. This article discusses the prevalence, symptoms and current management of anxiety and depression in children and adolescents, focusing on information from recently updated guidelines.

BACKGROUND AND PREVALENCE

In Canada, approximately 1.2 million children and youth are struggling with mental health issues serious enough to impact daily functioning and development. A 2021 poll revealed that two-thirds of Canadian parents felt their child's mental health had deteriorated since the beginning of the COVID-19 pandemic and that almost 50% of parents felt their child was facing new challenges with mental health during this time.

Anxiety

Anxiety disorders are the most common mental health conditions affecting children and adolescents and their prevalence appears to be increasing in recent years. Worldwide, an estimated 7% of youth have an anxiety disorder. In 2009, approximately 4% of Canadian youth 12 to 19 years of age reported anxiety issues. Within the past 10 years, that rate has increased considerably, with current reports suggesting anxiety disorders affecting almost 9% of children and 11% to 19% of adolescents. Similarly, a Canada-wide study reported that health professional-diagnosed anxiety disorders in patients aged 12 to 24 years doubled between 2011 and 2018. These increasing rates may reflect a rise in prevalence but could also be attributed to factors such as greater awareness of anxiety symptoms and treatment and decreased stigma surrounding mental health conditions. Anxiety, especially if left untreated, can negatively impact social development, education and overall quality of life. In addition, suicidal ideation and suicide attempts have been reported in approximately 9% and 6%, respectively, of adolescents with anxiety.

Depression

The incidence of depression in children (4 to 11 years of age) is generally low, ranging from 0.4% to 2.5%, but tends to increase in adolescents (12 to 17 years of age) from 3% to 8%. Recent pediatric guidelines indicate that 1 in 5 teenagers experience depression at some point during adolescence and prevalence rates may be as high as 28% in primary care settings. The rise in incidence upon adolescence may be due to a corresponding increase in sensitivity to stress exposure, resulting from concurrent physical, emotional and psychological changes that are occurring during this growth period. In the Canadian Community Health Survey, which spanned the years 2000 to 2014, rates of major depressive episodes were highest among females and patients 15 to 19 years of age. In addition to depression being the leading cause of *years lost to disability* in adolescents, these patients have increased risk of not finishing school, unemployment and early parenthood. Patients who develop depression during adolescence are considered to be at higher risk of continuation or recurrence of depression during adulthood and at greater risk of other negative outcomes such as substance use, violent behaviour, crime and suicide.

SYMPTOMS AND ONSET

Anxiety

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) describes anxiety as *excessive worry and apprehensive expectations, occurring more days than not for at least 6 months, about a number of events or activities, such as work or school performance.* While some degree of anxiety or worry is normal, the diagnosis of an anxiety disorder is dependent on symptoms creating significant distress or impairment in the ability to function on a daily basis. The term *anxiety disorder* in children and adolescents encompasses seven subtypes: generalized anxiety, separation anxiety, social anxiety, selective mutism, specific phobias, panic disorder and agoraphobia.

Signs and symptoms of anxiety in this age group include hyperarousal (e.g., nervousness, fear, irritability or agitation), avoidance behaviour (e.g., avoiding places that instil fears) and distorted cognitive thoughts (e.g., worried questions or exploring "what if" scenarios). Physical symptoms can include muscle tension and stomach aches. Children diagnosed with anxiety are often described by parents as being worriers, perfectionists, eager to please or quiet, while adolescents with anxiety may be described as overly emotional, shy, introverted or overly sensitive.

The median onset of anxiety disorders occurs at approximately 11 years of age but varies depending on the anxiety subtype and often correlates with a developmental phase. In general, separation anxiety and selective mutism occur in younger, preschool-age children; phobias in grade-school children; social anxiety in older-age children or early adolescence; and generalized anxiety in adolescent and young adult patients. The onset of anxiety symptoms can be acute, but the duration is typically chronic, often waxing and waning over time. Untreated, anxiety can impact all aspects of life (social, educational, occupational, health) and continue into adulthood.

Depression

Depression, also known as major depressive disorder (MDD), is a mood disorder whereby pediatric patients experience feelings of sadness, hopelessness or irritability while losing interest in previously enjoyed activities. Somatic and cognitive changes significantly impact the patient's ability to function. Diagnosis depends on persistence of symptoms for at least two weeks, although episodes may last much longer. Other forms of depression (e.g., dysthymia, premenstrual dysphoric disorder) exist but discussion of these is beyond the scope of this article.

The signs and symptoms of depression in young people can vary but usually involve mood disturbance (e.g., irritability, sadness or crankiness), physical or biological changes (e.g., changes in sleep patterns, weight loss or gain or restlessness) and changes in thinking, especially negatively (e.g., loss of concentration, inefficient thinking, low self-esteem).

The onset of depression tends to peak during adolescence and young adulthood. When symptoms develop at this early stage, depression is likely to be more severe and complex, with patients taking longer to respond to treatment the longer they are left untreated. It may be for this reason that the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) recommend adolescents over 12 years of age be screened annually for depressive disorders using a recognized and validated self-reporting screening tool.

RISK FACTORS AND DIAGNOSIS

Anxiety or Depression

Several genetic, biological, and environmental factors have been implicated in the development of mental illnesses such as anxiety and depression. Table 1 outlines some of the most common risk factors, acknowledging that this list is not all-inclusive. Numerous validated anxiety and depression screening tools are available to help with assessment of children and adolescents. Diagnosis of anxiety or MDD is based on meeting criteria outlined in the DSM-5 and by ruling out other conditions, medication or substance use that may present with similar symptoms. For a definitive diagnosis of either disorder, symptoms need to cause significant impairment in areas of normal daily functioning or clinically significant distress; in children and adolescents, this could include negative effects in school or engagement with peers.

Comorbid psychological conditions occur commonly in children and adolescents. In the United States (U.S.), approximately 74% of children aged 3 to 17 years with depression were reported to also have an anxiety disorder. Similarly, adolescents with anxiety disorders have significant rates of comorbid depression and a higher risk of developing this condition, particularly severe forms. It is also quite common for different subtypes of anxiety to co-exist.

Confirming the diagnosis of either disorder should also prioritize the assessment of self-harm and/or suicidal thinking. Suicide is the second leading cause of death in people 10 to 24 years of age and youth who are at risk may be missed if not screened adequately. Over 50% of adolescents had a diagnosis of depression in studies of completed suicide. In patients with anxiety, suicidal behaviour significantly increases in the presence of comorbid mood disorders.

TREATMENT

Most mental health issues identified in young adults develop during childhood or adolescence, thus, it is ideal to diagnose and intervene early, implementing care that will have a lifelong impact on patient well-being. Early intervention is necessary for symptom relief and restoration of normal development.

Individual guidelines for the management of either anxiety or depression have been developed; guidelines for anxiety pertain to children and adolescents while those for treatment of depression focus on patients over 10 years of age. The recommended treatment pathways for both disorders employ a stepped care approach, taking into consideration symptom severity, functional impairment, safety concerns, comorbid conditions and accessibility of services. In general, a multimodal approach of psychoeducation, psychotherapy and/or pharmacotherapy is most effective.

In the presence of mild symptoms, psychoeducation, the practice of educating the patient and their family on typical symptoms, causes, possible stressors and coping strategies can help mitigate mild anxiety or depression. Psychotherapy in the form of cognitive behavioural therapy (CBT) is commonly recommended first-line for the management of mild to moderate anxiety, as well as for moderate to severe depression. Patients with mild depression whose symptoms persist after active monitoring may also be candidates for CBT with or without medication. CBT is evidence-based and teaches patients to recognize symptoms and strategies to cope.

For patients with more severe or persistent symptoms of either anxiety or depression, pharmacotherapy on its own or in combination with CBT, may be considered. In clinical trials, monotherapy with either CBT or medication for treatment of depression produced either mixed results or was no better than no treatment, depending on the outcomes measured. Instead, a *combination* of psychotherapy and pharmacotherapy has demonstrated superior efficacy to either alone and is the recommended choice. Several good-quality clinical trials in adolescents with depression have demonstrated the achievement of symptom remission or a reduction in relapse rates when fluoxetine was combined with CBT. Similar results were seen in studies of anxiety. A Cochrane review of 87 studies found that CBT alone was more efficacious at achieving remission of anxiety in children when compared to no treatment. Although CBT is still the best studied psychosocial intervention for this age group, current evidence suggests its use in combination with sertraline was more effective than either treatment used alone. A large trial, the Child-Adolescent Anxiety Multimodal Study (CAMS), also demonstrated that a strong predictor of long-term improvement was the initial patient response to treatment. Use of a combination of sertraline and CBT *early* in the treatment course was significantly superior to the monotreatment arms in achieving remission, boding well for long-term outcomes.

Evidence-based guidelines for anxiety in children and adolescents state that selective serotonin reuptake inhibitors (SSRIs) are the most effective agents, although selective norepinephrine reuptake inhibitors (SNRIs) may also be useful. Guidelines for depression typically recommend only SSRIs. Comparative data within each class is lacking. Currently, fluoxetine is the SSRI of choice due to demonstrated efficacy in numerous clinical trials. Fluoxetine is also preferred due to its long half-life, which makes it a

more tolerable option, particularly when adherence may be difficult in children. U.S.-based guidelines favour specific SSRIs based on FDA approval in these age groups; fluoxetine is approved for treatment of depression in patients ≥8 years of age and escitalopram is approved for the same indication in youth ≥12 years of age. The American Academy of Child and Adolescent Psychiatry endorses the use of SSRIs as the preferred medication for treating anxiety in children and adolescents 6 to 18 years of age. The selection of a specific agent for treatment of either condition should also be based on the potential for side effects, drug interactions and the impact of other medical issues. Table 2 provides an overview of pharmacotherapy choices for use in anxiety and in depression in children and adolescents.

A key factor to using these medications successfully in this younger population is conservative dosing. It is recommended to initiate therapy at a subtherapeutic dose then titrate up in small increments every 1 to 4 weeks, depending on medication half-life and response, until a therapeutic dose is reached. In patients with severe symptoms, titrating at a faster rate (if tolerated) may be needed. Improvement in symptoms may be seen within the first 2 to 3 weeks of use, however, clinically significant improvement is not typically seen until a minimum of 4 to 6 weeks for depression and 6 to 8 weeks for anxiety. For patients with anxiety, maximum benefit may not be achieved until 12 weeks or more of therapy. If partial or no improvement is seen, the dose may be increased to the maximum recommended dose; if already reached, a switch to an alternate medication and/or consultation with a mental health specialist may be warranted.

Once symptom resolution occurs, it is recommended to continue pharmacotherapy for a minimum of one year and regular monitoring is suggested during this time. Monitoring should continue after medication is discontinued, as one study found that the greatest risk of relapse occurred 8 to 12 weeks after stopping medication.

SSRIs/SNRIs AND RISK OF SUICIDE

An increased risk of suicide ideation and/or attempts is a concern in *untreated* anxiety or depression and should be part of the initial assessment. A boxed warning for increased suicidal thinking and behaviour in patients <18 years of age has been added to antidepressant product monographs,

Table 1. Risk Factors for the Development of Anxiety or Depression in Children and Adolescents

Risk Factor		Anxiety	Depression
Biological	Family history of anxiety or parent with anxiety disorder	✓	
	Family history of depression or parent with mental illness		✓
	Being female*	✓	✓
	LGBTIQ identification**		✓
	Frequent somatic complaints	✓	✓
	Weight problems	✓	✓
	Early puberty (females)		✓
	Chronic illness	✓	✓
Psychological	Personal history of other mental health issues including previous depression	✓	✓
	Decreased emotional attachment/connection to others (family, peers, teachers)	✓	✓
	History of use/abuse of alcohol, tobacco, cannabis or illicit drugs	✓	✓
	Loneliness	✓	
	High scores on previous depression screening tools without a depression diagnosis		✓
	Low self-esteem; negative thinking		✓
	Problematic use of social media		✓
	Internet gaming or video game addiction		✓
Environmental	Culturally or linguistically diverse backgrounds with perceived or actual potential for discrimination		✓
	Victim of abuse or bullying	✓	✓
	Exposure to natural disasters, trauma or violence	✓	✓
	Loss of a loved one	✓	✓
	Poor academic performance including learning disabilities (e.g., ADHD, dyslexia)		✓
	Low education	✓	
	Low socioeconomic status / homelessness / housing and food insecurity	✓	✓
	Foster care or adoption		✓
	Limited or excessive parental involvement, aversive parental behaviours (e.g., criticism, conflict), inconsistent parental discipline, lack of parental warmth, poor family functioning	✓	✓
	High leisure-time screen use		✓
	Living in remote or rural areas		✓
	Low physical activity		✓
	Poor sleep patterns		✓
	Lack of autonomy		✓
	Unhealthy diet		✓

ADHD=attention deficit hyperactivity disorder; **LGBTIQ**=lesbian, gay, bisexual, transgender, intersex, queer or questioning

* The risk of depression is higher in adolescent females but the difference in risk between sexes decreases in adulthood.

** Identifying as LGBTIQ may increase a patient's risk of discrimination, marginalization or trauma

based on early meta-analyses findings. For example, pooled absolute rates of suicidal ideation in youth being treated for anxiety were 1% for those taking an antidepressant compared to 0.2% for placebo, with a pooled risk difference of 0.7%. A recent meta-analysis assessing treatment of depression in children and adolescents found no significant risk differences in suicidality between treatment with an SSRI versus placebo. The Canadian Paediatric Society's statement on use of SSRI medications for the treatment of child and adolescent mental illness suggests that the potential benefit of these medications outweigh the potential harms, but that close initial monitoring should always take place.

CONCLUSIONS

Anxiety and depression disorders are becoming more prevalent in children and adolescents. Early intervention with defined treatment options can ensure these patients achieve normal developmental milestones and improved overall well-being. A brief overview of the management of anxiety and depression in children and adolescents has been provided herein; given that inclusion of comprehensive information is beyond the scope of this article, pharmacists are encouraged to seek out the respective guidelines for more detailed information.

Table 2: Medications Used in the Management of Anxiety and Depression in Children and Adolescents

Drug Class Indication for Use in Children / Adolescents	**Generic Drug Name***	**Target Dose Range (mg/day)**	**Tolerability / Precautions**	**Comments**
SSRI • Anxiety • Depression	Citalopram	10 – 40	• Generally well-tolerated. • Most AEs occur within the first few weeks of treatment, are dose-dependent and subside over time. Common AEs: • Dry mouth • Constipation, diarrhea • Nausea, heartburn • Headache • Insomnia, somnolence, sleep disturbances (vivid dreams) • Appetite or weight changes • Myalgia • Sweating • Nervousness • Rashes Serious AEs: • Discontinuation syndrome; most notable with acute disruption of fluvoxamine or sertraline • Behavioural activation: restlessness, agitation, impulsivity, talkativeness; more frequent in children (vs. adolescents) and in anxiety (vs. depression) • Arrhythmia, QT prolongation when citalopram used at doses >40 mg/day • Increased suicidality • Mania, hypomania (rare) • Serotonin syndrome; particularly when combined with other serotonergic medications • Abnormal bleeding (rare); caution use with ASA or NSAIDs • Seizures Drug interactions: • All can interact via CYP450 isoenzyme routes. • Fluvoxamine has the greatest potential. • Citalopram and escitalopram have the lowest.	Choice of Medication: Anxiety: • Fluoxetine is the SSRI of choice. • Fluvoxamine and sertraline have demonstrated some efficacy in clinical trials. Depression: • Fluoxetine is the SSRI of choice in both children and adolescents. • Escitalopram is also used extensively in adolescents. • Citalopram and sertraline have shown efficacy in studies. • Paroxetine is not typically used as it produced negative results in depression studies. In addition, it is considered one of the least tolerable of the SSRIs and is associated with a higher risk of suicidality. • No SSRI is Health Canada-approved for use in patients <18 years of age. • Older antidepressants (MAOIs, TCAs) have not demonstrated efficacy in this patient population. Dosing Considerations: • Effective dose in children/adolescents tends to be lower than that for adults for the same indication. • Younger children or patients with lower body weight may require lower doses. • When treating anxiety with an SSRI, it may be useful to start with a subtherapeutic dose, as initial AEs may include anxiety or agitation. • SSRIs with shorter half-lives (escitalopram, citalopram, sertraline) can be dose-titrated every 1-2 weeks while fluoxetine (longer half-life) should be dose-adjusted every 3-4 weeks. • Discontinuing any SSRI should involve a slow taper to avoid withdrawal effects.
	Escitalopram	5 – 20		
	Fluoxetine	10 – 60		
	Fluvoxamine	100 – 300		

Table 2: Medications Used in the Management of Anxiety and Depression in Children and Adolescents (Continued)

Drug Class Indication for Use in Children / Adolescents	Generic Drug Name*	Target Dose Range (mg/day)	Tolerability / Precautions	Comments
SNRI • Anxiety	Duloxetine	30 – 120	Common AEs: • Dry mouth • Nausea, vomiting, diarrhea • Abdominal discomfort • Dizziness • Headache • Insomnia, somnolence, fatigue • Reduced appetite/weight • Myalgia • Sweating • Tremor • Restlessness/irritability • Hypertension • Tachycardia Serious AEs: • Hepatic failure (abdominal pain, hepatomegaly, elevated transaminase levels) and cholestatic jaundice have been associated with duloxetine. • Severe skin reactions (erythema multiforme, Stevens-Johnson syndrome) have been reported with duloxetine. • Discontinuation syndrome can occur with missed doses or abrupt discontinuation • Behavioural activation/agitation • Increased suicidality, particularly with venlafaxine • Mania, hypomania • Serotonin syndrome • Abnormal bleeding (rare) • Seizures • Potential for overdose fatalities Drug interactions: • Can interact via CYP450 isoenzyme routes. • Duloxetine can interact with drugs metabolized via CYP1A2 and CYP2D6. • Venlafaxine has the least effect on CYP450 routes.	Choice of Medication: • Use of SNRIs in child/adolescent anxiety is considered an additional treatment option. • May be considered for social anxiety, generalized anxiety disorder, separation anxiety or panic disorder. • Most study data regarding use of SNRIs in anxiety is with venlafaxine or duloxetine. • Venlafaxine may have a higher suicide risk.
	Venlafaxine	37.5 – 225		

AE=adverse effect; **ASA**=acetylsalicylic acid; **CYP**=cytochrome P(450); **MAOI**=monoamine oxidase inhibitor; **mg**=milligram(s); **NSAID**=non-steroidal anti-inflammatory drug; **SNRI**=selective norepinephrine reuptake inhibitor; **SSRI**=selective serotonin reuptake inhibitor; **TCA**=tricyclic antidepressant

* Only those SSRI and SNRI agents included in the respective anxiety or depression guidelines for children and adolescents have been included.

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