Pharmacotherapy for anxiety disorders in children and adolescents

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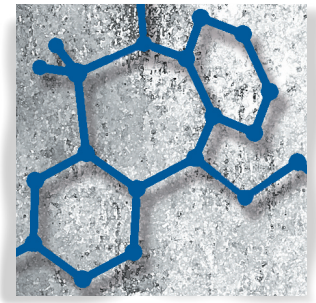

Anxiety disorders are the most common mental health diagnoses in youth, and carry risks for ongoing impairments and subsequent development of other psychiatric comorbidities into adulthood. This article discusses considerations for assessment and treatment of anxiety disorders in youth, with a focus on the evidence base of pharmacologic treatment and important clinical considerations to optimize care. We then briefly describe the impact of anxiety on neuronal elements of fear circuitry to highlight how treatments may ameliorate impairments through enhanced plasticity. Overall, pharmacotherapy for anxiety disorders is effective in improving clinical symptoms, particularly in combination with psychotherapy. Response is typically seen within several weeks, yet longitudinal studies are limited. Selective serotonin reuptake inhibitors are thought to be relatively safe and effective for acute treatment of several classes of anxiety disorders in youth, with increasing evidence supporting the role of neuronal plasticity in recovery.

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Introduction

Anxiety is a normal response to environmental stressors, and promotes safety by facilitating behavioral avoidance of threatening stimuli. This sense of threat is modulated by fear circuitry, including amygdala, hippocampus, and prefrontal regions. Anxiety disorders are thought to involve alterations in fear responsivity, driven by adjustments in the tuning of specific circuit components, including deficiencies in the dampening of amygdala stress responses by prefrontal regions.[1] The neuronal circuitry involved in the regulation of anxiety operates within a context of environmental cues and across a developmental landscape, such that assessment of normal developmental tasks and environmental stressors are essential for clinical evaluation. The distress associated with clinical anxiety often elicits intense escape urges, offering immediate symptom relief. This avoidance is so reinforcing that it may rapidly become habitual, resulting in increasingly impaired functioning. Treatment requires reducing reinforcements associated with avoidance while gradually empowering youth to tolerate anxiety in the face of potentially stressful challenges.

Pharmacologic interventions may confer clinical benefit by reducing the degree of anxious reactivity, thereby

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increasing the range of opportunities for children to learn more adaptive responses to stressful stimuli. With successful treatment, extinction of recurrent anxiety symptoms is thought to require neuronal plasticity to take effect, similar to other forms of learning. Selective serotonin uptake inhibitors (SSRIs) and other treatment modalities are thought to facilitate these neurochemical and neuroanatomical enhancements, contributing to clinical effectiveness.[2] This enhanced neuroplasticity may also contribute to better response rates by augmenting other interventions such as psychotherapy.

Assessment and diagnosis of anxiety

Initial identification of anxiety disorders in children and adolescents often occurs during medical visits to primary care providers. Presenting concerns typically include avoidance of age-appropriate tasks, or excessive physical complaints such as headaches, dizziness, or stomachaches, which are particularly common presenting signs of anxiety at younger ages.[3] Physical complaints related to anxiety can be diverse,[4] and are often highly concerning to parents. A timeline of physical, psychological, and behavioral symptoms, elicited from both the child and parents, is valuable to assess the evolution of symptoms and consider exacerbating factors. A broad review focused on the association between symptoms and psychosocial stress is also recommended, including past medical history and family history of psychiatric illnesses and substance abuse. General screening measures tailored to developmental level are available for providers to help identify children with psychosocial difficulties,[5] and self-reports may help to identify anxiety in children who are disinclined to reveal symptoms during examination.[6]

Medical evaluation

Despite the potential for physical symptoms to represent somatic complaints driven by anxiety, consideration of common medical issues related to anxiety disorders is essential.[9,7] Physical examination and judicious laboratory testing targeting potential underlying relevant medical problems should be performed.[8] Common screens include tests for endocrine abnormalities (thyroid and fasting glucose), urine toxicology, respiratory problems, sleep abnormalities, cardiac conduction defects (particularly if considering tricyclic agents), and seizure activity. Pertinent findings can guide more specialized and optimum management of symptoms, yet excessive testing or otherwise providing reinforcement of symptom emergence through heightened interventions is not recommended.

Treatment of anxiety disorders

A multimodal treatment approach, including a combination of medication, therapy, and environmental interventions, is increasingly shown to confer greater improvement in symptoms compared with unimodal treatments. Although the essential elements of successful therapy are not clear, cognitive-behavioral therapy (CBT) studies have extensively demonstrated effectiveness in individual, group, and family formats.[9] Randomized controlled trials (RCTs) of CBT have shown benefit for Generalized Anxiety Disorder (GAD),[10-14] social anxiety disorder,[10-14] panic disorder,[13] obsessive–compulsive disorder (OCD),[14-16] and post-traumatic stress disorder (PTSD).[18] These benefits have also been found to be maintained over time.[19] Therefore, for youth who meet criteria for anxiety disorders with mild-to-moderate functional impairments, the American Academy of Child and Adolescent Psychiatry recommends psychoeducation for patients and their families and initially deferring use of medication to CBT.[20]

However, for youth with moderate to severe anxiety symptoms, multimodal treatment is recommended, including medication in combination with CBT.[21] Multiple RCTs support the efficacy of SSRIs, both alone and in combination with therapy, for the treatment of anxiety disorders in children and adolescents. Medication intervention may be started concurrently with psychotherapy, or may be initiated before starting therapy to reduce the impairing nature of severe symptoms and promote treatment effectiveness. Medication can also be added after engagement in CBT if initial psychotherapy does not provide satisfactory relief of symptoms. It is important to recognize that both psychotherapy and medication management result in improvement, but not necessarily in full remission of symptoms.

When considering pharmacologic agents, selection should be guided by the evidence base and clinical guidelines, with special consideration for side-effect profiles and unique clinical characteristics to optimally tailor care. Informed consent is required from parents, and when possible, from the child or adolescent. States vary in policies regarding obtaining consent or assent from

youth. Even if not required, direct discussion of medication use with the patient is likely to improve compliance and engagement irrespective of age.

When initiating medications, frequent visits with the prescriber, typically every 2 to 4 weeks, are recommended to closely monitor for effectiveness and tolerance. Regular communication between the prescriber and the treating therapist is also encouraged. More frequent provider contact is also recommended when there is a history of depression, a strong familial preference, or when compliance is a concern. Standardized rating scales should be used to measure treatment effectiveness. After an effective dose of medication is reached, visit frequency may be reduced. Even after symptom resolution, cautious treatment calls for medication maintenance for 1 year, followed by a gradual tapering off to allow observation of any recurrence of symptoms.[22]

Evidence for effectiveness of SSRIs and SNRIs

A limited number of RCTs have evaluated antianxiety agents in children and adolescents. To date, no medications have been approved by the FDA for treatment of non-OCD anxiety in youth. Four medications have been approved for OCD treatment in children and adolescents. Medication and placebo response rates range across studies, which are difficult to compare due to limited clinical samples and variability in measures of assessment and clinical response. Yet positive results have been demonstrated for multiple agents in the treatment of anxiety in both youth and adults, particularly medications targeting serotonin reuptake. A meta-analysis of RCTs examining the tolerability and efficacy of pharmacotherapy for anxiety disorders in youth found that SSRIs and SNRIs showed clear benefit with an overall response rate almost double that of placebo.[23]

Regarding specific pediatric anxiety subtypes, OCD has the largest number of positive RCTs, which reveal clinical benefit after treatment with sertraline,[15,24] fluoxetine,[25,26] fluvoxamine,[27] or paroxetine.[28,29] Evidence for citalopram is limited to open-label studies[30-32] and comparison with fluoxetine without placebo.[33] SSRIs are first-line therapy for pharmacologic management of anxiety disorders in youth, and three of the four medications approved by the FDA for treatment of OCD in children and adolescents are SSRIs: sertraline (≥6), fluoxetine (≥7), and fluvoxamine (≥8).[3]

The highest regarded clinical trial examining the impact of both manualized psychotherapy and medication on symptoms of OCD in youth is the Pediatric OCD Treatment Study (POTS). In this study, sertraline's effectiveness in pediatric OCD for 12 weeks was compared with CBT, combined treatment, and placebo.[13] Each active treatment arm proved superior to placebo, and combined treatment was superior to either CBT or sertraline alone. Another RCT examining sertraline for youth with OCD also found significantly greater improvement after active treatment compared with placebo,[24] with lasting effects in 70% of patients who were examined 12 months later.[35]

A 10-week RCT of pediatric outpatients with OCD showed fluvoxamine to be effective.[27] Despite the common clinical finding that weeks of treatment with SSRIs are required prior to symptom response, improvements beyond placebo were evident by the first week and showed gains through the course of treatment.

Other SSRIs with RCTs demonstrating effectiveness in the treatment of pediatric OCD include paroxetine[28,29] and fluoxetine.[25,26] Notably, fluoxetine treatment required 8 weeks prior to showing effectiveness over placebo, and a higher dose only lengthened this response time. Secondary analyses also showed that paroxetine demonstrated significantly lower response rates among youth with OCD and comorbid illness such as ADHD, tic disorders, or oppositional defiant disorder (ODD).[29] Overall, these clinical studies suggest a moderate treatment effect that is relatively similar across SSRIs.[23]

Despite the much greater prevalence of non-OCD anxiety disorders, studies are more limited in children and adolescents. Furthermore, subtypes are often mixed within treatment arms, limiting the ability to compare response to treatment by specific disorder. Nevertheless, RCTs of SSRIs have demonstrated efficacy in the treatment of GAD, separation anxiety disorder (SAD), and social phobia, often in mixed populations with any one or a combination of these *(Table I)*. Although the data are limited, the average likelihood of pharmacologic treatment response for non-OCD disorders appears to be slightly greater than for OCD.[23]

The largest RCT of non-OCD anxiety disorders to date is the Childhood Anxiety Multimodal Study (CAMS), which evaluated treatment of SAD, GAD, and social phobia.[36] Treatment groups included sertraline only, CBT only,[37] combination treatment, or placebo. All three active treatments were superior to placebo (24%), with

the highest response in the combined condition. These findings again suggest that, while monotherapy with either medication or psychotherapy alone can be effective for treating anxiety disorders, a multimodal approach is more likely to be successful. This method is also thought to apply to pediatric depression[38] and complex forms of ADHD,[39] while evidence for combination therapy is limited for youth with PTSD.[40,41]

Other agents with demonstrated efficacy for youth with non-OCD anxiety include fluvoxamine[42,43] and fluoxetine.[44] An open-label follow-up study showed that 94% of the fluvoxamine responders exhibited a sustained benefit after 6 months.[44] Furthermore, nonresponders to initial fluvoxamine treatment still exhibited a high rate of response to a subsequent open-label trial of fluoxetine, supporting the clinical benefit of a subsequent trial using alternative SSRIs despite an initial lack of response to one agent.

Fewer studies have examined selective cohorts with diagnoses of specific non-OCD anxiety disorders. An RCT examining paroxetine treatment in youth specifically with social anxiety showed efficacy over placebo.[35] In addition, a small RCT of youth with GAD found a robust response to sertraline after 9 weeks, in contrast to a low placebo response.[45] RCTs of medication response in youth with PTSD indicate limited improvement in

RCT Author	Medication	Length (weeks)	Dosing (mean)	Total *N*	Ages and diagnoses	Effect size of treatment	Number needed to treat	Clinical outcome/ response rate	Notable side effects
RUPP Anxiety Study Group, 2001[43]	Fluvoxamine (FLV)	8	Fixed-flexible. (4.0 mg/kg/day)	128	6–17 GAD, SoP, SAD	1.1	2	CGI-I ≤ 2 FLV 76% PBO 29%	Abdominal discomfort, ↑ Activity
Rynn, Siqueland, & Rickels, 2001[46]	Sertraline (SER)	9	Fixed. (50 mg)	22	5–17 GAD	1.9	1	CGI–I ≤ 2 SER 90% PBO 10%	
Birmaher et al, 2003[45]	Fluoxetine (FLX)	12	Fixed. (20 mg)	74	7–17 GAD, SoP, SAD	0.4	4	CGI-I ≤ 2 FLX 61% PBO 35%	Abdominal pain, agitation
Wagner et al, 2004[36]	Paroxetine (PAR)	16	Flexible. 10–50 mg/day (24.8 mg)	322	8–17 SoP	N/A	3	CGI-I ≤ 2 PAR 78% PBO 38%	Insomnia, ↓ Appetite, vomiting, agitation
Black & Uhde, 1994[133]	Fluoxetine (FLX)	12	Fixed. (0.6 mg/kg/day)	15	6–11 Elective mutism	0.67	N/A	CGI-I ≤ 3 FLX 80% PBO 40%	
Walkup et al, 2008[37]	Sertraline (SERT)	12	Fixed-flexible. COMB (133.7 mg) SERT (146.0 mg)	488	7-17 GAD, SoP, SAD	COMB=0.86 SERT=0.45 CBT=0.31	COMB=1.7 SERT=3.2 CBT=2.8	CGI-I ≤ 2 COMB=80.7% SERT=54.9% CBT=59.7% PBO=23.7	Insomnia, fatigue, restlessness
March et al, 2007[50]	Venlafaxine ER (VFX)	16	Weight-based flexible. (141.5mg)	293	8-17 SoP	0.46	5	CGI-I ≤ 2 VFX=56% PBO=37%	Anorexia, asthenia, nausea
Rynn et al, 2007[49] (pooled studies)	Venlafaxine ER (VFX)	8	Weight-based, flexible.	320	6-17 GAD	0.42	N/A	CGI-I ≤ 2 VFX=69% PBO=48%	Headache, abdominal pain, anorexia

Table I. Randomized controlled trials of SSRIs and SNRIs in pediatric non-OCD anxiety disorders. CGI–I: Clinical Global Impressions-Improvement Scale; COMB: combined; CBT: cognitive-behavioral therapy

symptoms with the addition of sertraline to trauma-focused CBT,[40] and lack of efficacy compared with placebo after 10 weeks.[41] Some studies have shown benefit from SSRIs,[47] yet trauma-focused CBT has shown more consistent effectiveness.[47] To date, no RCTs have examined medication effects in children or adolescents with panic disorder.

Aside from SSRIs, medications with dual inhibiting actions on serotonin and norepinephrine (SNRIs) have also been tested in youth with anxiety disorders. Specifically, venlafaxine XR was examined in two 8-week RCTs in children with GAD. Despite insignificant improvement on a primary measure in one of the trials, pooled results revealed significantly greater response in the active medication group compared with placebo.[48] Another 16-week RCT of venlafaxine XR in children with social anxiety showed significant benefit beyond placebo.[49] However, studies of venlafaxine in children indicated a risk for elevated blood pressure, decreased growth rate, and increased suicidal ideation, which should be considered with families prior to initiating treatment. A meta-analysis of RCTs examining the tolerability and efficacy of pharmacotherapy for anxiety disorders found that SSRIs and SNRIs showed clear benefit with an overall response rate almost double that of placebo treatment, with SSRIs slightly more beneficial than venlafaxine XR.[23]

Due to the lack of comparative head-to-head RCTs of SSRIs or SNRIs, choice of agent is often based on side-effect profiles, interactions with other medications, and family history of medication response. Furthermore, only short-term benefits have been evaluated in RCTs, and research findings may not generalize to clinic populations due to exclusion of youth with medical or psychiatric comorbidities.

Age may also be an important consideration in pharmacotherapy. Despite age-related differences in metabolism and observations that SSRIs may be more effective in the treatment of adolescent depression compared with depressed younger children, findings from RCTs in anxious youth do not show differential effects based on age.[23,50] The evidence base is particularly limited for pharmacologic treatment of anxiety in children under the age of 6.[51] Given the limited pharmacologic data, CBT, tailored to developmental level, is considered to be the first line treatment in children this young. In cases with high acuity unresponsive to psychotherapy, medication treatment may be considered.

Safety concerns with SSRIs and SNRIs

Heightened concern for the negative effects of SSRIs and SNRIs in youth, particularly for activation and emerging suicidality, have impacted familial willingness and clinical practice to initiate treatment with these agents, particularly for children with anxiety.[52] Clinical practice suggests that children with anxiety tend to be more sensitive to potential side effects of these medications, particularly physical discomfort. Lower starting doses should be considered to mitigate these effects. Other common side effects include nausea, headaches, sleep abnormalities, and sexual side effects of reduced libido and physical responsiveness. Dropouts in RCTs as a result of adverse events from SSRIs and SNRIs were almost twice as common among subjects taking active medication compared with placebo.[24] Side effects tend to emerge earlier in the course of treatment or during dosage adjustments, and may subside over days to weeks. Importantly, antidepressants carry a black-box warning from the FDA out of concern that they may potentiate suicidal thinking, a low-frequency event that nevertheless warrants prior consent[53] and the development of a monitoring strategy. Suicidal thoughts may be related to the activating effects of SSRIs, resulting in heightened somatic experiences of anxiety, increased emotional lability, and impulsivity. Results from a RCT examining activation as a side effect of fluvoxamine in anxious youth indicated heightened risk of activation throughout the course of titration.[54]

Despite their relative safety and tolerance, abrupt discontinuation of shorter-acting agents often results in generalized discomfort and flu-like symptoms. Medications often require 4 to 8 weeks to provide clinical benefit, and potentially longer when starting with low doses. Educating families about these expectations and concerns often prevents them from abandoning medication trials prematurely.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have also shown efficacy in several RCTs of youth with anxiety, particularly clomipramine, which carries an FDA indication for treatment of OCD in children aged 10 and over. RCTs examining treatment of social anxiety or school refusal have shown benefits of both imipramine[55-57] and clomipramine.[58,59] Although TCAs may be considered for

patients who have experienced intolerance to SSRIs, or as augmentation to SSRIs for partial response in youth with OCD.[60] TCAs are generally less preferred because they require EKG monitoring due to the potential for cardiac abnormalities, carry high risk of fatality in overdose, and have constipation and sedation as side effects.

Other agents

Controlled trials do not support the use of benzodiazepines in children[61,62] yet open-label studies indicate symptomatic benefit,[63] and multiple agents in this category are used in clinical practice for highly anxious children. Prior to initiating treatment, it is important to discuss management issues, the potential for tolerance, risk of seizure from abrupt discontinuation, and that short-term rather than long-term use is preferred due to addiction potential. Benzodiazepines can also cause cognitive blunting or disinhibition in some children, leading to behavioral agitation. Nonetheless, when children have severe symptoms unresponsive to other treatments, benzodiazepine use early in treatment can help to reduce symptoms and promote participation in therapy or school attendance, particularly before SSRIs become effective. No long-term studies are available for use in children, but benzodiazapines are noted to have potential for psychological and physical dependence in adults.[64]

Several other agents have been used in clinical practice, but have more limited support in the literature. Buspirone, a partial agonist of serotonin receptors, demonstrated effectiveness at 2 weeks with no adverse effects compared with placebo in a small placebo-controlled study with mixed anxiety disorders.[65]

Central α-agonists, guanfacine and clonidine, have been considered in treatment of youth with PTSD and dysregulated behavior.[66] However, controlled research supporting the use of these agents is lacking. A small open-label study of clonidine in patients aged 3 to 6 with PTSD was shown to decrease arousal, aggression, and anxiety.[67]

Mirtazapine is an antidepressant with some evidence of efficacy for treating anxiety in adults.[68] Evidence in youth is limited, with one positive open-label study for social phobia.[69] This agent may be a consideration to capitalize on its sedating and appetite-stimulating properties for

Treatment algorithm	**Select SSRI. Titrate up every 2-4 weeks until symptoms respond, until side effects preclude further dose increases, or when reach max dose. If ineffective or intolerable, use alternate SSRI for 2nd trial.** →				
Class	**SSRI**				
Medication	**Sertraline**	**Fluoxetine**	**Fluvoxamine**	**Citalopram**	**Paroxetine[a]**
Starting dose	12.5-25 mg	5-10 mg	12.5-25 mg	5-10 mg	5–10 mg
Total therapeutic dose range	50-200 mg	10-60 mg	50-200 mg (Rx bid above 50 mg)	10-40 mg	10-40 mg
Common side-effect profile	Nausea, sedation, headache	Activation, nausea, insomnia	Hyperactivity, abdominal discomfort	Somnolence, insomnia, diaphoresis	Sedation, nausea, dry mouth
Special warning/ monitoring	Suicidality, activation (restlessness, impulsivity), Serotonin Syndrome; Develop safety plan and means to assess early side effects, which may resolve in 1-2 weeks; avoid abrupt discontinuation with paroxetine, sertraline, fluvoxamine, and citalopram.				
Specific indications	GAD	Long half-life		No RCTs; little interactions	Social phobia; non-depressed
FDA approval	For OCD; ≥ 6	For OCD; ≥ 7	For OCD; ≥ 8	For adults	For adults

Table II. Treatment algorithm for pediatric anxiety pharmacotherapy. [a]In June 2003, the FDA recommended against the use of paroxetine for Major Depressive Disorder in children and adolescents. EKG, electrocardiogram; BP, blood pressure; 5-HTa PA, serotonin partial agonist; Rx, prescribe; HTN, hypertension; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor; GAD, generalized anxiety disorder

patients with insomnia or low appetite who are unresponsive to SSRIs.

Propranolol is another agent with some evidence of effectiveness in adults, but lacks systematic data to support its use in children and adolescents. A crossover pilot study of propranolol in 11 pediatric patients with PTSD also showed improvements relative to placebo in treating symptoms of hyperarousal and intrusivity in the majority of patients.[70]

There are also a variety of other agents that are occasionally used despite the lack of controlled evidence. For example, buproprion, an inhibitor of dopamine and norepinephrine, has not been studied in children or adolescents with anxiety. Similarly, gabapentin has limited evidence of improvement in anxiety symptoms in adults,[71,72] but has not been tested in youth.

Another intriguing possibility is D-cycloserine, a partial agonist at the N-methyl-D-aspartate receptor that is thought to potentiate gains from exposure therapy. Two RCTs have supported its use as an augmentation strategy for youth with OCD[73] and social anxiety disorder.[74] While D-cycloserine does not have direct benefits in the absence of other treatments, it is thought to increase the efficacy of psychotherapy by facilitating mechanisms of neuroplasticity.[75]

Complementary and alternative remedies are often tried by families prior to seeking psychiatric treatment. One study found that "anxiety and stress" was the third most common reason for the use of complementary and alternative medicines in children and adolescents.[76-77] While rigorous evidence is lacking to support the use of naturopathic medications, the plant Kava has some evidence of effectiveness in multiple treatment trials.[78] In addition, a review of medicinal plants for the treatment of anxiety disorder found that ginkgo biloba and matricaria recutita showed effect sizes similar to those in studies of antidepressants and benzodiazapines.[79]

Overall, the use of SSRIs remains the first-line treatment, with the best evidence-base. However, for the patients who can not tolerate or do not benefit from SSRIs, a variety of other treatment options can be considered. A proposed treatment algorithm is described in *Table II*, and is expected to need refinement as clinical evidence grows.

After 2 failed SSRI trials, reassess or consult, consider clomipramine for OCD; VFX for non-OCD. →		**If still no response, or familial preference, consider buspirone or mirtazepine, alone or as augmentation.** →		**Consider benzodiazepines for acute relief of severe symptoms or after no response to multiple trials.** →	
Tricyclic	**SNRI**	**5-HTa PA**	**Tetracyclic**	**Benzodiazepine**	
Clomipramine	**Venlafaxine XR (VFX)**	**Buspirone**	**Mirtazapine**	**Clonazepam**	**Lorazepam**
25 mg	37.5 mg	5 mg tid	7.5-15 mg	0.25-0.5 mg	0.5-1 mg
100–150 mg	75–225 mg (Rx qhs or bid)	1–60 mg (Rx tid)	7.5–30 mg (Rx qhs)	0.25– mg (Rx qd-tid)	0.5– 6 mg (Rx qd-qid)
Dry mouth, constipation, diaphoresis	Nausea, sedation, dizziness	Sedation, disinhibition, headache	Hunger, sedation, dizziness	Sedation, confusion	Sedation, confusion
Hypotension, rebound HTN, lethal in OD; level ≤400	HTN, tachycardia, suicidality	Safe with benzodiazepines	Weight gain	Disinhibition, tolerance, seizure from discontinuation	Disinhibition, tolerance, seizure from discontinuation
OCD; EKG, BP. Monitoring to minimize overdose risk	GAD; Non-depressed	Augmentation; sexual side effects	Appetite stimulation, insomnia; few interactions	Short-term relief of acute anxiety; longer acting	Short-term relief of acute anxiety; shorter acting; liver impaired
For OCD; ≥ 10	For adults	For adults	For adults	For adults	For adults

Table II. Continued

Treatment considerations informed by diagnosis

Youth diagnosed with one anxiety disorder are quite likely to have multiple anxiety disorders concurrently, including Major Depressive Disorder, Attention Deficit-Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Tourette's Disorder.[36,80] In CAMS, among youth who met criteria for one or more anxiety disorders, 46% met criteria for other internalizing disorders, 11.9% for ADHD, 9.4% for ODD, and 2.7% for tic disorders.[36] Providers should therefore broadly evaluate anxiety symptoms, and assess the degree of impairment thought to be driven by subtypes in order to prioritize treatment. Attention to these comorbidities is essential for comprehensive treatment but may require a stepwise approach.

Risk factors for having a combination of depression and anxiety include older age and greater severity of anxiety symptoms.[80] Although most RCTs of anxiety exclude depressive disorder diagnosis from entry, open-label use of citalopram showed a significantly lower rate of response in patients with comorbid anxiety and depression versus either alone.[32]

Children with behavioral dysregulation as a result of anxiety may consequently display features of oppositionality, leading to diagnoses of disruptive behavior disorder or ODD. Anxious children may intently refuse to comply with demands of authority figures, such as leaving the house on time or reading aloud in class, and refrain from communicating the intense and often embarrassing fear that drives this oppositionality. Family psychoeducation and school coordination may thus reduce conflict. Following treatment, features of externalizing disorders should be re-evaluated.

Anxiety disorders in children also often co-occur with ADHD.[81] Anxious children may have difficulty paying attention because of hypervigilance or preoccupation with peer concerns, as opposed to ADHD-related impairments. Careful assessment is therefore essential to address the core symptomatology, and also to monitor for potential anxiogenic effects of medications during stimulant trials. Children with ADHD and comorbid anxiety who continued to exhibit anxious features following stimulant treatment did not exhibit any further anxiety benefit from the addition of fluvoxamine to their stimulant regimen when compared with adding a placebo,[82] indicating that polypharmacy should not be assumed to confer improved efficacy in comorbid disorders.

The majority of adolescents with substance abuse disorders have comorbid psychiatric diagnoses, especially anxiety.[83,84] Substance use increases risk for traumatic events and often interferes with appropriate detection and treatment of anxiety disorders.[85]

Anxiety disorders also pose greater risk for developing eating disorders, including anorexia nervosa,[86] and binge eating.[87] Patients may vigilantly attend to food limits to address their anxiety around eating and its consequences, while nutritional benefits often impair brain function and judgment. Fear of eating may further result in extreme avoidance to psychotherapy. There is minimal evidence supporting the use of SSRIs to aid weight restoration,[88] yet pharmacologic management may nevertheless be helpful to address co-occurring anxiety or depression.

Children with Autism Spectrum Disorders (ASDs) often exhibit agitation and anxious responses to many stimuli, including ritualistic and obsessive behaviors.[89] The most common comorbid diagnosis with ASDs is social anxiety disorder.[90] One meta-analysis of the limited data on treatment of children with ASDs found that SSRI treatment was associated with reduced anxiety, decreased repetitive behaviors, and improved global function.[91] However, two recent autism studies using citalopram and fluoxetine for ritualistic behaviors were negative, and another meta-analysis raised concerns for lack of efficacy and risk of side effects when compared with placebo groups.[92,93] Clinical recommendations nevertheless include consideration of SSRI use with symptoms of anxiety in some children and adolescents with autism spectrum disorder.[94]

Although trichotillomania, or impulsive repetitive hair-pulling, is listed as an impulse control disorder, the triggers for repetitive hair-pulling are often anxious thoughts,[95] and urges to pull are typically accompanied by anxiety.[95,96] However, treatment studies using SSRIs have shown low response rates.[97,98] CBT with "habit reversal therapy" is the recommended first-line treatment.[99] While co-occurrence of the motor impairments of Tourette's Disorder with OCD is very common, treatment of one disorder is not thought to significantly impact the symptomatic impairments related to the other.[100]

In contrast to pharmacotherapy for anxiety disorders in youth, there are many more FDA approved-medications for the treatment of anxiety in adults. These include multiple benzodiazepindes (alprazolam, clomipramine, clorazepate, lorazepam, oxazepam); multiple SSRIs (parox-

etine, fluoxetine, fluvoxamine, escitalopram, sertraline); SNRIs (venlafaxine); tricyclics (amitriptyline), MAO inhibitors (phenelzine), and miscellaneous agents (buspirone and hydroxyzine). These findings do not necessarily support use in youth.

Neuroscience perspectives on anxiety disorders and treatments

As described elsewhere in this issue, anxiety disorders in children and adults involve alterations in fear responsivity, driven by adjustments in the tuning of specific components of fear circuitry.[101,102] Excessive fear responses are further thought to induce lasting structural changes in several components of synaptic connectivity and plasticity, contributing to the maintenance of anxiety symptomatology, even when stressors are strictly avoided.[103] Increasing understanding of anxiety treatments, including both pharmacotherapy and CBT, reveals that beyond avoiding stressors or simply forgetting past associations, alleviating the negative impact of experiences requires active learning mechanisms, thought to reorganize brain structure and function. Behavioral improvements in animal models of anxiety are thus prevented when these plasticity mechanisms are experimentally inhibited.[104] Successful treatments likely facilitate further neuronal adaptation to meet the demands of appropriately responding to stressful stimuli. Improvements in the understanding of neural circuitry related to this adaptive resilience, in addition to understanding the processes that catalyze change in these circuits, allows for emerging neuronal targets to enhance treatment.

Multiple types of learning are known to induce structural adaptation in brain connectivity and function, and this response is tailored to meet the demands of the specific learning tasks; while the aerobic demands of treadmill activity induce greater blood vessel growth in rat cerebellar cortex, the increased learning demands of acrobat training are associated with growth of synaptic connectivity, termed synaptogenesis.[105] Stress can induce emotional learning and similarly cause a specific patterns of alterations in synaptic architecture. Evidence from human childhood trauma studies suggest these alterations may become maladaptive in extreme stress, resulting in future volumetric reductions in hippocampal regions when associated with subsequent PTSD.[106] Rodent models of chronic restraint stress (CRS) from repeated confinement results in behavioral changes suggestive of anxiety and depression. Neuroatanomic changes include significant decreases in prefrontal and hippocampal neuron dendrites, including reduced length, branching, and postsynaptic spine number.[107] This morphologic plasticity may initially be an adaptive response to potential cytotoxicity, limiting vulnerability from exposed excitatory receptors,[108] but when excessive, eventually leads to impairments in structural plasticity.[109,110] Despite the known adverse effects of severe stress on neuronal circuitry and plasticity,[111] some stressful experiences may actually confer future resilience, particularly under later high stress conditions.[112,113]

Similar to synaptogenesis and dendritic remodeling, neurogenesis is understood as a lifelong adaptive brain response which may be impacted by anxiety and its treatments. Neurogenesis is upregulated by experiential factors such as enriched experience, while decreased in many animal paradigms of stress and depression.[114] Similarly, the expression of neurotrophins and their receptors, thought to underlie rapid changes in dendritic and synaptic architecture, is impaired by stress and enhanced under many learning conditions.[115] Interference with neurogenesis or neurotrophic factor production in the hippocampus prevents the behavioral effects of antidepressants to improve fearful responses in experimental animals.[116] Medications and CBT may therefore ameliorate maladaptive structural and neurochemical responses by increasing the resilience of stress circuitry to impairments in neuronal and synaptic proliferation, thus allowing greater synaptic connectivity, adaptability, and preserved function.[107]

This notion is supported by experimental findings of SSRI-induced trophic changes in several neuronal elements, including promoting neurotrophin expression and neurogenesis in brain regions relevant to anxiety disorders.[117] SSRIs have been shown to block the impairing effect of stress on hippocampal neurogenesis and induce both improved behavioral responses and elevations in multiple synaptic remodeling proteins.[118] Furthermore, chronic, but not acute, administration of SSRIs increase the expression of neurotrophic factors,[115] suggesting that the delay in clinical response to SSRIs may reflect the time course of neurogenesis or other changes in neuronal excitability.[11]

Several other antianxiety medications, including SNRIs, have been found to normalize behavior, and also restore neurotrophin levels, in experimental animals. After

repeated restraint stress to rats, venlafaxine accelerated restoration of neurotrophin levels and hippocampal neurogenesis.[120] Duloxetine was also shown to increase local neurotrophin transcription at synapses, enhancing plasticity, and this effect was only seen after chronic administration.[121]

Several of the mediators known to affect anxiety responsivity, including both stressful experiences and therapeutic medications, are further thought to operate through epigenetic mechanisms involving changes in the regulation of chromatin arrangements by histone proteins.[122,123] Similar neurotrophic effects in animals, mediated by histone acetylation, are seen following environmental enrichment treatments, with improved plasticity and learning, even in mice with history of severe stress or neurodegeneration.[124-126]

As neurogenesis is limited to circumscribed brain regions after early brain development, and SSRIs have been shown to induce synaptic remodeling and behavioral improvements even when neurogenesis is prevented,[127] it is unlikely that one plasticity mechanism is solely responsible for the improvements related to pharmacotherapy for anxiety and mood disorders. Indeed, aside from changes in synaptic architecture, neurochemical, physiologic, hormonal, and molecular mediators are also thought to play essential roles in the response to stress and its treatments.[128] Furthermore, while neuronal plasticity and dendritic enhancements allow for change and implementation of more adaptive neuronal networks, they may also confer risk to greater consolidation of maladaptive responses,[129] as proliferation is not strictly adaptive. In fact, dendritic proliferation is selectively increased in some amygdala and orbitofrontal neurons in response to stress, and is thought to contribute to impaired reactivity.[130,131]

These findings broadly indicate that anxiety treatments should not exclusively target neurotransmitter deficits but should focus on facilitating more adaptive neuronal reorganization by enhancing the mechanisms of plasticity thought to be impaired as a consequence of pathologic anxiety.[115] Multiple forms of treatment may work synergistically to enhance this adaptive response. Future pharmacologic agents might allow for greater precision in targeting specific neuronal elements thought to modulate this process, particularly those affected in various forms of psychiatric illness.

Conclusion

Anxiety disorders are common in children and adolescents, and contribute to significant impairments in quality of life, often stemming from behavioral avoidance that may limit normative developmental tasks. While there are many more RCTs of pharmacologic treatment of anxiety disorders in adults as compared with youth, there is increasing evidence that carefully implemented intervention with medications improves symptoms in children and adolescents, particularly when high acuity is present. Best practice is for a combination approach of CBT which adheres to manualized models, coupled with medications. SSRIs are the agents of first choice for anxiety disorders, with subsequent switch to an alternative SSRI if a first trial is not successful. Other medication options, including use of tricyclic antidepressants and short-term use of benzodiazepines, may be considered, but lack the evidence base and carry additional risks.

Emerging evidence from animal and human studies suggests that anxiety disorders are associated with changes in neuronal structure and function, and that effective treatments with psychotherapy or medications refine these abnormalities in a number of ways. Future treatments may focus on enhancing this process to allow emotional learning to facilitate resilience, as opposed to contributing to maladaptive stress reactivity. ❑

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Farmacoterapia de los trastornos ansiosos en niños y adolescentes

Los trastornos ansiosos son los diagnósticos más comunes de salud mental en los jóvenes y conllevan riesgos de permanente deterioro y posterior desarrollo de otras comorbilidades en la adultez. En este artículo se discuten los aspectos a tener en cuenta para la evaluación y tratamiento de los trastornos ansiosos en la juventud focalizándose en los fundamentos para la evidencia del tratamiento farmacológico y en importantes consideraciones clínicas para optimizar el manejo. Además se describe brevemente el impacto de la ansiedad en los elementos neurales del circuito del miedo y se destaca cómo los tratamientos pueden disminuir los deterioros al mejorar la plasticidad. En general la farmacoterapia de los trastornos ansiosos es efectiva en la mejoría de los síntomas clínicos, especialmente en combinación con la psicoterapia. Típicamente la respuesta se observa en algunas semanas, aunque los estudios longitudinales son limitados. Se cree que los inhibidores selectivos de la recaptura de serotonina son relativamente seguros y efectivos para el tratamiento agudo de diversas clases de trastornos ansiosos en la juventud, y hay evidencias crecientes que dan sustento al papel de la plasticidad neuronal en la recuperación.

Pharmacothérapie des troubles anxieux chez les enfants et les adolescents

Le diagnostic des troubles anxieux est le diagnostic de santé mentale le plus courant chez les jeunes ; il comporte des risques de détériorations permanentes et de développement ultérieur d'autres comorbidités psychiatriques à l'âge adulte. Cet article analyse les critères d'évaluation et de traitement des troubles anxieux chez les jeunes, et il insiste sur la pertinence du traitement pharmacologique et sur certains aspects cliniques importants pour optimiser les soins. Nous décrivons ensuite brièvement l'impact de l'anxiété sur les éléments neuronaux du circuit de la peur pour souligner comment les traitements peuvent améliorer les troubles par une augmentation de la plasticité. De manière générale, le traitement pharmacologique des troubles anxieux améliore les symptômes cliniques, en particulier en association avec une psychothérapie. La réponse intervient généralement sous plusieurs semaines, mais les études longitudinales restent encore limitées. Les inhibiteurs sélectifs de la recapture de la sérotonine sont relativement sûrs et efficaces pour le traitement aigu de plusieurs types de troubles anxieux chez les jeunes, avec de plus en plus d'arguments en faveur du rôle de la plasticité neuronale dans la guérison.

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