Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders

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Anxiety disorders are among the most common psychiatric disorders in children and adolescents. As reviewed in this guideline, both cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medication have considerable empirical support as safe and effective short-term treatments for anxiety in children and adolescents. Serotonin norepinephrine reuptake inhibitor (SNRI) medication has some empirical support as an additional treatment option. In the context of a protracted severe shortage of child and adolescent−trained behavioral health specialists, research demonstrating convenient, efficient, cost-effective, and user-friendly delivery mechanisms for safe and effective treatments for child and adolescent anxiety disorders is an urgent priority. The comparative effectiveness of anxiety treatments, delineation of mediators and moderators of effective anxiety treatments, long-term effects of SSRI and SNRI use in children and adolescents, and additional evaluation of the degree of suicide risk associated with SSRIs and SNRIs remain other key research needs.

Key Words: clinical practice guideline, anxiety, child psychiatry, assessment, treatment

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The objective of this Clinical Practice Guideline is to enhance the quality of care and clinical outcomes for children and adolescents with anxiety disorders as defined by the *Diagnostic and Statistical Manual of Mental Disorders*.[1] The primary aim of the guideline is to summarize empirically based guidance about the psychosocial and psychopharmacologic treatment of anxiety. A secondary aim is to summarize expert-based guidance about the assessment of anxiety as an integral part of treatment and the implementation of empirically based treatments in clinical practice.

Anxiety disorders are among the most common psychiatric disorders in children and adolescents. At any given time, nearly 7% of youths worldwide have an anxiety disorder[2]; estimated lifetime prevalence in the United States approximates 20% to 30%.[3,4] For specific anxiety disorders among youths 13 to 18 years old, lifetime prevalence rates approximate 20% for specific phobia, 9% for social anxiety, 8% for separation anxiety, and 2% each for agoraphobia, panic, and generalized anxiety.[3]

The median age of onset of anxiety disorders approximates 11 years[5]; however, each anxiety disorder often (but not always) onsets during a specific developmental phase: separation anxiety during the preschool/early school-age years; specific phobias in the school-age years; social anxiety in the later school-age and early adolescent years; and generalized anxiety, panic, and agoraphobia in the later adolescent/young adult years.[6] The development of an anxiety disorder may be foreshadowed by behavioral inhibition,[7] autonomic hyperreactivity,[8] or negative affectivity.[9] Parent/parenting factors,[10] stressful/traumatic exposures,[11] and insecure attachment[12] also may play important etiologic roles. Anxiety disorders (especially generalized anxiety) are highly comorbid with each other and with other psychiatric disorders,[13,14] particularly depression[15] but also bipolar, attention-deficit/hyperactivity disorder (ADHD), learning/language, behavior, obsessive-compulsive, eating, and substance-related disorders. For comorbid occurrences, multifaceted treatment plans likely are necessary.[16]

Although onset can be acute, the course of anxiety tends to be chronic,[17] often with waxing and waning, and exhibits both homotypic (prediction of a disorder by the same disorder) and heterotypic (prediction of a disorder by a different disorder) continuity.[18] Likely reflecting a common underlying vulnerability (eg, "negative valence systems"),[19] examples of heterotypic continuity are the prediction of

panic and depressive disorders in adolescence and adulthood by separation anxiety in childhood, and the prediction of social anxiety in adolescence and adulthood by selective mutism in childhood.

The sequelae of untreated child and adolescent anxiety disorders are manifold, including impairments in social, educational, occupational, health, and mental health outcomes extending from childhood into adulthood.[20-22] Among adolescents with anxiety, 9% were reported to have had suicidal ideation, and 6% made suicide attempts[23]; panic disorder[24] and generalized anxiety disorder with comorbid depression[25] may convey the greatest risk.

Despite the availability of effective treatments for anxiety,[26] less than one-half of youths needing mental health treatment receive any care, and fewer still receive evidence-based care.[27-30] Better identification, assessment, and treatment of anxiety disorders by clinicians from multiple disciplines could have a substantial impact on the individual and public health burden of mental illness in children and adolescents.

OVERVIEW OF THE GUIDELINE DEVELOPMENT PROCESS

Authorship, Source, and Scientific Review

The authors of this guideline (the Guideline Writing Group) are co-chairs and members of the AACAP Committee on Quality Issues (CQI) (https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx).[31] The CQI is charged by AACAP with the development of Clinical Practice Guidelines in accordance with standards promulgated by the Institute of Medicine (IOM)[32] and the Appraisal of Guidelines Research & Evaluation (AGREE) Next Steps Consortium.[33] Both standard sets emphasize *rigor* (critically appraised empirical evidence) and *transparency* (minimization of conflicts of interest and well-delineated guideline development process). CQI chairs are nominated by the AACAP president based upon their expertise and experience in the synthesis of psychiatric knowledge and their lack of relevant conflicts of interest. CQI members are nominated by CQI co-chairs to broadly represent AACAP members in geographic, gender, and professional practice type, duration and setting domains, and to have no relevant conflicts of interest. Prospective CQI members are reviewed and approved by the AACAP president.

In this guideline, statements about the treatment of anxiety disorders are based upon empirical evidence derived from a critical systematic review of the scientific literature conducted by the Mayo Clinic Evidence-based Practice Center under contract with the Agency for Healthcare Research and Quality (AHRQ).[34-36] (Because selective mutism was not included as a primary disorder in studies included in the AHRQ/Mayo review, the treatment of this disorder is not addressed in this guideline). Insofar as available, evidence from meta-analyses published since the AHRQ/Mayo review are presented to support or refute the AHRQ/Mayo findings.[37-43]

Because of sparse or absent empirical evidence, clinical guidance about the assessment of anxiety disorders and about the implementation of empirically based treatments is based primarily upon expert opinion and consensus as presented in chapters in leading textbooks of child and adolescent psychiatry,[44-61] the *DSM-5*,[1] previously published clinical practice guidelines,[62-65] and government-affiliated prescription drug information websites (https://dailymed.nlm.nih.gov/dailymed/[66]; https://www.fda.gov/Drugs[67]).

The peer review and approval process for the draft guideline spanned the period February 1, 2019, to March 11, 2020, and included reviewers representing the following stakeholder groups (see end of this document for complete list): 1) topic experts; 2) other members of the AACAP CQI; 3) other relevant AACAP committees; 4) the AACAP Assembly of Regional Organizations; 5) relevant external organizations; and 6) AACAP members. All suggested edits were considered; however, the CQI Guideline Writing Group exercised editorial authority as to whether the suggested edits were included in the final document. Final approval of the guideline as an AACAP Official Action rested with the AACAP Council.

ASSESSMENT OF ANXIETY

Diagnostic evaluation is an essential prerequisite for the treatment of an anxiety disorder. Specialized clinical education, training, and experience are necessary to conduct a diagnostic evaluation of a child or adolescent in accordance with current psychiatric nomenclature (*DSM-5*[1]). A diagnostic evaluation identifies the following: symptoms; syndromal symptom combinations; symptom frequency, severity, onset, and duration; degree of associated distress and functional impairment; developmental deviations; and physical signs. Clinical expertise is required to differentiate anxiety disorders from normal psychological processes common to human experience.

Identification

At present, there is no empirically based (eg, U.S. Preventive Services Task Force) recommendation for universal

screening for anxiety disorders in children and adolescents. However, in primary care, school, or other child-serving settings, freely available general social—emotional screening instruments (eg, Pediatric Symptom Checklist [https://www.massgeneral.org/psychiatry/treatments-and-services/pediatric-symptom-checklist/[68]]; Strengths and Difficulties Questionnaire [http://www.sdqinfo.com[69]]) can be deployed systematically to standardize identification of anxiety concerns. Early identification of an anxiety concern, if confirmed as a problem upon follow-up assessment, can facilitate early intervention, including guided self-management and focused intervention for subclinical and mild presentations.

In the context of a psychiatric evaluation, symptoms of anxiety typically are identified through spontaneous youth or parent report (the presenting problem or chief complaint), during the clinician's review of psychiatric symptoms, the conduct of the mental status examination, or through input from referral sources. However, because of the variability inherent in nonsystematic methods of identification, a more standardized approach may be useful. As one option, the American Psychiatric Association (APA) developed the freely available parent- and self-rated Level 1 Cross-Cutting Symptom Measures (https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures[70]) to screen for multiple psychiatric disorders including anxiety. These instruments could be included in intake packets to systematically and efficiently gather information about presenting problems prior to the evaluation. The parent and self-rated versions of the Level 1 Cross-Cutting measure have demonstrated good reliability in the *DSM-5* field trials conducted in pediatric clinical samples across the United States.[71]

Evaluation

Clinically significant anxiety (ie, an anxiety disorder) must be distinguished from everyday worries and fears, which are common to the human experience and normative (even when exaggerated) in specific developmental stages (eg, being startled and exposure to strangers in infants, separation from caregiver in toddlers, supernatural creatures in preschoolers, physical well-being and natural disasters in school-aged children, and social and existential concerns in adolescents). In *DSM-5,*[1] mental disorders are defined as "a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning." By *DSM* convention, a mental disorder is diagnosed if all or a threshold of diagnostic criteria for the given disorder are met. Included in most diagnostic criteria

sets is the requirement for a specific frequency and duration of symptoms as well as clinically significant distress and functional impairment, along with the caveat that alternative mental, medical, and substance-related explanations for the symptom presentation must have been ruled out before the diagnosis is applied.

In *DSM-5,*[1] diagnostic criteria are provided for 11 anxiety disorders (one with 8 subcategories).[a] Although the boundaries between psychiatric disorders are now recognized as porous, such that different disorders within and across categories may share similar symptoms, risk factors, and neural substrates, diagnostic precision nonetheless is key for understanding disorder course and prognosis and for guiding empirically based treatment recommendations.

According to *DSM-5,*[1] separation anxiety is characterized by developmentally inappropriate, excessive worry or distress associated with separation from a primary caregiver or major attachment figure. Selective mutism is characterized by absence of speech in certain social situations despite the presence of speech in other situations (usually at home). Specific phobia is characterized by excessive fear or worry about a specific object or situation. Social anxiety is characterized by excessive fear or worry about being negatively evaluated by others in social situations. Panic (ie, abrupt surge of intense fear or discomfort) is characterized by recurrent unexpected panic attacks with physical and cognitive manifestations. Agoraphobia is characterized by excessive fear or worry about being in situations (eg, crowds, enclosed spaces) in which the individual may be unable to escape or get help should panic-like or other overwhelming or embarrassing symptoms occur. Generalized anxiety is characterized by excessive, uncontrollable worries regarding numerous everyday situations or activities. Substance/medication-induced anxiety and anxiety due to another medical condition are characterized by anxiety occurring in the context of substance/medication use or a physical illness. When diagnostic criteria are not fully met for a given anxiety disorder or if a precise diagnosis is not possible due to limited information or other factors, *DSM-5* includes "other specified" and "unspecified" diagnoses to be applied in these circumstances. The "unspecified" diagnosis may be the best diagnostic choice for nonbehavioral health

[a]*DSM-5* Anxiety Disorders with *International Classification of Diseases–10* code: Separation Anxiety Disorder (ICD F93.0); Selective Mutism (ICD F94.0); Specific Phobia (Animal: ICD F40.218, Natural environment: ICD F40.228, Fear of blood: ICD F40.230, Fear of injections and transfusions: F40.231, Fear of other medical care: F40.232, Fear of injury: F40.233, Situational: F40.248, Other: F40.298); Social Anxiety Disorder (F40.10); Panic Disorder (F41.0); Agoraphobia (F40.00); Generalized Anxiety Disorder (F41.1); Substance/Medication-Induced Anxiety Disorder (see substance-specific codes), Anxiety Disorder Due to Another Medical Condition (F06.4); Other Specified Anxiety Disorder (F41.8); and Unspecified Anxiety Disorder (F41.9).

clinicians, who may not possess detailed knowledge of *DSM-5* criteria for specific anxiety disorders.

Evaluation Structure. A diagnostic interview for anxiety includes the parent/guardian and patient, either separately or together or both as developmentally and clinically indicated. Interview of the patient requires a developmentally sensitive approach that may use multiple age-appropriate assessment techniques (eg, direct and indirect questioning, interactive and projective techniques, symptom rating scales, behavioral approach tests). Family assessment can reveal environmental reinforcements for anxiety, and observations of parenting styles and behaviors can identify those that are potentially anxiogenic. Input from collateral sources (records, interviews, rating scales), including (as applicable and with parent/guardian—patient consent) other family members, teachers, primary care and behavioral health clinicians, and/or child agency workers, can add depth and breadth to diagnostic information. Because of the multiple sources of information, a diagnostic evaluation of a child or adolescent may involve more than one session as allowed by current diagnostic billing code (Current Procedural Codes [CPT] 90791, 90792) specifications.

As lack of appropriate linguistic ability or interpreter support has been associated with misdiagnosis as well as adverse clinical outcomes,[72] it is optimal to conduct the diagnostic evaluation in the language in which the child and parents/guardians are proficient. If live interpreter services are not available, telephonic or televideo interpreter services may be an alternative.

Differential Diagnosis. The primary goal of the history of present illness is to determine whether *DSM-5*[1] diagnostic criteria for a specific anxiety disorder are met, and to rule out alternative explanations ("masqueraders") for the symptom presentation. In addition, characterization of previous anxiety presentations and response to previous treatments will inform current treatment choice.

Medical conditions associated with anxiety include (but are not limited to) hyperthyroidism, caffeinism, migraine, asthma, diabetes, chronic pain/illness, lead intoxication, hypoglycemic episodes, hypoxia, pheochromocytoma, central nervous system disorders, cardiac arrhythmias, cardiac valvular disease, systemic lupus erythematosus, allergic reactions, and dysmenorrhea. Although laboratory testing is not routine in the evaluation of a suspected anxiety disorder, in collaboration with the child's primary care practitioner, testing (eg, glucose, thyroid function) can be completed if suggested by signs and symptoms of a medical condition. For anxious youths presenting with somatic symptoms, the nature and severity of those symptoms are noted at baseline

so that the somatic symptoms are not falsely attributed to adverse effects of medication treatment.

Medications that can cause anxiety include (but are not limited to) bronchodilators, nasal decongestants and other sympathomimetics, antihistamines, steroids, dietary supplements, stimulants, antidepressants, antipsychotics, and withdrawal from benzodiazepines (particularly short-acting). Medication reconciliation is a routine part of an evaluation for a suspected anxiety disorder.

A wide array of licit and illicit substances can cause anxiety, including (but not limited to) marijuana, cocaine, anabolic steroids, hallucinogens, phencyclidine, and withdrawal from nicotine, alcohol, and caffeine. Environmental etiologies such as exposure to organophosphates and ingestion of metals (eg, lead, arsenic) can also be considered. Although drug and toxin testing are not routine in the evaluation of a suspected anxiety disorder, testing can be considered if exposure is reported.

Mental conditions that may include symptoms that are similar to those of anxiety disorders are ADHD (distractibility, restlessness), depression (distractibility, insomnia, somatic complaints), bipolar disorder (distractibility, restlessness, irritability, insomnia), obsessive-compulsive disorder (intrusive thoughts, avoidance, reassurance seeking), psychotic disorders (restlessness, agitation, social withdrawal, distractibility), autism spectrum disorder (social withdrawal, social skills deficits, distractibility), and learning disorders (worries about school performance).

Psychiatric Comorbidities. Anxiety disorders commonly co-occur with each other; other common comorbidities include (but are not limited to) depression, ADHD, and behavior, bipolar, obsessive-compulsive, eating, learning, language, and substance-related disorders. With selective mutism, developmental and communication disorders frequently co-occur. Comorbidities may heighten distress and functional impairment and may worsen treatment outcomes. Each comorbid disorder may require a separate treatment plan and may influence the selection of treatment for the anxiety disorder.

Use of the Parent- and Self-Rated Level 1 Cross-Cutting Symptom Measures[70] or screening questions embedded in structured interview guides can standardize and enhance the efficiency of the psychiatric review of symptoms to assess for psychiatric comorbidities. If screen questions on these instruments are positively endorsed, the ensuing interview can ascertain whether full diagnostic criteria are met for the given disorder. Each condition for which full diagnostic criteria are met are diagnosed as such, unless *DSM-5* hierarchical rules[1] apply.

Medical Comorbidities. Children and adolescents with anxiety disorders are more likely to present with a variety of health problems, including headaches, asthma, gastrointestinal disorders, and allergies. The anxiety and physical disorders variously can be coincidental, in which the anxiety that precedes or follows the physical disorder is related to factors other than the illness itself, or can be causal, in which the anxiety contributes to or results from the physical illness. Examples of the latter include physical/physiological pathology secondary to anxiety symptoms, anxiety symptoms secondary to physical pathology/physiology, and anxiety as a reaction to physical illness and/or treatment. Whatever the presumed type of association, each disorder, whether physical or psychological, is separately assessed and treated.

Structured Interview Guides. Although the use of completely structured interview guides is infrequent in nonresearch settings, such guides have been shown to substantially enhance the reliability of psychiatric diagnosis over unstructured clinician interviews, which are vulnerable to a number of information collection biases.[73] Structured interview guides for children and adolescents have generally similar, moderately acceptable psychometric properties; hence, the decision to use a structured interview as part of a diagnostic evaluation will depend upon consideration of the advantages (eg, enhanced diagnostic accuracy) and disadvantages (eg, time, cost, burden) specific to each situation and setting. The use of computerized versions of interview guides could enable a psychiatric symptom review before the first appointment (ideally at home through a secure portal) as a structured, comprehensive first step in elucidating the differential diagnosis.[74]

The proprietary Anxiety Disorders Interview Schedule (ADIS), considered in research settings to be a gold standard for assessing childhood anxiety, addresses all *DSM-IV* anxiety disorders; in addition, screening sections for other psychiatric disorders are included to allow assessment of comorbidities.[75] A freely available option for structured assessment is the K-SADS PL (Present and Lifetime) *DSM-5* interview guide (https://www.pediatricbipolar.pitt.edu/sites/default/files/KSADS_DSM_5_Supp3_AnxietyDO_Final.pdf[76]), which includes sections assessing panic, agoraphobia, separation anxiety, social anxiety, selective mutism, specific phobia, and generalized anxiety disorders. The K-SADS-PL *DSM-5* also includes screening and follow-up questions for other disorder categories, which can facilitate efficient identification of potential anxiety masqueraders and comorbidities.

Symptom Rating Scales. Although not diagnostic, standardized symptom rating scales can be useful to support an anxiety diagnosis, to characterize the nature and breadth of specific symptoms, and to quantify pretreatment symptom severity as a baseline for tracking response to treatment over time. Moreover, in some situations, individual or combinations of multi-informant symptom rating scales may predict anxiety diagnoses as well as the ADIS structured interview, thereby reducing assessment burden.[77] Several anxiety rating scales with acceptable psychometric properties are freely available, both for the general construct of anxiety as well as for specific anxiety disorders; for example:

- Screen for Child Anxiety Related Emotional Disorders (SCARED), parent and child versions https://www.pediatricbipolar.pitt.edu/resources/instruments[78]
- Spence Children's Anxiety Scale (SCAS), parent and child versions https://www.scaswebsite.com[79]
- Preschool Anxiety Scale, parent version https://www.scaswebsite.com[79]
- Generalized Anxiety Disorder−7 (GAD-7), teen/adult version https://www.phqscreeners.com[80]

In addition, the APA offers the field-tested[1] parent- and self-rated Level 2 Cross-Cutting Symptom Measures for Anxiety that explore anxiety endorsed on the Level 1 Measure ("mild" or greater on any anxiety item) in greater depth, and the self-rated Disorder-Specific Severity Measures for clinically diagnosed separation anxiety, specific phobia, social anxiety, agoraphobia, and generalized anxiety disorders to track response to treatment over time (https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures[70]).

There is poor to moderate agreement between parent and youth reports on structured interview guides and symptom rating scales.[81,82] However, discrepancies between informants are to be expected, as they reveal each informant's unique view of the child's anxiety symptoms, which are internal and may not be readily or accurately discerned by others. Although the youth's report is generally considered to be paramount for internalizing disorders,[83,84] the simple rule of regarding a symptom as being present by any informant's report can be an acceptable resolution of discrepancies.

Mental Status Examination. In the mental status examination, signs of anxiety can include fastidious or disheveled appearance, poor eye contact, poor engagement/uncooperativeness, shy demeanor, clinginess, tremor, fidgetiness/restlessness, "nervous" habits, hypervigilance, poverty of or pressured speech, perseverative or ruminative thought processes, worry- or fear-laden thought content, distractibility, irritability/agitation, and poor insight and judgment.

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Because these signs are nonspecific to anxiety (and may be absent), they are largely adjunctive to other diagnostic information.

Clinical Formulation. Beyond diagnosis, the contextual (eg, stressors, strengths, environmental supports, cultural/spiritual/gender/sexual orientation) and historical (eg, medical, developmental, educational, family, social) sections of the diagnostic evaluation guide the development of a clinical formulation, which summarizes hypotheses regarding the biological, psychological, and social factors that may have predisposed, precipitated, or perpetuated the symptom presentation.

Key biological vulnerabilities for anxiety include family history of an anxiety disorder signaling inherited vulnerabilities in brain structure and function; acquired insult to the developing brain; autonomic hyperreactivity; temperament characterized by negative affectivity, behavioral inhibition, or sleeping/eating irregularity; and chronic medical conditions. Hypothesized psychological vulnerabilities include those derived from attachment theory (insecure attachment), cognitive-behavioral theory (maladaptive cognitive schemas, information-processing errors, negative self-evaluations, disconnects between feelings and behaviors), psychodynamic theory (ego deficits, problems in internalized object relations, unconscious conflicts), and mindfulness theory (instability of affect management). Key social vulnerabilities include stressful/traumatic life events, anxiogenic parenting behaviors (overprotection/overcontrol, high rejection/criticism, modeling anxious thoughts), social skills deficits, peer rejection, inappropriate expectations for achievement, lack of support/opportunities for competency development, and sociodemographic/cultural discordance with prevailing norms (poor "fit" in a given environment).

The biopsychosocial formulation can be organized to reflect predisposing, precipitating, perpetuating, and protective (ameliorating) factors ("4 P's") influencing the development of psychopathology.[85] Predisposing factors are areas of vulnerability that increase the risk for psychopathology and encompass primarily the biological factors of the biopsychosocial formulation. Precipitating factors are stressors or other contextual events that have a chronologic association with symptom onset. Perpetuating factors are any aspects of the patient, family, or community that serve to perpetuate the symptoms. Protective (ameliorating) factors include the patient's own areas of strength as well as strengths in the family and community. The cross-organization of both biopsychosocial and 4P factors can optimize the comprehensiveness of the treatment plan.

Safety. Safety risks, including but not limited to suicidal thoughts and behaviors, self-harm, risk-taking behaviors, and impulsivity, are assessed both at the time of evaluation and during treatment of an anxiety disorder, as these risks have been associated both with anxiety and more rarely with its treatment with antidepressant medications. Anxiety disorders in general and separation anxiety in particular may suggest the need for exploration of exposure to traumatic events. In the case of abuse or neglect, reporting to the state child welfare authority is required. Gathering information from multiple sources and by varied culturally and developmentally sensitive techniques may be needed in evaluating safety risks. Assessment culminates in two basic questions: Is the patient at current risk? Are the patient and family able to adhere to recommendations regarding supervision, safeguarding, and follow-up care? The answers to these questions can lead to the appropriate level and intensity of care. Psychiatric hospitalization is likely indicated when the youth actively voices intent to harm and in the context of altered mental status (including severe anxiety/agitation), multiple previous self-harm attempts, previous unsuccessful treatment, and caregiver incapacity.

Treatment Planning. Treatment planning derives from the diagnoses and clinical formulation. High-quality treatment plans are safe, timely, effective, efficient, feasible, equitable, and child and family centered.[86] A range of potentially effective treatments and other interventions are explained in accordance with the cognitive/linguistic/cultural level of the parents/guardians and patient, prioritized according to the acuity, severity, distress, and impairment associated with each diagnosed disorder. Reviewing the patient and parent/guardian preferences regarding the treatment options presented can increase the likelihood of engagement and adherence to the plan. Level of care decisions are informed by diagnosis, the current severity of symptoms, the presence of comorbid medical or psychiatric disorders, the assessment of the child's risk to self or others, the child's prior illness course and complications, the child's potential supports, and the treatment alliance between the clinician and the child and family.

In clinical practice, five components that generally are included in a discussion seeking to obtain informed consent for treatment are as follows[87]: 1) the diagnosis; 2) the nature and purpose of the proposed treatment; 3) the attendant risks and benefits of the proposed treatment; 4) alternative treatments and their risks and benefits; and 5) the risks and benefits of declining treatment. Strategies for improving parent/guardians' and patients' comprehension of risks and benefits can include providing written educational materials, multimedia presentations, decision-making worksheets, and standardized consent forms; asking for a "repeat back" of information provided; and engaging in back-and-

forth discussions until understanding is achieved. Documentation of the informed consent process provides evidence that the patient and parent/guardian were adequately prepared to provide assent/consent for treatment.

The incorporation of cultural and spiritual values, beliefs, and attitudes in treatment interventions can enhance the child's and family's participation in treatment and treatment effectiveness.[72] Treatment recommendations can draw from those proved to be effective in the minority population in question, and reflect ethnopharmacologic factors (eg, pharmacogenomic, dietary, herbal) that may influence the child's response to medications or experience of adverse effects.

Successful treatment is a collaborative effort among all involved parties with well-defined roles and responsibilities, including the clinician's role in generating motivation in the child and parents/guardians to adhere to the treatment plan. Inquiring about the parents' understanding of the outcomes of the assessment, addressing any questions or concerns, and discussing the logistics of treatment recommendations improves the chance that barriers to treatment are adequately addressed. If treatment will be elsewhere, assisting the family with the referral improves the likelihood of referral completion. Parents/guardians who themselves struggle with anxiety can benefit from additional psychoeducation and support in fostering their child's successful anxiety management; a referral for parental treatment may be appropriate.

Feedback to the patient's medical care team is generally permissible with basic consent for treatment, although definitions of care team and regulations vary by state. If parents/guardians specifically consent, feedback to child-serving systems with which the patient is involved (medical, educational, juvenile justice, child welfare) can facilitate coordination of care. Prompt, concise, and jargon-free feedback is most helpful; for example, feedback might include reiteration of the presenting problem/reason for referral, a brief description of the assessment process, the diagnoses given, and the treatments recommended.

TREATMENT OF ANXIETY
Development of Treatment Statements From the AHRQ/Mayo Systematic Review
The objective of the AHRQ/Mayo review[34-36] was to evaluate the effectiveness of psychotherapy and pharmacotherapy for the treatment of specific child and adolescent anxiety disorders and to evaluate the safety concerns associated with these treatments. In August 2017, the AHRQ/Mayo systematic review[34] was made available in its entirety on the Internet and as a synopsis in a pediatric journal.[35]

Errata from the original review were published in July 2018.[36]

To be eligible for the AHRQ/Mayo review, studies must have met all of the following criteria: 1) included children and adolescents between 3 and 18 years old with a confirmed diagnosis of panic, social anxiety, specific phobia (including school phobia), generalized anxiety, or separation anxiety disorder who 2) received any psychotherapy or pharmacotherapy, alone or combined; and 3) reported specified outcomes. Specified outcomes included the following: 1) primary anxiety symptoms from measures completed by the patient, parent, or clinician; 2) secondary anxiety outcomes such as coping, avoidance, or anxious thoughts; 3) global function; 4) social function; 5) satisfaction with treatment; 6) response to treatment; and 7) remission of the disorder (see AHRQ/Mayo review for measures used for each outcome category[36]). Both randomized controlled trials (RCTs) and comparative observational studies were included for effectiveness outcomes; case reports or case series were also used to identify adverse events (AEs).

The key questions of the AHRQ/Mayo review were twofold: 1) what is the comparative effectiveness of the available treatments[b] for panic, social anxiety, specific phobia (including school phobia), generalized anxiety, and separation anxiety disorders? 2) What are the comparative potential harms regarding the available treatments for these disorders?

AHRQ/Mayo Systematic Review Rating Procedure. The strength of evidence (SOE) for each measured outcome (eg, parent-rated anxiety symptoms) within each comparison (eg, fluoxetine vs. CBT) across all studies included in the AHRQ/Mayo review was rated via a consensus process by the Mayo reviewers in accordance with the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[88] Randomized controlled trials (RCTs) started with high SOE; observational studies started with low SOE. Initial SOE ratings based upon study type were then raised or lowered in accordance with the SOE assessed across five additional domains: 1) risk of bias (impact on inference); 2) precision (sample size, confidence intervals); 3) directness (relevance to patient); 4) consistency (degree of heterogeneity of findings); and 5) publication bias (nonpublication

[b]Psychotherapy treatments: cognitive-behavioral therapy, parent-child interaction therapy, problem-solving therapy, third-wave (mindfulness) therapy, psychodynamic psychotherapy, family therapy, attention modification, motivational interviewing, eye movement desensitization reprocessing therapy (EMDR); pharmacologic treatments: sertraline, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, venlafaxine, atomoxetine, reboxetine, duloxetine, alprazolam, chlordiazepoxide, clonazepam, imipramine, clomipramine, mebicarum, buspirone, mirtazapine, and nefazodone.

of study results). For RCTs, risk of bias was assessed using the Cochrane Risk of Bias tool[89] (assessing random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; attrition bias; incomplete outcome data; selective reporting). For observational studies, risk of bias was assessed using the Newcastle−Ottawa Scale[90] (assessing representativeness of the study population; selection of cohorts; ascertainment of exposure and outcomes; adequacy of follow-up; possible conflicts of interest). If insufficient evidence was available to determine SOE, that finding was noted. The AHRQ/Mayo review process, including the flow chart, search strategy, study inclusion/exclusion criteria, and individual study characteristics are presented in detail in the published review.[36]

CQI Treatment Statement Rating/Grading Procedure. Based upon the findings from the AHRQ/Mayo review, the CQI Guideline Writing Group via a consensus process developed treatment statements for each comparison for which sufficient evidence was available. Each treatment statement was assigned a numerical rating for SOE and a letter grade for the balance of benefits and harms as described below. If insufficient evidence was available, no treatment statement was developed; instead, the comparison was noted as in need of additional research.

The treatment statement SOE ratings were determined by arraying the AHRQ/Mayo SOE ratings for each individual outcome across **six key outcomes** as available (ie, **child-rated anxiety symptoms; parent-rated anxiety symptoms; clinician-rated anxiety symptoms; response; remission; global function**).

- If the preponderance of AHRQ/Mayo SOE ratings across the six key outcomes for a given comparison was high, the SOE rating for the corresponding treatment statement was high (denoted by the letter A).
- If the preponderance of AHRQ/Mayo SOE ratings across the six key outcomes was moderate, the SOE rating for the treatment statement was moderate (denoted by the letter B).
- If the preponderance of AHRQ/Mayo SOE ratings across the six key outcomes was low, the SOE rating for the treatment statement was low (denoted by the letter C).

The treatment statement benefit/harm grades were determined by the CQI Guideline Writing Group via a consensus process in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[91] convention by weighing the potential benefits and harms of each treatment statement action and the level of confidence in that determination based upon the underlying SOE.

- **A recommendation statement (denoted by the numeral 1) indicates confidence that the benefits of the action clearly outweigh the harms.**
- **A suggestion statement (denoted by the numeral 2) indicates greater uncertainty, in that the benefits of the action are considered likely to outweigh the harms, but the balance is more difficult to judge.**

The extent to which AHRQ/Mayo review−derived treatment statements were supported or refuted by more recent meta-analyses[37-43] was presented as additional evidence after each statement.

Treatment statements underwent iterative blind voting by the CQI Guideline Writing Group members until at least majority consensus was achieved. If a voting outcome had not been unanimous, a dissenting opinion could have been written to accompany the statement.

Applicability of Treatment Findings From the AHRQ/ Mayo Review. The treatment findings from the AHRQ/ Mayo review[36] were stated to be "likely widely applicable to a heterogeneous population of children and adolescents with separation anxiety, generalized anxiety, social anxiety, panic, and specific phobia disorders, with minimal psychiatric comorbidities, who are on average 8 to 18 years old and have ready access to mental health professionals who can provide CBT or have access to medical professionals who are willing to prescribe SSRIs or SNRIs."

Of the disorders named above, because specific phobia was not represented as the primary disorder in medication studies included in the AHRQ/Mayo review, this disorder was not included in the AACAP medication treatment statements. Although the AHRQ/Mayo findings were said to apply to children and adolescents who were "on average" 8 to 18 years old, both medication and therapy studies in the AHRQ/Mayo review included children as young as 6 years old. Accordingly, the treatment statements in this guideline extend downward to age 6. Although the majority of studies in the AHRQ/Mayo review were conducted with populations that were predominantly of White ethnicity, there is no compelling rationale for rendering the treatment statements inapplicable to minority populations.

Treatment Statements[c]

1. AACAP recommends (1C) that cognitive-behavioral therapy (CBT) be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, specific phobia, or panic disorder.

Benefits and Harms. Of the psychotherapy treatments eligible for the AHRQ/Mayo review, only CBT had sufficient outcome data for planned comparisons. A total of 60 RCTs and 3 nonrandomized comparative studies compared CBT to waitlist/no treatment, 29 RCTs and one non-randomized comparative study compared CBT to attention control/treatment as usual, and 3 RCTs compared CBT to pill placebo (see AHRQ/Mayo review[36] for study details). Overall, 6,978 patients were included (47.9% male; mean age 11.2 years, range 6−18 years).

Compared to inactive controls (waitlist/no treatment), CBT improved primary anxiety symptoms (child, parent, and clinician report), global function, and response to treatment (all moderate SOE), and may have improved remission of disorder (low SOE). However, there was evidence of publication bias for studies using the waitlist/no treatment comparison, which lowered their SOE. CBT did not separate from waitlist/no treatment for satisfaction with care and secondary measures (both low SOE), and there was insufficient evidence for social function.

Compared to active controls (attention control/treatment as usual), CBT improved only primary anxiety (child report) (moderate SOE); CBT did not separate from attention control/treatment as usual for primary anxiety (parent and clinician report), satisfaction, secondary measures, or remission of disorder (all low SOE). There was insufficient evidence for global function, social function, and response to treatment.

CBT did not separate from pill placebo for primary anxiety (child report) or secondary measures (all low SOE). There was insufficient evidence for primary anxiety (clinician report), global function, or social function.

Except as noted, CBT did not separate from pill placebo, waitlist/no treatment, or attention control/treatment as usual with respect to any short-term AEs (all low SOE). Compared to pill placebo, CBT reduced dropouts (low SOE) and compared to waitlist/no treatment, CBT reduced dropouts due to AEs (low SOE).

[c]The treatment statements below are intended to apply to the named anxiety disorders for which all diagnostic criteria are met, including the requirements for duration, frequency/severity, and clinically significant distress and/or functional impairment. Although the AHRQ/Mayo review findings were insufficient to recommend or suggest the sequence in which treatments should be offered, prudent sequencing may prioritize CBT over SSRI for recent onset of milder, less distressing, and less functionally impairing anxiety presentations.

Additional Support. This recommendation was supported by the findings from four meta-analyses published since the AHRQ/Mayo review.[40-43] No meta-analyses or systematic reviews published since the AHRQ/Mayo review refuted this recommendation. One of the recent meta-analyses[43] suggested the possible superiority of group CBT over all other assessed psychotherapies and control conditions.

Differences of Opinion. There were no differences of opinion. The CQI Guideline Writing Group voted unanimously in favor of this recommendation.

Quality Measurement Considerations. CBT should be considered among treatments offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, specific phobia, or panic disorders.

Implementation. CBT is a diverse group of interventions targeted at the three primary dimensions of anxiety: cognitive (eg, cognitive distortions about the likelihood of harm), behavioral (eg, avoidance of potentially harmful situations), and physiologic (eg, autonomic arousal and other somatic symptoms). Therapeutic interventions are individually tailored to illustrate connections among worries and fears, thoughts, and behaviors, and are strategically directed toward eliminating emotional and physical distress, changing maladaptive beliefs and attitudes, and alleviating avoidance behavior. CBT typically is organized according to an agenda that involves homework assignments for practice opportunities that reinforce skills and generalize them to the natural environment. Treatment is characterized by collaboration among the patient, family, and therapist, and, in some cases, school personnel. The goal of structured CBT is to achieve meaningful symptomatic and functional improvement within 12 to 20 sessions. Systematic assessment of treatment effectiveness using standardized symptom rating scales can supplement the clinical interview, as use of these scales has been shown to optimize therapists' ability to accurately assess treatment response and remission.[92]

Specialized education, training, and experience are necessary for the effective delivery of CBT. Specific CBT elements for anxiety disorders can include the following: education about anxiety; behavioral goal setting with contingent rewards; self-monitoring for connections between worries/fears, thoughts, and behaviors; relaxation techniques including deep breathing, progressive muscle relaxation, and guided imagery; cognitive restructuring that challenges distortions such as catastrophizing, overgeneralization, negative prediction, and all-or-nothing thinking; graduated exposure incorporating graded

exposure to a feared stimulus; and problem-solving and social skills training relevant to anxiogenic situations. The number and combination of these elements vary according to the specific anxiety disorder being treated and the patient's clinical presentation. Graduated exposure, in which the patient creates a fear hierarchy that is then mastered in a stepwise manner, is the cornerstone of treatment for anxiety generated by a specific situation, such as in separation anxiety, specific phobias, and social anxiety. Developmentally appropriate modifications of graduated exposure may include use of real-life desensitization (in vivo), emotive imagery (narrative stories), live modeling (demonstration of nonfearful response), and contingency management (positive reinforcement). Exposure is tailored to the individual and calibrated in intensity in a manner similar to dosage calibration in medication management.[93]

Although CBT emphasizes cognitive, behavioral, and physiologic processes that lead to and maintain anxiety symptoms, these processes are learned and function in a social context. As such, family-directed interventions that improve parent—child relationships, strengthen family problem-solving and communication skills, reduce parental anxiety, and foster anxiety-reducing parenting skills often supplement individual treatment. In addition, school-directed interventions that educate teachers about the student's anxiety and how to foster effective problem-solving, coping, and anxiety management strategies in the school setting can be part of the treatment plan. Specific plans for anxiety management at school can be written into the student's 504 plan or individualized education plan (eg, graduated school re-entry with contingent rewards for separation anxiety; graduated practice opportunities for social anxiety).

2. AACAP recommends (1B) that selective serotonergic reuptake inhibitors (SSRIs) be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, or panic disorder.

Benefits and Harms. In the AHRQ/Mayo review (see AHRQ/Mayo review[36] for study details), 13 RCTs compared SSRIs to pill placebo. Overall, 1,708 patients were included (54.1% male; mean age 11.6 years, range: 6—18 years).

Compared to pill placebo, SSRIs as a class improved primary anxiety symptoms (parent and clinician report), response to treatment, and remission of disorder (all moderate SOE), as well as global function (high SOE). SSRIs did not separate from pill placebo for primary anxiety symptoms (child report), secondary measures, or social function (all low SOE).

Except as noted, SSRIs as a class did not separate from pill placebo with respect to short-term AEs (all moderate to low SOE). Insufficient data precluded assessment of AEs related to suicidal ideation or behavior. Insufficient data also precluded assessment of AEs related to neurologic or oral (dry mouth) AEs.

Additional Support. This recommendation was supported by the findings from three meta-analyses published since the AHRQ/Mayo review.[37-39] No meta-analyses or systematic reviews published since the AHRQ/Mayo review refuted this recommendation.

Differences of Opinion. There were no differences of opinion. The CQI Guideline Writing Group voted unanimously in favor of this recommendation.

Quality Measurement Considerations. A medication from the SSRI class should be considered among treatments offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, and panic disorders.

Implementation. Serotonergic function is believed to play a key role in the ability of the brain to modulate fear, worry, and stress as well as to facilitate cognitive processing of those emotions.[94] The SSRI medication class is a group of chemically and pharmacologically different compounds that inhibit the presynaptic reuptake of serotonin in the brain, thereby increasing availability of serotonin at the synaptic cleft. This blockade over time is believed to lead to a downregulation of inhibitory serotonin autoreceptors, which eventually heightens the serotonergic neuronal firing rate, which in turn leads to increased serotonin release. This multistep process is hypothesized to be related to the delay in onset of the SSRI treatment effect.

Medications from the SSRI class currently marketed in the United States are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone. In the AHRQ/Mayo review, the SSRIs for which sufficient data were available for comparisons were fluoxetine, fluvoxamine, paroxetine, and sertraline. Although mechanisms of action vary somewhat across SSRIs (eg, effects on other neurotransmitter receptors affecting degree of serotonin selectivity), the primary mechanism was deemed in the AHRQ/Mayo review to be sufficiently similar across individual medications to warrant extension of the findings to the medication class.

Although there is substantial empirical support for the effectiveness and safety of the SSRI class of medications for the treatment of anxiety, no specific SSRIs have U.S. Food and Drug Administration (FDA) approval for this indication. The choice of a specific SSRI is governed by considerations such as pharmacokinetics, pharmacodynamics,

tolerability, cost, insurance formularies, and unique risks leading to warnings or precautions.

At present, there is no clear role for pharmacogenomic testing in medication selection, although this may change as additional evidence accumulates.[95]

Limited data are available on drug pharmacokinetics and pharmacodynamics for SSRIs in young people. Most SSRIs (particularly fluoxetine because of its active metabolite) have sufficiently long elimination half-lives to permit single daily dosing. However, at low doses of sertraline[96] and at any dose of fluvoxamine, youths may require twice-daily dosing.

The best-fitting model for SSRI response may be a logarithmic model demonstrating statistically (but not clinically) significant improvement in anxiety symptoms within 2 weeks of treatment initiation, clinically significant improvement by week 6, and maximal improvement by week 12 or later.[38] This pharmacodynamic profile supports slow up-titration to avoid unintentionally exceeding the optimal medication dose.

As a group, the SSRIs are generally well tolerated by children and adolescents. Most adverse effects emerge within the first few weeks of treatment, and can include (but are not limited to) dry mouth, nausea, diarrhea, heartburn, headache, somnolence, insomnia, dizziness, vivid dreams, changes in appetite, weight loss or gain, fatigue, nervousness, tremor, bruxism, and diaphoresis. Potentially serious adverse effects include (but are not limited to) suicidal thinking and behavior, behavioral activation/agitation, hypomania, mania, sexual dysfunction, seizures, abnormal bleeding, and serotonin syndrome.

All of the SSRIs have a boxed warning for suicidal thinking and behavior through age 24 years. The pooled absolute rates for suicidal ideation across all antidepressant classes and all non-OCD anxiety indications have been reported to be 1% for youths treated with an antidepressant and 0.2% for youths treated with a placebo.[97] The pooled risk difference has been reported to be 0.7% (95% confidence interval −0.4% to 2%; $p = .21$), yielding a number needed to harm (NNH) of 143 (compared to a number needed to treat [to achieve response] of 3).[97] Despite the low apparent risk, close monitoring for suicidality is recommended by the FDA, especially in the first months of treatment and following dosage adjustments. Although the margin of safety of SSRIs in overdose is greater than for other antidepressants, deaths have been reported following very large ingestions.

Behavioral activation/agitation[98] (eg, motor or mental restlessness, insomnia, impulsiveness, talkativeness, disinhibited behavior, aggression), more common in younger children than adolescents and in anxiety disorders compared

to depressive disorders, may occur early in SSRI treatment, with dose increases, or with concomitant administration of drugs that inhibit the metabolism of SSRIs. The potential for dose-related behavioral activation/agitation early in treatment supports slow up-titration and close monitoring (particularly in younger children), and underscores the importance of educating parents/guardians and patients in advance about this potential side effect.

As with other antidepressants, there have been rare reports of mania/hypomania that can be difficult to distinguish from behavioral activation. In general, behavioral activation may be more likely to occur early in treatment (first month) or with dose increases, whereas mania/hypomania may appear later. Moreover, behavioral activation usually improves quickly after SSRI dose decrease or discontinuation, whereas mania may persist and require more active pharmacological intervention. Sexual dysfunction (erectile dysfunction, delayed ejaculation, anorgasmia) can occur with SSRIs in adolescents. Because seizures have been observed in the context of SSRI use, SSRIs should be used cautiously in patients with a history of a seizure disorder. Abnormal bleeding, especially with concomitant administration of aspirin or nonsteroidal anti-inflammatory drugs, can occur with SSRIs; rare bleeding events include ecchymosis, hematoma, epistaxis, petechiae, and hemorrhage.

Serotonin syndrome, caused by elevated brain serotonin levels, can be triggered when serotonergic medications are combined.[99] Symptoms can arise within 24 to 48 hours after combining medications and are characterized by mental status changes (confusion, agitation, anxiety); neuromuscular hyperactivity (tremors, clonus, hyperreflexia, muscle rigidity); and autonomic hyperactivity (hypertension, tachycardia, arrhythmias, tachypnea, diaphoresis, shivering, vomiting, diarrhea). Advanced symptoms include fever, seizures, arrhythmias, and unconsciousness, which can lead to fatalities. Treatment is hospital based and includes discontinuation of all serotonergic agents and supportive care with continuous cardiac monitoring. Monoamine oxidase inhibitors (MAOIs), including phenelzine, isocarboxazid, moclobemide, isoniazid, and linezolid play a role in most cases of serotonin syndrome and should be avoided in combination with any other serotonergic drug, including another MAOI. Moreover, caution should be exercised when combining two or more non-MAOI serotonergic drugs, including antidepressants (eg, SSRIs, SNRIs, TCAs, atypical antidepressants); opioids and other pain medications (eg, tramadol, meperidine, methadone, fentanyl); stimulants (eg, amphetamine and possibly methylphenidate classes); cough/cold/allergy medications (eg, dextromethorphan, chlorpheniramine); other over-the-

counter products (eg, St. John's wort, L-tryptophan, diet pills); and illicit drugs (eg, ecstasy, methamphetamine, cocaine, LSD). Caution entails starting the second non-MAOI serotonergic drug at a low dose, increasing the dose slowly, and monitoring for symptoms, especially in the first 24 to 48 hours after dosage changes.

Each SSRI has special prescribing considerations. Paroxetine, fluvoxamine, and sertraline have been associated with discontinuation syndrome[100] (see below for syndrome description). As noted below, fluvoxamine may have greater potential for drug—drug interactions. Citalopram may cause QT prolongation associated with Torsade de Pointes, ventricular tachycardia, and sudden death at daily doses exceeding 40 mg/d and should be avoided in patients with long QT syndrome. Paroxetine has been associated with increased risk of suicidal thinking or behavior compared to other SSRIs.

SSRIs vary in their potential for drug—drug interactions.[101] Concomitant administration of any of the SSRIs with any of the monoamine oxidase inhibitors (MAOIs) is contraindicated because of increased risk of serotonin syndrome. SSRIs (especially citalopram) also may interact with drugs that prolong the QT interval; fluoxetine, paroxetine, and sertraline may interact with drugs metabolized by CYP2D6, and fluvoxamine may interact with drugs metabolized by CYP1A2, CYP2C19, CYP2C9, CYP3A4, and CYP2D6. Citalopram/escitalopram may have the least effect on CYP450 isoenzymes compared with other SSRIs and as such may have a lower propensity for drug interactions.

Medical education, training, and experience are necessary to safely and effectively prescribe antidepressant medications. A conservative medication trial for mild to moderate anxiety presentations may entail increasing the dose as tolerated (if adherence is confirmed) within the therapeutic dosage range in the smallest available increments at approximately 1- to 2-week intervals when prescribing shorter half-life SSRIs (eg, sertraline, citalopram, escitalopram) to approximately 3- to 4-week intervals when prescribing longer half-life SSRIs (eg, fluoxetine) until the benefit-to-harm ratio is optimized and remission is achieved. Faster up-titration may be indicated as tolerated for more severe anxiety presentations; however, it is not clear that dose of medication is related to magnitude of response, and higher doses or blood concentrations can be associated with more adverse effects.[38] Because an initial adverse effect of SSRIs can be anxiety or agitation, it may be advisable to start with a subtherapeutic dose as a "test" dose. Systematic assessment of treatment response using standardized symptom rating scales can be considered as a supplement to the clinical interview, along with reported and observed adverse events. If a concerning adverse effect is reported or observed that could reasonably be linked to the medication, in general the dose of medication would be reduced, and if the concerning adverse effect persists, the medication would be discontinued. For all SSRIs, medical monitoring can include height and weight; no specific laboratory tests are recommended. The optimal duration of pharmacologic treatment of anxiety disorders for continued symptom remission is unclear, but a generally accepted approach would be to continue an effective, tolerated dose for approximately 12 months after remission, monitoring for several months after discontinuation for re-emergence of symptoms. Discontinuation generally should occur during a relatively stress-free period. Some youths with severe and chronic anxiety presentations may require lengthier medication treatment.

Determinants of nonadherence to medication regimens are multidetermined, including social/economic, health system, illness, patient, and treatment factors.[102] Although evidence is mixed, some effective strategies include behavioral (motivational), educational (information pamphlets), integrated care (care coordination), self-management (illness management skills), risk communication (harm avoidance), and packaging/daily reminder (physical or technological) approaches.[102] In children and adolescents, parental oversight of medication regimens is of paramount importance.

A discontinuation syndrome characterized variously by dizziness, fatigue, lethargy, general malaise, myalgias, chills, headaches, nausea, vomiting, diarrhea, insomnia, imbalance, vertigo, sensory disturbances, paresthesias, anxiety, irritability, and agitation has been reported following missed doses or acute discontinuation of shorter-acting SSRIs, notably paroxetine but also (to a lesser extent) fluvoxamine and sertraline.[103] Accordingly, these medications warrant close adherence to the prescribed regimen and a slow discontinuation taper. In contrast, fluoxetine, likely because of the long half-life of its active metabolite, is unlikely to be associated with discontinuation syndrome and has not been associated with withdrawal symptoms when doses are missed.

There is no definitive empirical guidance for switching from one SSRI to another.[104] Although the most conservative approach would entail tapering and discontinuing the first SSRI before adding the second (with a washout interval if the first SSRI is fluoxetine), this approach entails the risk of exacerbation of the original symptoms, or discontinuation symptoms if the first SSRI (other than fluoxetine) is stopped abruptly. Cross-tapering may avoid these outcomes, but should be closely monitored.

3. **AACAP suggests (2C) that combination treatment (CBT and an SSRI) could be offered preferentially over CBT alone or an SSRI alone to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, or panic disorder.**

Benefits and Harms. In the AHRQ/Mayo review, two RCTs compared combination treatment (CBT and an SSRI) to either treatment alone (see AHRQ/Mayo review[36] for study details). These 2 studies included 550 patients (52.6% male; mean age 12.2 years, range 7−17 years).

Compared to CBT alone and to sertraline alone, combination CBT plus sertraline improved primary anxiety (clinician report), global function, response to treatment, and remission of disorder (all moderate SOE).

Combination CBT plus fluoxetine did not separate from CBT alone for global function, secondary measures, or response to treatment (all low SOE) and may have reduced remission of disorder compared to CBT alone (low SOE).

Except as noted, combination CBT plus sertraline did not differ from CBT alone with respect to short-term AEs including suicidal ideation or behavior (all low SOE). Compared to CBT alone, combination CBT plus sertraline increased AEs related to behavior activation (moderate SOE) and increased any AEs and AEs related to sleep (both low SOE).

Except as noted, combination CBT plus sertraline did not differ from sertraline alone with respect to short-term AEs (all low SOE). Compared to sertraline alone, combination CBT plus sertraline increased AEs related to behavior activation and reduced AEs due to fatigue/somnolence (both moderate SOE). Insufficient evidence precluded assessment of AEs related to suicidal ideation or behavior.

Compared to CBT alone, combination CBT plus fluoxetine did not differ with respect to dropouts (low SOE).

Additional Support. This suggestion was not supported or refuted by the findings from any meta-analyses or systematic reviews published since the AHRQ/Mayo review.

Differences of Opinion. There were no differences of opinion. The CQI Guideline Writing Group voted unanimously in favor of this suggestion.

Quality Measurement Considerations. Combination treatment (CBT plus an SSRI) can be considered among treatments offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, and panic disorders.

Implementation. Because there were only two studies with conflicting results, the AHRQ/Mayo review did not find definitive evidence for the superiority of combination treatment over monotreatment (therapy or medication alone). Largely derived from the findings from one of the studies (the Child-Adolescent Anxiety Multimodal Study [CAMS]),[105] expert consensus generally supports the prioritization of combination treatment over monotreatment. In CAMS,[106] youths who received combination treatment had significantly higher rates of remission compared to monotreatment with SSRI or CBT or with placebo treatment at week 12 and week 24. In clinical practice, combination treatment may be favored if there is a need for acute symptom reduction in a severe, functionally impairing disorder or a partial response to monotreatment.

Combination treatment typically involves concurrent administration of psychotherapy (CBT in the AHRQ/Mayo-included studies) and medication (an SSRI in the AHRQ/Mayo-included studies). Optimally, combination treatment would be delivered in the same facility to enhance convenience for the patient and family as well as communication between treatment providers.

Naturalistic follow-up of the CAMS study (Child/Adolescent Anxiety Multimodal Extended Long-term Study [CAMELS])[107] failed to demonstrate long-term maintenance of the initial superiority of combination over monotreatment. However, a strong predictor of long-term outcome was initial response to treatment, which, in the CAMS study, was significantly superior in the combination treatment compared to the monotreatment arms.[106] This finding may suggest the importance of delivering what may be the most potent treatment (combination) early in the treatment course.

4. **AACAP suggests (2C) that serotonin norepinephrine reuptake inhibitors (SNRIs) could be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, or panic disorder.**

Benefits and Harms. In the AHRQ/Mayo review, 4 RCTs compared SNRIs to pill placebo (see AHRQ/Mayo review[36] for study details). These studies included 911 patients (63.4% male; mean age 12.4 years, range 6−17 years).

Compared to pill placebo, SNRIs as a class improved primary anxiety symptoms (clinician report) (high SOE). SNRIs did not separate from pill placebo for primary anxiety (parent report) or global function (both low SOE). Insufficient data precluded assessment of primary anxiety (child report).

Except as noted, SNRIs as a class did not separate from pill placebo with respect to short-term AEs including suicidal ideation or behavior (all moderate to low SOE). Compared to pill placebo, SNRIs were associated with

increased fatigue/somnolence (moderate SOE). Insufficient data precluded assessment of AEs related to infections.

Additional Support. This suggestion was supported by the findings from three meta-analyses published since the AHRQ/Mayo review.[37-39] There were no meta-analyses or systematic reviews published since the AHRQ/Mayo review that refuted this suggestion.

Differences of Opinion. There were no differences of opinion. The CQI Guideline Writing Group voted unanimously in favor of this suggestion.

Quality Measurement Considerations. A medication from the SNRI class can be considered among treatments offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, and panic disorders.

Implementation. The SNRI medication class is a group of chemically and pharmacologically different compounds that inhibit the presynaptic reuptake of both norepinephrine and serotonin in the brain.[94] Stress responses including alertness, arousal, attentiveness, and vigilance are believed to be modulated by noradrenergic neurons. Although associated with the stress response ("fight or flight") and the generation of fear and anxiety, paradoxically noradrenergic medications have been shown empirically to be effective in the treatment of anxiety disorders, likely because of complex interactions with other neurotransmitters including serotonin.

Medications from the SNRI class currently marketed in the United States are venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran. In the AHRQ/Mayo review, the SNRIs for which sufficient data were available for comparisons were venlafaxine and duloxetine. Atomoxetine (a selective norepinephrine reuptake inhibitor) also was included in the AHRQ/Mayo review under the SNRI class; however, at present, the effectiveness of atomoxetine for the treatment of anxiety as the primary disorder has not been established, and as such atomoxetine is not further addressed in this guideline.

Although mechanisms of action vary somewhat across SNRIs (eg, effects on other neurotransmitter receptors affecting degree of serotonin and norepinephrine selectivity), the primary mechanism was deemed in the AHRQ/Mayo review to be sufficiently similar across individual medications to warrant extension of the findings to the medication class.

Duloxetine is the only SNRI to have an FDA indication for the treatment of any anxiety disorder (specifically, generalized anxiety disorder in children and adolescents 7−17 years old). However, the choice of medication for anxiety within the SNRI class may also be governed by other considerations such as pharmacokinetics, pharmacodynamics, tolerability, cost, insurance formularies, and unique risks leading to warnings or precautions. At present, there is no clear role for pharmacogenomic testing in medication choice, although this may change as evidence accumulates.

Limited data are available on drug pharmacokinetics and pharmacodynamics of SNRIs for young people. Venlafaxine extended release, desvenlafaxine, and duloxetine have sufficiently long elimination half-lives to permit single daily dosing. Because of its short elimination half-life, venlafaxine immediate release may require twice- or thrice-daily dosing.

Adverse effects of SNRIs can include (but are not limited to) diaphoresis, dry mouth, abdominal discomfort, nausea, vomiting, diarrhea, dizziness, headache, tremor, insomnia, somnolence, decreased appetite, and weight loss. The SNRIs also have been associated with sustained clinical hypertension, increased blood pressure, and increased pulse.

As described above for SSRIs, uncommon but potentially serious adverse effects across the SNRI class include suicidal thinking and behavior (through age 24 years), behavioral activation/agitation, hypomania, mania, sexual dysfunction, seizures, abnormal bleeding, and serotonin syndrome. In addition, individual SNRI medications have also been associated with distinctive, potentially serious (albeit rare) adverse effects.

Venlafaxine may be associated with greater suicide risk than the other SNRIs,[108,109] and both venlafaxine and desvenlafaxine have been associated with overdose fatalities. Venlafaxine also has been associated with discontinuation symptoms.

Duloxetine has been associated with hepatic failure presenting as abdominal pain, hepatomegaly, and elevation of transaminase levels. Cholestatic jaundice also has been reported. Duloxetine should be discontinued and not restarted in patients who develop jaundice or other evidence of clinically significant liver dysfunction. Severe skin reactions, including erythema multiforme and Stevens−Johnson syndrome, can occur with duloxetine; accordingly, duloxetine should be discontinued and not restarted at the first appearance of blisters, peeling rash, mucosal erosions, or other signs of hypersensitivity.

SNRIs vary in their potential for drug−drug interactions. Concomitant administration of any of the SNRIs and any of the MAOIs is contraindicated because of increased risk of serotonin syndrome. Duloxetine may interact with drugs metabolized by CYP1A2 and CYP2D6. Compared to SSRIs, venlafaxine may have the least effect on the CYP450 system.[110]

Medical education, training, and experience are necessary to safely and effectively prescribe antidepressant

medications. The recommendations for an adequate SNRI trial are the same as those delineated above for SSRIs. For all SNRIs, medical monitoring should include height, weight, pulse, and blood pressure; no specific laboratory tests are recommended.

As with SSRIs, a discontinuation syndrome has been reported[103] following missed doses or acute discontinuation of SNRIs. Accordingly, SNRIs also warrant a slow discontinuation taper.

Areas for Additional Treatment Research

For many important domains of treatment for anxiety (listed below), the AHRQ/Mayo review yielded insufficient information to draw conclusions about the benefits or harms of the treatment. As such, treatment statements for these domains are not offered. Research is urgently needed to support additional treatment statements in these domains for future guidelines.

- Circumstances suggesting preferential use of SSRIs or CBT[d]
- Preferential sequencing of SSRIs and CBT[e]
- Treatment effect modifiers (eg, child/family characteristics, treatment setting, disorder severity, comorbidities)[f]
- Use of non-CBT psychotherapies[g]
- Use of benzodiazepines[h]
- Long-term safety risks of pharmacologic treatment[i]
- Effectiveness of psychosocial and pharmacologic treatments in underserved populations and minorities[j]

LIMITATIONS

The limitations of the Treatment section of this guideline reflect the derivation of the treatment statements from the findings of a single, time-limited, critical systematic review of the literature by the AHRQ-contracted Mayo Clinic Evidence-based Practice Center in which reviewers' judgment played a role in rating the strength of the empirical evidence. Despite the rigor and transparency of the systematic review process as delineated in the AHRQ/Mayo review,[36] differences in professional judgment are possible. However, any differences are deemed unlikely to affect the overall conclusions of the guideline. Other limitations of the AHRQ/Mayo review are as follows:

[d]AHRQ/Mayo review: equivocal head-to-head comparisons of SSRI vs CBT
[e]AHRQ/Mayo review: no data
[f]AHRQ/Mayo review: equivocal subgroup analyses
[g]AHRQ/Mayo review: excluded from analyses due to heterogeneity of therapies
[h]AHRQ/Mayo review: one poor quality trial of BZP versus placebo
[i]AHRQ/Mayo review: no data
[j]AHRQ/Mayo review: no data

- Relatively small body of evidence, especially for medication studies
- Brief follow-up of most studies
- Use of different symptom rating scales across studies to assess improvement
- Lacking, sparse, or unstratified descriptions of potentially mediating and moderating variables (eg, intervention components, participant demographics, comorbidities, symptom severity)
- Poor representation across studies of both very young children and young adults
- Poor representation across studies of multiracial youths
- Paucity or lack of medication studies addressing selective mutism, specific phobias, panic, or agoraphobia as the primary disorder
- Variable methods for reporting treatment-emergent adverse events and serious adverse events
- Insufficient data to assess risk of suicidal behavior

The limitations of the Assessment and Implementation sections of this guideline reflect the derivation of the narrative from a single time-limited review by the CQI Guideline Writing Group of published expert opinion and consensus. When expert opinions differed, judgment was exercised by the CQI Guideline Writing Group to select among equally supported opinions. Although differences in professional judgment are possible, any differences are deemed unlikely to affect the overall conclusions of the guideline.

CONCLUSIONS

Congruent with previous national and international guidelines,[62-65] in this guideline both cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medication have considerable empirical support as safe and effective short-term treatments for anxiety in children and adolescents. Serotonin norepinephrine reuptake inhibitor (SNRI) medication has some empirical support as an additional treatment option. CBT may be considered to be the first-line treatment for anxiety in children and adolescents, particularly for mild to moderate presentations, with SSRI (and possibly SNRI) medication an alternative treatment consideration, particularly for more severe presentations or when quality CBT is unavailable. Combination treatment (CBT and SSRI) may be a more effective short-term treatment for anxiety in children and adolescents than either treatment alone. Because effective treatment outcomes are predicated in part upon accuracy of the diagnosis, depth of the clinical formulation, and breadth of the treatment plan, comprehensive, evidence-based assessment may enhance evidence-based treatment.

In the context of a protracted severe shortage of child and adolescent−trained behavioral health specialists, research demonstrating convenient, efficient, cost-effective, and user-friendly delivery mechanisms for safe and effective treatments for child and adolescent anxiety disorders is an urgent priority. Pharmacotherapeutic task-sharing with pediatric practitioners, particularly for moderate anxiety presentations, can greatly expand access to safe and effective care while conserving child and adolescent psychiatrists for the management of more severe and complex presentations. The comparative effectiveness of anxiety treatments, delineation of mediators and moderators of effective anxiety treatments, long-term effects of SSRI and SNRI use in children and adolescents, and additional evaluation of the degree of suicide risk associated with SSRIs and SNRIs, remain other key research needs.

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