AACAP OFFICIAL ACTION

Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Major and Persistent Depressive Disorders

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Objective: To enhance the quality of care and clinical outcomes for children and adolescents with major depressive disorder (MDD) and persistent depressive disorder (PDD). The aims are as follows: (1) to summarize empirically based guidance about the psychosocial and psychopharmacologic treatment of MDD and PDD in children and adolescents; and (2) to summarize expert-based guidance about the assessment of these disorders as an integral part of treatment, and the implementation of empirically based treatments for these disorders in clinical practice.

Method: Statements about the treatment of MDD and PDD are based upon empirical evidence derived from a critical systematic review of the scientific literature conducted by the Research Triangle Institute International–University of North Carolina at Chapel Hill (RTI-UNC) Evidence-based Practice Center under contract with the Agency for Healthcare Research and Quality (AHRQ). Evidence from meta-analyses published since the AHRQ/RTI-UNC review is also presented to support or refute the AHRQ findings. Guidance about the assessment and clinical implementation of treatments for MDD and PDD is informed by expert opinion and consensus as presented in previously published clinical practice guidelines, chapters in leading textbooks of child and adolescent psychiatry, the *DSM-5-TR,* and government-affiliated prescription drug information websites.

Results: Psychotherapy (specifically, cognitive–behavioral and interpersonal therapies) and selective serotonin reuptake inhibitor (SSRI) medication have some rigorous (randomized controlled trials, meta-analyses) empirical support as treatment options. 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 outcomes.

Conclusion: Disproportionate to the magnitude of the problem, there are significant limitations in the quality and quantity of rigorous empirical support for the etiology, assessment, and treatment of depression in children and adolescents. In the context of a protracted severe shortage of child and adolescent–trained behavioral health specialists, the demonstration of convenient, efficient, cost-effective, and user-friendly delivery mechanisms for safe and effective treatment of MDD and PDD is a key research need. Other research priorities include the sequencing and comparative effectiveness of depression treatments, delineation of treatment mediators and moderators, effective approaches to treatment nonresponders and disorder relapse/recurrence, long-term effects and degree of suicide risk with SSRI use, and the discovery of novel pharmacologic or interventional treatments.

Key words: clinical practice guideline; depression, depressive disorders; child psychiatry; child and adolescent 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 major depressive disorder (MDD) and persistent depressive disorder (PDD) as defined by the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*.[1] The primary aim of the guideline is to summarize **empirically based guidance** about the **psychosocial and psychopharmacologic treatment** of these disorders. A secondary aim is to summarize **expert-based guidance** about the **assessment** of MDD and PDD as an integral part of treatment, and about the **implementation** of empirically based treatments for MDD and PDD in clinical practice. The treatment of depression in very young children, the treatment of subsyndromal depression, and the prevention of depressive disorders in children and adolescents are beyond the scope of this guideline.

Depressive disorders are among the more common psychiatric disorders in children and adolescents. At any given time, nearly 3% of youth worldwide are reported to have a depressive disorder.[2] Estimated lifetime and past-year prevalence of MDD in a nationally representative sample of adolescents in the United States,[3] ascertained using DSM diagnostic criteria, was reported to be 11% and 7.5%,

respectively; the corresponding rates of severe MDD were 3% and 2.3%. The prevalence of dysthymia (PDD) was reported to be 1.8% (lifetime) and 1.3% (past year). Across adolescence, the prevalence of MDD increased significantly, with markedly greater increases among female than among male youth. Nearly 30% of youth with MDD reported some form of suicidality in the past year, and more than 10% reported a suicide attempt. Only 34% of adolescents with MDD were reported to receive disorder-specific treatment, and only 35% received treatment from the mental health sector.

Rates of depression in younger children are lower than in adolescents. In a study of prepubertal depression using *DSM* diagnostic criteria for case ascertainment in a regionally representative sample,[4] the 3-month rate of any depressive disorder was estimated to be 0.5% to 1.9%. Across several studies in preschoolers, the estimated prevalence of depression using developmentally modified *DSM* criteria also was reported to be less than 2.0%.[5]

From 2005 to 2014, the past year prevalence of MDD in a nationally representative sample[6] increased from 8.7% to 11.3% in adolescents, and from 8.8% to 9.6% in young adults. The extent to which 21st century sociocultural changes have contributed to the apparent increase in prevalence, or whether the increase is due to heightened awareness, improved identification, or other factors, is not known.

Depression manifests along a spectrum, ranging from subsyndromal to severe or (rarely) psychotic presentations.[1] Overall, the phenomenology of depression in youth is similar to that in adults, but there may be some developmental differences in presentation that complicate diagnosis. For example, in preschool children, absence of joyful play observed by caregivers may be a prominent sign,[5] whereas irritability, temper tantrums, low frustration tolerance, and somatic symptoms may predominate in school-aged children, and adolescents may more commonly present with sad mood, neurovegetative symptoms, and suicidality.[7]

MDD is episodic by *DSM* definition, presenting as a distinct change from previous function.[1] The median duration of MDD episodes has been estimated at 1 to 2 months and 8 months in community and clinical samples, respectively.[8] Approximately 10% of cases of MDD become chronic[9]; moreover, chronicity substantially increases the likelihood of underlying anxiety, substance use, and personality disorders and decreases the likelihood that treatment will be followed by full symptom resolution.[1] The duration of PDD has been estimated to approximate 3 to 4 years in both community and clinical samples.[8]

MDD is highly recurrent, with recurrence rates in adolescents estimated to be 20% to 60% in 1 to 2 years and 70% after 5 years.[8] In general, greater severity, chronicity or multiple recurrent episodes, comorbidity, presence of residual subsyndromal symptoms, negative cognitive style, family dysfunction, and exposure to ongoing stressful/traumatic events are associated with poor outcome.[8] The risk for bipolar disorder in prepubertal-onset depression has been estimated at around 10% to 20%, and is higher for patients who have a history of antidepressant-induced or spontaneous hypomania, psychotic features, hypersomnia, or a family history of bipolar disorder.[10]

Genetic factors convey substantial vulnerability for the development of depression (40%-60% heritability, higher in adolescents than in children),[11,12] although precise biological mechanisms remain elusive.[13] The serotonin transporter gene;[14] variations in cerebral structure and function;[15] and neuroendocrine,[16] neuroinflammatory,[17] neurochemical,[18] autonomic,[19] chronobiologic,[20] and gut microbiome[21] systems as well as interactions among these,[22] have been implicated. Potentially depressogenic psychological factors are wide ranging and include insecure attachment,[23] negative cognitive/attributional style,[24] difficult temperament/negative affectivity,[25] diminished reward effort,[26] dysfunctional interpersonal processes,[27] impaired self-regulation,[28] underdeveloped self-understanding,[29] underdeveloped mentalization,[30] and learned helplessness,[31] as well as complex developmental/psychological/biobehavioral interactions.[32] An extensive inventory of social−environmental factors contributing to depression risk[33] ranges from exposure to stressful or traumatic circumstances in the family (particularly emotional abuse[34] and unattuned/unsupportive parenting styles [eg, passive/withdrawn or discordant[35]]), to societal issues such as poverty,[36] income inequality,[37] racial/ethnic[38] and other forms of discrimination,[39] and acculturation stress.[40] Social−environmental factors may exert their effect in part through alterations to physiologic homeostasis.[34,41]

In longitudinal studies,[42-44] the onset of MDD in youth has been characterized by a complex pattern of exposure to adverse childhood circumstances and concurrent psychiatric comorbidity (anxiety, behavior, and attention disorders). The powerful impact of childhood adversities (eg, interpersonal loss, parental maladjustment, child maltreatment, economic adversity) on first-onset depression was reiterated in a national study[45] in which simulations estimated that childhood adversities were associated with 57.1% of childhood-onset (up to age 13 years) mood disorders, compared to 20.5% to 30.5% of later-onset mood disorders. The continuity of MDD in youth has been characterized as both homotypic (depression to depression) and heterotypic (depression to anxiety,

substance abuse, behavior problems) and is associated with impaired functioning (health, legal, social, educational, financial) well into adulthood.

Preschool (ages 3-6 years) depression ascertained through developmentally modified criteria also has been shown to be highly comorbid (anxiety, attention, and behavior disorders) and to have homotypic continuity into school age.[5] In regression analyses, school-age depression was strongly predicted by preschool depression, as well as by preschool-onset conduct disorder and maternal nonsupport.[46]

According to Luyten and Fonagy,[32] the dismantling of heterogeneity in depression as outlined above is a major and daunting task for the field of psychiatry. Whereas very early conceptualizations proposed 3 pathways to depression—one endogenous (biologically driven), one reactive (environmentally driven), and one arising from emotional instability acquired in part through exposure to childhood adversities[47]—newer integrative theories[32] highlight the role of childhood adversities in precipitating depressogenic biobehavioral developmental cascades grounded in, for example, the Research Domain Criteria approach.[48]

In sum, the overdetermined nature of depressive disorders, especially in children and adolescents, creates substantial diagnostic, formulation, and treatment challenges for the clinician and methodologic challenges for the researcher. As such, it is not surprising that definitive information about effective treatment is greatly limited. Nonetheless, better identification, assessment, and treatment of MDD and PDD by skilled clinicians from multiple disciplines is achievable, and could have a substantial impact on the individual and public health burden of mental illness in youth.

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). The CQI is charged by AACAP with the development of Clinical Practice Guidelines in accordance with standards promulgated by the Institute of Medicine (IOM)[49] and the Appraisal of Guidelines Research & Evaluation (AGREE) Next Steps Consortium.[50] Both standard sets emphasize *rigor* (critically appraised empirical evidence) and *transparency* (minimization of conflicts of interest and a 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, race/ethnicity, career duration, and practice type 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 MDD and PDD are based upon empirical evidence derived from a critical systematic review of the scientific literature conducted by the Research Triangle Institute International–University of North Carolina at Chapel Hill (RTI-UNC) Evidence-based Practice Center (EPC) under contract with the Agency for Healthcare Research and Quality (AHRQ).[51] Insofar as available, evidence from meta-analyses published since the AHRQ/RTI-UNC review are presented to support or refute the AHRQ findings.[52-59]

Because of sparse or absent empirical evidence, guidance about the assessment and clinical implementation of empirically based treatments for depressive disorders is informed by expert opinion and consensus as presented in previously published clinical practice guidelines,[8,60-62] chapters in leading textbooks of child and adolescent psychiatry,[63-82] the *DSM-5-TR*,[1] and government-affiliated prescription drug information websites.[83,84] Additional citations are provided in the assessment and implementation sections when information is presented that is not included in the above-noted sources.

The peer review and approval process for the draft guideline spanned the period November 15, 2021, to April 10, 2022, 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 DEPRESSION

Diagnostic evaluation is an essential prerequisite for the treatment of a depressive 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-TR*[1]). A diagnostic evaluation identifies symptoms; syndromal

symptom combinations; symptom frequency, severity, onset, and duration; degree of associated distress and functional impairment; developmental deviations; and physical signs, as well as factors predisposing, precipitating, perpetuating, or protecting from the symptom presentation.[1]

Identification

The US Preventive Services Task Force (USPSTF) recommends screening for MDD in adolescents aged 12 to 18 years on the basis of conveying a "moderate net benefit," provided that adolescents screening positive "are appropriately diagnosed and treated with evidence-based care."[85] At present, the USPSTF does not recommend screening for MDD in children aged 11 years or younger, based upon insufficient evidence of net benefit.[85] Nonetheless, early identification of a depression concern in children as well as adolescents can facilitate early intervention, including guided self-management and focused intervention for subclinical and mild presentations.[86]

In primary care, school, or other child-serving settings, psychometrically sound and freely available general social−emotional screening instruments (eg, Pediatric Symptom Checklist [https://www.massgeneral.org/psychiatry/treatments-and-services/pediatric-symptom-checklist],[87] Strengths and Difficulties Questionnaire [https://www.sdqinfo.org][88]) increasingly are deployed systematically (eg, well visits) to standardize identification of mental health concerns, including symptoms of sad or irritable mood, in pediatric primary care. However, for adolescents, the USPSTF suggests the use of a depression-focused instrument (such as the freely available Patient Health Questionnaire−9[89]) for initial screening. When using this and other instruments that include suicidality items remotely (eg, via patient portal) in advance of well visits in primary care settings, consideration must be given to the management of a positive response to the suicidality question, which necessitates urgent assessment. For this reason, primary care settings using remote screening might consider the adolescent-validated,[90] freely available PHQ-2 instrument, which does not include suicidality items (https://www.primarypediatrics.com/wp-content/uploads/2020/04/PHQ-2-Depression-Scale.pdf),[91] for the initial depression screen, to be followed by in-person administration of the PHQ-9 at the well visit if the PHQ-2 score is positive. For younger children, a similar remote screening consideration could be the child and adolescent−validated,[92-95]freely available Short Mood and Feelings Questionnaire (SMFQ), which does not include suicidality items, to be followed by in-person administration of the Long Mood and Feelings Questionnaire (LMFQ) at the well visit if the SMFQ score is positive (https://devepi.duhs.duke.edu/measures/the-mood-and-feelings-questionnaire-mfq/).[96]

In the context of a psychiatric evaluation, symptoms of depression typically are identified through input from referral sources; spontaneous youth or parent report (the presenting problem or chief complaint); or during the clinician's review of psychiatric symptoms or the conduct of the mental status examination. However, because of the variability inherent in nonsystematic methods of identification, a more standardized approach to symptom review 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)[97] to screen for multiple psychiatric disorders including depression. Both 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.[98] These instruments could be included in intake packets to systematically and efficiently gather information about presenting problems remotely, prior to the evaluation. As with remote use of the PHQ-9, remote administration of the Cross-Cutting measure must consider management of a positive response to the suicidality items, which necessitate urgent assessment; as such, the suicidality items may be deleted and deferred until the in-person visit.

Evaluation

Clinically significant depression (ie, a depressive *disorder*) must be distinguished from everyday sadness and irritability, which are common to the human experience and can be normative (even when exaggerated) in specific developmental stages (eg, irritability due to poor frustration tolerance in younger children, sad mood related to struggles with identity and intimacy in adolescents). In *DSM-5-TR,*[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,[1] a mental disorder is diagnosed if all 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 medical, substance, and psychiatric explanations for the symptom presentation must have been considered before the diagnosis is applied.[1]

In *DSM-5-TR*,[1] diagnostic criteria are provided for 8 depressive disorders.[a] The common features of these disorders are sad or irritable mood accompanied by somatic, cognitive, and behavioral changes that significantly affect the individual's capacity to cope and to function. Major Depressive Disorder, PDD, and Depressive Disorder Due to Another Medical Condition all have multiple specifiers that should also be coded; diagnostic precision is key for understanding disorder course and prognosis and for guiding empirically based treatment recommendations (eg, MDD with mixed features [manic symptoms] may respond less well to treatment and may convey greater risk for developing bipolar disorder; MDD with anxious distress may respond better to combination treatment [therapy and medication] than either treatment alone).[63]

According to *DSM-5-TR*,[1] MDD is characterized by a *discrete episode* of at least 2 weeks' duration (although most episodes last considerably longer) involving clear changes in mood, interest/pleasure, cognition, and neurovegetative functions; suicidality can also be present. Except for weight gain and suicidality, the criterion symptoms for MDD must be present for *most of the day, nearly every day* and must result in clinically significant *distress* or *functional impairment*. The initial presentation or chief complaint is variable: some youth present with sad or irritable mood, others with feelings of emptiness or boredom, others with somatic complaints, still others with social withdrawal, self-blame, or distractibility/poor school performance. Decreased energy, tiredness, and fatigue are common; self-care may decline. Suicidality may span thoughts of others being better off if the youth were dead, to transient but recurrent thoughts of committing suicide, to active suicidal intent and plan.

PDD is a *chronic* form of depression (duration at least 1 year) that incorporates previous *DSM* diagnoses of chronic major depression and dysthymia. If MDD persists for at least 1 year, a concurrent diagnosis of PDD can be considered ("double depression") if PDD criteria are also met. A new diagnosis of MDD also can be superimposed upon a pre-existing PDD diagnosis if MDD criteria are also met. In PDD, the mood disturbance is present *most of the day, more days than not*; cognitive and neurovegetative dysfunction is present but is less severe and pervasive than in MDD. Nonetheless, PDD can be associated with substantial functional impairment over a long period of time.

[a]DSM-5 Depressive Disorders with International Classification of Diseases–10 code: Disruptive Mood Dysregulation Disorder (ICD F34.81); Major Depressive Disorder (ICD F32.0-9/F33.0-9); Persistent Depressive Disorder (ICD F34.1); Premenstrual Dysphoric Disorder (ICD F32.81); Substance/Medication-Induced Depressive Disorder (substance-specific codes); Depressive Disorder Due to Another Medical Condition (ICD F06.31/32/34); Other Specified Depressive Disorder (ICD F32.89); Unspecified Depressive Disorder (ICD F32.A).

If diagnostic criteria are not fully met for a specific depressive disorder or if a precise diagnosis is not possible because of limited information or other factors, *DSM-5-TR* includes "other specified" and "unspecified" diagnoses to be applied in these circumstances. The "other specified" or "unspecified" diagnoses can be applied when depressive symptoms do not meet full diagnostic criteria for a specific depressive disorder but are nonetheless distressing and functionally impairing. Subsyndromal symptoms are important to recognize, as they convey increased risk for developing full diagnostic criteria for depression as well as suicidality,[99] and as such are an opportunity for early intervention. The "unspecified" diagnosis also may be a diagnostic option in the absence of detailed knowledge of *DSM-5-TR* criteria for specific depressive disorders (eg, emergency room or primary care settings).

Evaluation Structure. A diagnostic interview for depression 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 employ multiple age-appropriate assessment techniques (eg, direct and indirect questioning, interactive and projective techniques). Family assessment can reveal genetic vulnerabilities to and environmental precipitants of depression, and observations of parenting styles and behaviors may identify those that are potentially contributory or protective. Input from collateral sources (eg, records, interviews, symptom rating scales), including (as applicable and with specific 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 require more than one session as allowed by current diagnostic billing code (Current Procedural Terminology [CPT] Codes 90791, 90792) specifications.

Clinicians should conduct the diagnostic evaluation in the language in which both the child and parents/guardians are proficient, as lack of appropriate linguistic ability or interpreter support has been associated with misdiagnosis as well as adverse clinical outcomes.[100] If live interpreter services are not available, telephonic interpreter services may be an acceptable alternative.

Differential Diagnosis. When assessing depressive symptoms, a key goal of the history of present illness is to determine whether *DSM-5-TR*[1] diagnostic criteria for a

specific depressive disorder are met, and to rule out alternative explanations for the symptom presentation. In addition, characterization of previous depression presentations and response to previous treatments will inform current treatment choice.

Medical conditions associated with depression include (but are not limited to) hypothyroidism, mononucleosis, anemia, autoimmune diseases, chronic fatigue syndrome, migraine, epilepsy, asthma, inflammatory bowel disease, and certain cancers. Although laboratory testing is not routine in the evaluation of a suspected depressive disorder, in collaboration with the child's primary care practitioner, laboratory testing should be considered if suggested by signs and symptoms of a medical condition. For depressed youth presenting with specific somatic symptoms (eg, headaches, diarrhea, pain, fatigue), the nature and severity of those symptoms should be explored and documented at baseline, so that the somatic symptoms can be differentiated from adverse effects of a medication trial.

Medications that can cause depressive symptoms include (but are not limited to) narcotic analgesics, chemotherapy agents, cardiovascular medications, stimulants, corticosteroids, immunosuppressants, and oral contraceptives. Medication reconciliation including over-the-counter and naturopathic treatments should be performed as a routine part of an evaluation for a suspected depressive disorder.

A wide array of substances can cause depression, including (but not limited to) nicotine, alcohol, cannabis, opiates, cocaine, other stimulants, sedatives, and anabolic steroids. Environmental etiologies such as exposure to lead and carbon monoxide can also be considered. Although drug and toxin testing are not routine in the evaluation of a suspected depressive disorder, testing should be considered if exposure is reported or suspected.

Mental conditions that may include symptoms similar to those of depressive disorders are attention-deficit/hyperactivity disorder (ADHD) (distractibility), disruptive behavior disorders (irritability), anxiety (irritability, distractibility, insomnia, somatic complaints), posttraumatic stress disorder (irritability, distractibility, insomnia), bipolar depression (irritability), psychotic disorders (agitation, social withdrawal, distractibility), autism spectrum disorder (irritability, social withdrawal, distractibility), and learning disorders (sadness about school performance). Despite overlapping symptoms, each condition for which full diagnostic criteria are met should be diagnosed as such, unless *DSM-5-TR* hierarchical rules[1] apply.

Psychiatric Comorbidities. As many as 40% to 90% of youth with depressive disorders have psychiatric comorbidities.[63] Common comorbidities include (but are not limited to) anxiety, disruptive behavior, ADHD, and substance use disorders. 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 depressive disorder.

Use of the Parent- and Self-Rated Level 1 Cross-Cutting Symptom Measures 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.

Medical Comorbidities. Estimates of MDD prevalence in physically ill youth range from 11% to 29%.[101] Strong associations between depression and physical illness have been found for youth with neurological, gastrointestinal, autoimmune, and endocrine disorders; infectious diseases; metabolic and systemic disturbances; neoplasms; and nutritional deficiencies. Depression and physical disorders variously can be coincidental, in which the depression that precedes or follows the physical disorder is related to factors other than the illness itself, or causal, in which the depression contributes to or results from the physical illness. Examples of causal associations include physical/physiological pathology secondary to depressive symptoms, depressive symptoms secondary to physical pathology/physiology, and depression as a reaction to physical illness and/or treatment. Whatever the presumed type of association, each disorder, whether physical or psychological, should be separately assessed and treated. Counting discrete symptoms (eg, fatigue) as attributable to both the depressive disorder as well as the physical illness may be the most sensitive and reliable approach to diagnosis.[102]

Structured Interview Guides. Although the use of completely structured or semi-structured interviews is infrequent in nonresearch settings, such interviews 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.[103] 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, training, cost, burden) specific to each situation and setting. A freely available option for screening for and assessing MDD and PDD is the K-SADS PL (Present and Lifetime) *DSM-5* interview guide (https://www.pediatricbipolar.pitt.edu/sites/default/files/KSADS_DSM_5_Supp1_DepressiveDO_Final.pdf).[104] The K-SADS-PL *DSM-5* also includes screening (https://www.pediatricbipolar.pitt.edu/sites/default/files/KSADS_DSM_5_SCREEN_Final.pdf) and follow-up questions for other disorder categories, which can facilitate efficient identification of potential depression masqueraders and comorbidities. Also freely available online in draft form is a preschool-age structured interview guide, the Preschool Age Psychiatric Assessment (PAPA) for *DSM-5* (https://devepi.duhs.duke.edu/files/2018/06/PAPA-Core-Diagnostic-Modules-DSM-5-1.pdf)[105]; although not yet proved to be psychometrically valid, this guide could be helpful in formulating questions for an unstructured clinical interview.

Focused Symptom Rating Scales. Albeit not diagnostic, standardized focused symptom rating scales can be useful to support a depression 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 ("measurement-based treatment" [106,107]). Among the several freely available depression rating scales with acceptable psychometric properties[108,109] are the Patient Health Questionnaire−9 (PHQ-9) modified for adolescents[110-112]

(https://www.aacap.org/App_Themes/AACAP/docs/member_resources/toolbox_for_clinical_practice_and_outcomes/symptoms/GLAD-PC_PHQ-9.pdf); the Mood and Feelings Questionnaire (MFQ), parent and child versions[113,114]

(https://devepi.duhs.duke.edu/measures/the-mood-and-feelings-questionnaire-mfq/); and the Preschool Feelings Checklist[115]

(www.jaacap.org/article/S0890-8567(09)61320-4/fulltext).

In addition, the APA offers the field-tested parent- and self-rated Level 2 Cross-Cutting Symptom Measures for depression that explore depression endorsed on the Level 1 Measure ("mild" or greater on any depression item) in greater depth, and the self-rated Disorder-Specific Severity Measures for clinically diagnosed depression (https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures).[98,116]

There is poor-to-moderate agreement between parent and youth reports on structured interview guides and symptom rating scales.[117,118] However, discrepancies between informants are to be expected, as they reveal each informant's unique view of the child's depression symptoms, some of 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,[119,120] the simple rule of regarding a symptom as being present by any informant's report can be an acceptable resolution of discrepancies.

Measurement-based treatment may be underutilized in mental health care, despite evidence of improving outcomes.[121] According to a recent systematic review, measurement-based treatment occurred primarily in outpatient mental health settings; around one-third of programs had provider-only assessments, and one-half had both provider and self-assessments.[122] Perceived barriers to implementation of measurement-based treatment are many and occur at multiple levels: patient (eg, motivation, time, comfort/facility with applicable technologies, concerns about confidentiality breach); practitioner (eg, time, intrusive to clinical practice, disbelief in accuracy of measures, lack of training, concerns about impact on payments and coverage); organization (eg, lack of commitment by clinical leadership, infrastructure constraints, lack of training resources), and system (eg, competing requirements). Strategies to improve implementation include improving data input systems, using measurement feedback systems, leveraging local champions, forming learning collaboratives, training leadership, improving expert consultation with clinical staff, and generating incentives.[123,124] Krishna *et al.*[124] provide a useful guide to selecting and implementing various measurement infrastructure models suitable for a variety of settings.

Mental Status Examination. In the mental status examination, signs of depression can include poor eye contact, poor engagement/uncooperativeness, disheveled appearance, downcast facies, tearfulness, psychomotor agitation or retardation, sad mood, angry outbursts, poor frustration tolerance, distractibility, poverty of speech, perseverative or ruminative thought processes, guilt- or self-loathing- or self-blame−laden thought content, and poor insight and judgment. Because these signs are nonspecific to depression (and may be absent), they are largely adjunctive to other diagnostic information but should be documented when present.

Clinical Formulation. The development of a clinical formulation includes consideration of contextual (eg, stressors) and historical (eg, medical, developmental, educational, family, social) factors as well as child and family strengths, environmental supports, and gender/sexual/cultural/spiritual issues. The result is an understanding of the biological, psychological, and social factors that may be associated with the symptom presentation.

The biopsychosocial formulation can be organized to reflect predisposing, precipitating, perpetuating, and protective (ameliorating) factors ("4 P's")[1] influencing the development of psychopathology.[125] 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 prolong the problem. 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 a depressive disorder, as these risks have been associated with both depression and its treatment with antidepressant medications. Depressive disorders suggest the need for exploration of exposure to childhood adversities. 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 2 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 hopelessness, agitation, psychosis), multiple previous suicide attempts, previous unsuccessful treatment, and/or 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.[126] A range of potentially effective treatments and other interventions should be explained in accordance with the cognitive and linguistic level of the parents/guardians and patient, prioritized according to the acuity, severity, distress, and impairment associated with each diagnosed disorder. The clinician should provide sufficient information to enable the patient and parent/guardian to make an informed decision about treatment options. 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.

Although the specific definition of informed consent for treatment may vary from state to state,[127] many stakeholders agree on at least 4 basic elements of the informed consent process: (1) the decision maker (parent/guardian and older youth) should have the capacity to make decisions; (2) the clinician should disclose sufficient details for the decision maker to make an informed choice; (3) the decision maker should confirm his/her understanding of the disclosed information; and (4) the decision maker should freely authorize the treatment plan. In clinical practice, these 4 elements translate into 5 components that are included in a discussion seeking to obtain informed consent: (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 parents'/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 extended 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 and consent for treatment.

Clinicians should evaluate and incorporate cultural and spiritual values, beliefs, and attitudes in treatment interventions to enhance the child's and family's participation in treatment and treatment effectiveness.[100] If available, clinicians should preferentially recommend treatments that have been proved to be effective in the minority population in question, and should identify ethnopharmacologic factors (eg, pharmacogenomic, dietary, herbal) that may influence the child's response to medications or experience of adverse effects.

Together with the patient and family, the clinician can delineate the role of each participant in the treatment process, emphasizing that successful treatment is a collaborative effort among all involved parties. Parents/guardians who themselves

struggle with depression can benefit from additional psychoeducation and support to foster their child's successful depression management, and for moderate-to-severe cases, a referral for parental treatment can be considered. Families struggling with difficult psychosocial circumstances can be referred to social services agencies for needed supports. The clinician should address any questions or disagreements about treatment and discuss the logistics of treatment implementation. The clinician should inquire about the parents' understanding of the outcomes of the assessment and their feelings about the process. Finally, the clinician should support and encourage the youth and parents/guardians in their efforts to adhere to the treatment plan.

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

TREATMENT OF DEPRESSION

Development of Treatment Statements From the AHRQ/RTI-UNC EPC Systematic Review

The objective of the AHRQ/RTI-UNC review[51] was to examine the benefits and harms of pharmacological and nonpharmacological treatments for child and adolescent depressive disorders. In April 2020 the review was made available in its entirety on the internet (https://effectivehealthcare.ahrq.gov/products/childhood-depression/research).[128]

The key questions of the AHRQ/RTI-UNC review were 5-fold: in adolescents and children, (1) what are the benefits and harms of nonpharmacological interventions[b] for depressive disorders (DDs: MDD, PDD/dysthymic disorders, depressive disorder not otherwise specified [DD NOS])? (2) What are the benefits and harms of pharmacological interventions[c] for DDs? (3) What are the benefits and harms of combination interventions for DDs? (4) What are the benefits and harms of collaborative care interventions for DDs? (5) What are the comparative benefits and harms of treatments (nonpharmacological, pharmacological, combined, collaborative care) for DDs? Each of the key questions was paired with a subpopulation question: How do benefits and harms vary by subpopulation (eg, patient characteristics, disorder characteristics, history of previous treatment, comorbid condition, exposure to a traumatic life event)?

To be eligible for the AHRQ/RTI-UNC review, studies must have met all of the following criteria: (1) included children and adolescents with a confirmed diagnosis of MDD, PDD (or dysthymia), or DD NOS who (2) received any nonpharmacological or pharmacological interventions, alone or combined, for at least 6 weeks; and (3) reported specified end-of-treatment benefits and harms outcomes. Study time frame was any publication date; study settings were outpatient care in countries with a very high Human Development Index; study language was English. Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) were included for benefits outcomes; RCTs, CCTs, and observational studies were included to identify harms.

Overall, 60 studies were included in the AHRQ/RTI-UNC review; details of all included and excluded studies can be found in the review.[51] Excluded studies primarily were those deemed by AHRQ/RTI-UNC to fail to meet inclusion criteria or predetermined standards for methodologic rigor; specific reasons for exclusion are summarized in the Benefits and Harms sections under each treatment statement in this guideline.

Of the 60 included studies (reported in 94 articles), 39% each addressed key questions 1 and 2; less than 1% addressed key question 3; 0% addressed key question 4; and 49% addressed key question 5. In all, 72% of the studies were conducted in the United States. Eight percent of studies targeted children (age range from 5 to 12 years), 50% targeted adolescents (age range from 11 to 18 years), and 42% included both children and adolescents (age range from 7 to 18 years). In general, studies referred to "adolescents" as persons aged 11 or 12 years and older, and to "children" as persons aged 10 or 11 years and younger (generally down to age 7 or 8 years); these definitions were adopted in the Treatment Statements below. In all, 67% of

[b]Nonpharmacological treatments: cognitive–behavioral therapy, rational emotive behavior therapy, behavioral activation, other behavioral therapy, interpersonal therapy, directive counseling, Katathym-imaginative psychotherapy, family therapy, parent education, self-help groups, problem-solving therapy, autonomic training, combined-modality therapy, psychological adaptation therapies, exercise, diet therapy, mindfulness, meditation, relaxation therapy, massage therapy, music therapy, art therapy, integrative restoration, visualization, tai chi, yoga, spirituality, acupuncture, St. John's wort, SAMe, fish oil, melatonin, L-tryptophan, folic acid, 5-HTP, zinc, chromium, ginko biloba, vitamin E, omega-3 fatty acids, hypericum, inositol, selenium, electroconvulsive therapy, transcranial magnetic stimulation, light therapy, hypnotherapy, neurofeedback, deep brain stimulation, biofeedback.

[c]Pharmacological treatments: fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vilazodone, duloxetine, venlafaxine, amitriptyline, desipramine, imipramine, nortriptyline, doxepin, clomipramine, rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine, bupropion, mirtazapine, nefazodone, trazodone, vortioxetine.

studies had both mostly female and mostly White participants. Participants in 77% of studies were confirmed as having MDD, and participants in 23% of studies were confirmed as mixed, including various combinations of MDD, Dysthymia/PDD, or Not Otherwise Specified/Unspecified DD. Of the studies, 45% addressed nonpharmacological interventions, and 40% addressed pharmacological interventions; 15% addressed both.

AHRQ/RTI-UNC Risk of Bias Assessment of Individual Studies. The methodological risk of bias of all studies included in the AHRQ/RTI-UNC review was assessed by the RTI-UNC reviewers in accordance with the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[129] For observational studies, risk of bias was assessed with the ROBINS-1 tool[130] and for RCTs, the Cochrane RCT tool.[131] Risk-of-bias considerations included selection bias, confounding, performance bias, detection bias, attrition bias, adequacy of randomization (if applicable), similarity of groups at baseline, masking, intent-to-treat analysis, dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity. Reviewers assigned risk-of-bias ratings for each study as follows: low risk of bias (study met all criteria); some concerns (study met some criteria); high risk of bias (methodological shortcomings leading to high risk of bias in one or more categories); or unclear risk of bias (methods not reported clearly). When possible, sensitivity analyses were conducted to gauge the difference in conclusions upon including and excluding high risk-of-bias studies. For evidence that included meta-analyses, effect sizes with and without high risk-of-bias studies were reported. For all analyses, to account for heterogeneity across studies, random effects models were used to estimate pooled or comparative effects.

AHRQ/RTI-UNC Strength of Evidence Grading Procedure. For each comparison (eg, fluoxetine vs placebo), each individual outcome (eg, remission, serious adverse event) was graded for strength of evidence (SOE) across all studies of that comparison that included that outcome, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group guidance[132] and guidance established for the EPC Program.[133] Five domains were incorporated in the grades: risk of bias (impact on inference), consistency (degree of heterogeneity of findings), directness (relevance to patient), precision (sample size, confidence intervals), and publication bias (nonpublication of study results). Because all of the outcomes selected were direct outcomes, the evidence was not downgraded for indirectness.

Definitions of the grades of outcome-specific SOE were as follows:

- High SOE—High confidence that the evidence reflects the true effect. Further research is very unlikely to change confidence in the estimate of effect.
- Moderate SOE—Moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of the effect and may change the estimate.
- Low SOE—Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of the effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of effect.

Details of the AHRQ/RTI-UNC systematic review and evidence-grading process, including the flow diagram, search strategy, study inclusion/exclusion criteria, and individual study characteristics, are presented in the published review.[51]

CQI Treatment Statement Rating/Grading Procedure. For each comparison in the AHRQ/RTI-UNC review, the CQI Guideline Writing Group via a consensus process aggregated the AHRQ/RTI-UNC ratings for individual outcomes across all available outcomes to rate **overall SOE for the entire body of evidence** for that comparison (eg, fluoxetine vs placebo). **Benefit outcomes** included **clinician-, parent-, and self-reported depression symptom reduction, response, remission, relapse, recovery, and functional impairment**; **harm outcomes** included **suicidality, serious adverse events, and withdrawal due to serious adverse events**. Selection, definitions and measurement of outcomes were defined by each individual AHRQ/RTI-UNC–included study and varied across studies.

- **If the preponderance of AHRQ/RTI-UNC SOE grades across all available outcomes for a given comparison was high, the overall SOE rating for the corresponding treatment statement was high (denoted by the letter A).**
- **If the preponderance of AHRQ/RTI-UNC SOE grades across all available outcomes for a given comparison was moderate, the overall SOE rating for the corresponding treatment statement was moderate (denoted by the letter B).**
- **If the preponderance of AHRQ/RTI-UNC SOE grades across all available outcomes for a given comparison was low, the overall SOE rating for the corresponding treatment statement was low (denoted by the letter C).**

- **If the preponderance of AHRQ/RTI-UNC SOE grades across all available outcomes for a given comparison was insufficient but at least 2 outcome grades were low or better, the overall SOE rating for the corresponding treatment statement was insufficient (denoted by the letter I).**

Based upon these overall ratings, the CQI Guideline Writing Group via a consensus process developed treatment statements, which were then graded by the CQI Guideline Writing Group via a consensus process in accordance with GRADE convention[132] by weighing the potential benefits and harms of each treatment statement action and the level of confidence in that determination based upon the overall 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 fairly likely to outweigh the harms, but the balance is more difficult to judge.**

In addition to the findings from the AHRQ/RTI-UNC review, the CQI also considered the findings from high-level evidence (ie, systematic reviews/meta-analyses[52-59]) published since the AHRQ/RTI-UNC review as additional evidence of consistency or inconsistency of treatment findings. For one treatment (interpersonal therapy), new meta-analyses led to inclusion of a treatment option based upon additional evidence inconsistent with AHRQ/RTI-UNC findings.

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/RTI-UNC Review. The applicability of findings from the AHRQ/RTI-UNC review was assessed in accordance with the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[129] Factors identified *a priori* that could limit the applicability of evidence included age range of the sample in each study, severity or type of DD, comorbid conditions, exposure to a traumatic life event, history of previous depressive episodes or depression treatment, and treatment setting. Clinical judgment and family preference necessarily must play a key role in determining the applicability of treatment statements to individual patients.

Treatment Statements[d]

1. **AACAP suggests (2I) that cognitive-behavioral therapy and interpersonal therapy could be offered to adolescents and children with major depressive disorder or persistent depressive disorder.**

A total of 25 studies of nonpharmacological interventions were included in the AHRQ/RTI-UNC review (see the review for study summaries[51]), including 6 RCTs of cognitive-behavioral therapy (CBT),[134-143] 3 RCTs of interpersonal therapy,[134,144,145] and 5 RCTs of family therapies.[146-150] Insufficient rigorous evidence of benefit for modified CBT (parent-involved, trauma-focused), attachment-based family therapy, family therapy, parent−child interaction therapy, short-term psychoanalytic therapy, exercise, spirituality-informed therapy, and omega-3 supplementation precluded inclusion of these modalities in the above treatment statement.

Differences of Opinion. None. The Guideline Writing Group voted unanimously in favor of this suggestion.

Cognitive-Behavioral Therapy

Benefits and Harms. Adolescents. Among adolescents with MDD and/or PDD, compared to waitlist, CBT improved self-reported depressive symptoms and clinician-reported functional impairment (both low SOE); there was insufficient evidence for harms. Evidence was insufficient for benefits or harms for CBT vs active control and CBT vs pill placebo.

Children. No RCTs of CBT in children were included in the AHRQ/RTI-UNC review; however, studies including children are presented under Additional Support below.

Additional Support. The benefits of CBT were mixed in 2 meta-analyses of RCTs published since the AHRQ/RTI-UNC review. These analyses reported change in depressive symptoms in children and adolescents with MDD/PDD for CBT vs the named comparator as follows: overall standardized mean difference (SMD) 0.05 (−0.61, 0.70); subgroup SMDs: wait-list SMD −0.94 (−1.40, −0.48),

[d]The treatment statements below are intended to apply to the named depressive 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 review findings were insufficient to recommend or suggest the sequence in which treatments should be offered, prudent sequencing may prioritize brief education/supportive intervention for subsyndromal and mild presentations, and empirically validated psychotherapy and/or medication for moderate and severe presentations.

"psychological placebo" SMD −0.27 (−0.72, 0.18), and treatment as usual (TAU) SMD −0.22 (−0.67, 0.23)[52]; and wait-list SMD −1.29 (−2.54, −0.04) and "named control group" SMD −1.16 (−2.15, −0.18).[56] In summary, in subgroup analyses, statistically significant improvements in depression in children and adolescents were found for CBT vs wait-list and "named control group," but not for CBT vs "psychological placebo" or TAU.

It should be noted that these 2 meta-analyses included RCTs that were excluded from the AHRQ/RTI-UNC review because of ineligible populations. In addition, neither meta-analysis reported separate effects for children and adolescents, whereas the preponderance of RCTs targeted adolescents.

Implementation. CBT is a diverse group of interventions targeted at the primary manifestations of depressive disorders: cognitive (eg, cognitive distortions and intrusive negative thoughts) and behavioral (eg, anhedonia/decreased motivation). Hence, core elements of CBT for depression may include cognitive restructuring (ie, deployment of prefrontal cortical resources to enhance cognitive processing of beliefs and control of emotional states) and behavioral activation (ie, activation of reward-related brain circuitry to enhance motivation toward adaptive changes). In cognitive restructuring, the therapist endeavors to enhance the patient's awareness of habitual negative distortions and the skills to counteract these distortions. In behavioral activation, the therapist endeavors to motivate the patient to set goals to regularly engage in pleasurable activities. In these ways, the therapist seeks to interrupt the cycle of negative thoughts, dysphoric feelings, and maladaptive behaviors. This process is enhanced through self-monitoring, that is, tracking and analyzing the associations between the negative cycle components.

Other CBT elements also can be deployed in the treatment of depression, including the following: goal setting; relaxation; and training in problem-solving, assertiveness, conflict management, communication, interpersonal skills, and affect regulation/distress tolerance. The number and combination of these elements vary according to the specific symptom presentation.

Specialized education, training, and experience are necessary for the effective delivery of CBT, although most psychotherapists are likely to have received some training in some CBT elements. The goal of structured CBT is to achieve meaningful symptomatic and functional improvement within 12 to 24 sessions (or fewer if the symptoms are mild). In the initial stage of a typical treatment, the presenting problem is assessed, a therapeutic alliance is fostered, and education about the course of treatment is provided. In the next phase, information about the nature, cause, and course of depression is provided, with a focus on a cognitive-behavioral understanding of the symptoms as the rationale for treatment. In the next phase, active treatment occurs. CBT typically is organized according to a weekly agenda that involves homework assignments for practice opportunities that foster skills mastery. The final phase focuses on generalization and maintenance of skills as well as relapse prevention. At this stage, treatment frequency diminishes as the patient assumes self-responsibility for implementation of learned skills on an ongoing basis. However, it is not uncommon for patients to benefit from "booster" sessions after treatment termination has occurred to maximize long-term skills maintenance.

Systematic assessment of treatment effectiveness using standardized symptom rating scales (eg, PHQ-9 modified for adolescents) should be considered as a supplement to the clinical interview during treatment, as use of these scales can optimize therapists' ability to accurately assess treatment response and adjust treatment as indicated. Treatment termination can be informed by normalization of symptoms as measured by these instruments.

Although CBT emphasizes cognitive and behavioral processes that maintain sad/irritable mood, these processes are learned and function in a social context. As such, treatment is characterized by collaboration among the patient, family, and therapist, and, in some cases, school personnel. Case-specific circumstances help to determine whether to work with a patient individually or with the patient in conjunction with family members. Family-directed interventions that improve parent−child relationships and parenting style, strengthen family problem-solving and communication skills, and reduce parental modeling of mood dysregulation can provide adjunctive benefit.

In addition, school-directed interventions that educate teachers about the student's difficulties with depression and how to foster effective problem-solving, communication, and coping strategies in the school setting can be part of a comprehensive treatment plan. Specific plans for depression management at school can be written into the student's 504 plan or individualized education program (eg, extended time for completing assignments while under initial treatment).

A developmental perspective is essential when implementing CBT with children. Developmental considerations include considering the child's level of autonomy and independence and the role of caregivers in the treatment process; adapting cognitive elements of treatment in accordance with the child's ability to think abstractly; and integrating CBT into play-based interactions, in which the

primary mechanism for teaching is modeling. In general, younger children may benefit more from behavioral techniques than cognitive techniques; nonetheless, cognitive techniques from which younger children can benefit include relaxation and positive self-talk. In nearly all cases, younger children will require substantial involvement of caregivers to master the therapy skills.

Interpersonal Therapy

Benefits and Harms. Two RCTs[134,144] in adolescents of standard IPT and 1 RCT of family-based IPT[145] were included in the AHRQ/RTI-UNC review (see the review for study summaries[51]). Among adolescents with MDD and/or PDD, compared to wait-list or active control, evidence was insufficient for benefits or harms for standard IPT. Among children with MDD and/or PDD, compared to active control, family-based IPT improved clinician-reported depressive symptoms, parent-reported depressive symptoms, and self-reported depressive symptoms (all low SOE); there was insufficient evidence for harms.

Additional Support. In contrast to the AHRQ/RTI-UNC review, the benefits of standard IPT were supported in part by 3 meta-analyses of RCTs published since the AHRQ/RTI-UNC review. These analyses reported change in depressive symptoms in children and adolescents with DD for IPT vs the named comparator as follows: overall SMD −0.38 (−1.24, 0.47), subgroup SMDs: wait-list SMD −1.37 (−2.04, −0.70), "psychological placebo" SMD −0.70 (−1.29, −0.12), and TAU SMD −0.66 (−1.22, −0.09)[52]; wait-list SMD −1.51 (−2.63, −0.38), TAU SMD −0.94 (−1.72, −0.17), and "named control group" SMD −1.38 (−2.56, −0.20)[56]; and in a subgroup analysis of a meta-analysis, mean posttreatment effect size of IPT: $g = 0.78$ compared to CBT: $g = 0.31$, $p = .14$.[55] The first 2 analyses included both children and adolescents, the data for which were not disaggregated; the third analysis was restricted to adolescent study participants. In summary, in subgroup analyses, statistically significant improvements in depression in children and adolescents were found for IPT vs wait-list, "psychological placebo," TAU, and "named control group."

It should be noted that these 3 meta-analyses included RCTs that were excluded from the AHRQ/RTI-UNC review because of methodologic problems, including ineligible population, ineligible country, and ineligible outcomes. However, the consistency of findings across the 3 meta-analyses was deemed to warrant inclusion of this modality in the treatment statement.

Implementation. Interpersonal therapy (IPT) is conceptualized as occurring within an interpersonal matrix in which interpersonal relationships contribute to the onset or perpetuation of a depressive disorder. As such, the main goals of IPT include expanding social support, decreasing interpersonal stress, enhancing the processing of emotions, and improving social functioning within significant relationships.

Specialized education, training, and experience are necessary for the effective delivery of IPT. A course of IPT typically is designed to be delivered once a week for 12 weeks, although intensity and duration can vary with the specifics of the presentation. Parental participation is recommended but not required; parental session attendance can range from no sessions to several sessions across the 3 treatment stages. In the initial stage of treatment, the presenting problem is assessed, a therapeutic alliance is fostered, and education about the nature, cause, and course of depression as well as the course of treatment is provided. Then the therapist conducts the interpersonal inventory, which is a detailed review of the patient's significant relationships, both current and past, with their emotional valence. This inventory leads to the interpersonal formulation, which links the patient's interpersonal situation with the depressed mood and typically identifies one of 4 main problem areas: loss, disputes, role disputes or transitions, and interpersonal deficits.

In the middle phase of treatment, the therapist works with the patient to resolve the identified problem area through, for example, linking mood to interpersonal events, grief work, communication and problem-solving training, perspective-taking, role adaptation, and addressing problematic interpersonal processes. In the termination phase, generalization and maintenance of skills outside of the therapy setting and relapse prevention become the treatment foci. The patient is helped to identify warning signs of depression that suggest the need for additional treatment.

A developmental perspective and appropriate modifications in technique are essential when implementing IPT with children, including family involvement (as in family-based IPT).

2. **AACAP suggests (2I) that selective serotonin reuptake inhibitor medication (except paroxetine), preferably fluoxetine, could be offered to adolescents and children with major depressive disorder.**

A total of 27 studies of pharmacological interventions were included in the AHRQ/RTI-UNC review (see the review for study summaries[51]), including 14 RCTs of selective serotonin reuptake inhibitors (SSRIs) with 8 RCTs

of fluoxetine,[151-160] and one RCT of escitalopram,[161,162] and the remaining RCTs of citalopram, vilazodone, and paroxetine. Insufficient rigorous evidence of benefit for other classes of medication included in the AHRQ/RTI-UNC review (serotonin norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants, and monoamine oxidase inhibitors) precluded inclusion of these modalities in the treatment statement. Although one meta-analysis published since the AHRQ/RTI-UNC review[58] found benefit for duloxetine, no other recent meta-analyses supported the SNRI class of medication.

Differences of Opinion. None. The Guideline Writing Group voted unanimously in favor of this suggestion.

Benefits and Harms. Adolescents—fluoxetine. Among adolescents with MDD, compared to placebo, fluoxetine improved clinician-reported depressive symptoms and response (both low SOE); evidence was insufficient for harms.

Adolescents—escitalopram. In the one included study, among adolescents with MDD, compared to placebo escitalopram improved clinician-reported depressive symptoms, response, remission, and clinician-reported functional status at 24 weeks (all low SOE); evidence was insufficient for harms.

Children—fluoxetine. Insufficient evidence was available for benefits or harms of fluoxetine in children with MDD or PDD

Adolescents and children—other SSRIs. Evidence for benefits of citalopram, paroxetine, and vilazodone individually was insufficient. Evidence of harms for citalopram and vilazodone individually was insufficient. Compared to placebo, for adolescents and children with MDD, paroxetine had worse suicidal ideation or behaviors and treatment withdrawal because of adverse events (low SOE).

Adolescents and children—pooled SSRIs. In pooled studies of 2 or more SSRIs including fluoxetine, escitalopram, citalopram, paroxetine, and vilazodone, compared to placebo SSRIs improved response and functional status for adolescents and children with MDD (both low SOE). Compared to placebo, pooled SSRIs had worse serious adverse events and treatment withdrawal because of adverse events for adolescents and children with MDD (low SOE).

Additional Support. Fluoxetine. The benefits of fluoxetine were supported by 3 meta-analyses of RCTs published since the AHRQ/RTI-UNC review. These analyses reported improvement in depressive symptoms in children and adolescents with MDD[57,58] or MDD/PDD[52] for the fluoxetine vs placebo comparison: SMD −0.51 (−0.84, −0.18)[52]; SMD −0.51 (−0.99, −0.03)[57]; and mean difference (MD) −2.84 (−4.12, −1.56).[58] In summary, statistically significant improvements in depression in children and adolescents were found for fluoxetine vs placebo.

Escitalopram. The benefits of escitalopram reported in the AHRQ/RTI-UNC review were not supported by 3 meta-analyses of RCTs published since the AHRQ/RTI-UNC review. These analyses reported no improvement in depressive symptoms in children and adolescents with MDD[57,58] or MDD/PDD[52] for the escitalopram vs placebo comparison: SMD −0.17 (−0.88, 0.54)[52]; SMD −0.17 (−1.15, 0.81)[57]; and mean difference (MD) −2.62 (−5.29, 0.04).[58] In summary, no statistically significant improvements in depression in children and adolescents were found for escitalopram vs placebo.

It should be noted that the above-reported meta-analyses included RCTs that were excluded from the AHRQ/RTI-UNC review because of methodologic problems, including ineligible design, non-English language, abstract superseded by publication, and industry reports. In addition, none of these meta-analyses reported separate effects for children and adolescents, whereas the preponderance of RCTs targeted adolescents.

Other SSRIs. One meta-analysis of RCTs published since the AHRQ/RTI-UNC review reported improvement in depressive symptoms in children and adolescents with MDD for the sertraline vs placebo comparison: MD −3.51 (−6.99, −0.04) but the benefit did not persist when high risk of bias studies were excluded.[58] Two other RCTs did not report improvement with sertraline: SMD 0.11 (−0.49, 0.71)[52] and SMD −0.23 (−1.21, 0.77).[57]

Evidence also was insufficient in the newer meta-analyses for benefits and harms for other individual SSRIs except harms for paroxetine, which reported worse suicide-related outcomes when high risk of bias studies were removed (MD 2.55 [1.08, 6.02]), and vilazodone, which reported worse overall adverse outcomes (MD 2.25 [1.22, 4.17]).[58]

For SSRIs as a class, compared to placebo, SSRIs improved depressive symptoms (MD with high risk of bias studies: −2.30 [−3.20, −1.39]; MD without high risk of bias studies: −2.25 [−3.32, −1.18]) and worsened suicide-related outcomes (odds ratio with high risk of bias studies: 1.30 [1.04, 1.63]; odds ratio without high risk of bias studies: 1.46 [1.07, 1.99]).[58]

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 facilitate cognitive processing of those emotions.[163] The SSRI medication class is a group of

chemically and pharmacologically different compounds that inhibit the pre-synaptic 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 multi-step process is hypothesized to be related to the delay in the full SSRI treatment effect. Suggested mechanisms of action for SSRIs include effects on brain plasticity, corticolimbic circuitry, and affective processing, and environmental interactions.[164]

Medications from the SSRI class currently marketed in the United States are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone. Currently, only 2 SSRIs are approved by the US Food and Drug Administration (FDA) for the treatment of depression in youth: fluoxetine, for youth aged 8 years and older, and escitalopram, for youth aged 12 years and older.

Mechanisms of action vary somewhat across SSRIs (eg, effects on other neurotransmitter receptors affecting the degree of serotonin selectivity). The choice of an SSRI medication is based upon factors such as risk−benefit ratio for each medication, potential drug interactions, favorable experience of a family member, cost, and availability in formularies. At present, there is no clear role for pharmacogenomic testing in medication selection, although this may change as additional evidence accumulates.[165]

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[166] and at any dose of fluvoxamine, youth may require twice-daily dosing to avoid withdrawal side effects.

The best-fitting model for SSRI response may be a logarithmic model demonstrating significant improvement in depression symptoms within the first month of treatment initiation, with two-thirds of SSRI treatment benefits occurring by week 2 and maximal benefit by week 4.[167] This pharmacodynamic profile suggests that 2-month clinical SSRI trials in pediatric depression may unnecessarily prolong an ineffective treatment, if response or remission is not observed in the first 4 to 6 weeks.

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 (see below for syndrome description). It may be helpful when starting a new SSRI to begin with a sub-therapeutic dose, to minimize the chance of adverse effects. The combination of early adverse effects and delayed efficacy can lead patients, families, and clinicians to discontinue medications before they can be effective. As such, it is important to provide education about the time-course of improvement and adverse effects to prevent unnecessary termination of a potentially effective medication trial.[168]

All 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 the MDD indication in one analysis have been reported to be 3% for youth treated with an antidepressant and 2% for youth treated with a placebo.[169] The pooled risk difference has been reported to be 1% (95% CI −0.1% to 2%; $p = .08$), yielding a number needed to harm (NNH) of 112 (compared to a number needed to treat [to achieve response] of 10).[169] 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.

Medication-induced behavioral agitation[170] (eg, motor or mental restlessness, insomnia, impulsiveness, talkativeness, disinhibited behavior, aggression), more common in younger children than in adolescents,[171] may occur early in SSRI treatment, with dose increases or with concomitant administration of drugs that inhibit the metabolism of SSRIs. Because the likelihood of activation events has been associated with higher antidepressant plasma levels,[172] slow up-titration and close monitoring (particularly in younger children) is warranted, 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 (<2%)[173] reports of mania/hypomania that can be difficult to distinguish from medication-induced behavioral activation/agitation. Although not empirically demonstrated, behavioral activation/agitation may be more likely to occur early in treatment (first month) or with dose increases, whereas mania/hypomania may appear variably or later. Moreover, behavioral activation/agitation may improve quickly after SSRI dose decrease or discontinuation, whereas mania may persist or 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 and can cause surgical risk; rare bleeding events include ecchymosis, hematoma, epistaxis, petechiae, and hemorrhage.

Serotonin syndrome,[174] caused by elevated brain serotonin levels, can be triggered when multiple serotonergic medications are prescribed concomitantly. 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) 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 2 or more non-MAOI serotonergic drugs, including antidepressants, opioids and other pain medications, stimulants, cough/cold/allergy medications, and other over-the-counter products. 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. Adolescents should be informed that certain recreational drugs (eg, dextromethorphan, "ecstasy") are highly serotonergic and can cause serious interactions with antidepressants.

Each SSRI has special prescribing considerations. Paroxetine, fluvoxamine, and sertraline have been associated with discontinuation syndrome[175] (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 per day 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.[176] Concomitant administration of any of the SSRIs with any of the 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. Antidepressant treatment has been organized into 3 phases: *acute*, *continuation*, and *maintenance*. The goal of the acute phase is to achieve response and ultimately remission, whereas the goals of the continuation and maintenance phases are to prevent relapse and recurrence. Treatment goals have been defined in some research settings as follows: *response*: a significant (eg, >50%) reduction in symptoms for at least 2 weeks; *remission*: a period of at least 2 weeks but less than 2 months with few or no symptoms; *recovery*: absence of significant symptoms for 2 months or greater; *relapse*: a new episode of depression during the period of remission; and *recurrence*: a new episode of depression during recovery.[8]

An illustrative medication trial for mild-to-moderate depression presentations entails prescribing the recommended therapeutic dose (adjusted for age in some cases), monitoring weekly for adverse effects, and assessing for response (ideally with both clinical interview and standardized symptom rating scale) in 4 to 6 weeks (acute phase). Minimal data support an association between higher dosing and higher efficacy, and higher doses typically result in more adverse effects.[177] Accordingly, if the 4- to 6-week assessments show minimal response, a trial of a second SSRI could be considered (although, in some situations, dose increase of the initial SSRI may be warranted). In the Treatment of Resistant Depression in Adolescents (TORDIA) study, 55% of adolescents with MDD who were nonresponders to an initial SSRI demonstrated a significant response when prescribed a second SSRI or an SNRI with CBT.[178] Little rigorous evidence is currently available regarding other approaches to treatment-resistant depression.

Treatment resistance can arise from many factors, which should be thoroughly explored and remedied; these include inadequate medication dose or duration, misdiagnosis, untreated comorbidities, discontinuation because of adverse medication effects, exposure to significant environmental stressors, inadequate fit with or skill level of treating practitioners, and nonadherence to the medication regimen. Determinants of nonadherence are multi-determined,

including social/economic, health care system, illness, patient, and treatment factors.[179] Although evidence is mixed, some effective strategies include behavioral (motivational), educational (information pamphlets), integrated care (care coordination and support), self-management (illness management skills), risk communication (harm avoidance), and packaging/daily reminder (physical [pill box] or technological) approaches.[179] In children and adolescents, parental oversight of medication regimens is of paramount importance.

There is no definitive empirical guidance for switching from one SSRI to another.[180] 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.

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 in the absence of relevant underlying comorbidities (eg, cardiac abnormalities in the context of citalopram prescribing).

The optimal duration of pharmacologic treatment of an initial depressive disorder for continued symptom remission is uncertain, but a generally accepted approach to minimize risk of relapse or recurrence would be to continue an effective, tolerated dose for approximately 6 to 12 months after remission (continuation phase, see Suggestion 4 below). Discontinuation generally should occur during a relatively stress-free period. Expert opinion has suggested that depression with greater severity, a longer duration, or a higher number of recurrences may benefit from longer treatment (maintenance phase), from more than 1 year to several years or longer.[8]

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.[181] 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 (which can be advantageous when adherence is a concern).

3. **AACAP suggests (2I) that combination treatment (cognitive-behavioral therapy plus fluoxetine) could be offered to adolescents and children with major depressive disorder.**

One RCT[156] of combination treatment (CBT + fluoxetine) in adolescents with MDD was included in the AHRQ/RTI-UNC review (see the review for study summary[51]).

Differences of Opinion. None. The Guideline Writing Group voted unanimously in favor of this suggestion.

Benefits and Harm. In the one included study, in adolescents with MDD, compared to placebo fluoxetine + CBT improved clinician-reported depressive symptoms, response, remission, and clinician-reported functional status (all low SOE). Evidence for harms was insufficient.

See Additional Support under treatment Statements 1 and 2 as support for including children in this statement.

Additional Support. The benefits of combination treatment (CBT + fluoxetine) for adolescents and children with DD were supported by one meta-analysis[52] published since the AHRQ/RTI-UNC review. In this analysis, CBT plus fluoxetine was more effective than CBT alone: SMD −0.73 (−1.39, −0.07). It should be noted that this meta-analysis included RCTs that were excluded from the AHRQ/RTI-UNC review because of methodologic problems, including ineligible design, non-English language, abstract superseded by publication, and industry reports. In addition, this meta-analysis did not report separate effects for children and adolescents, whereas the preponderance of RCTs targeted adolescents.

Implementation. Although the 2 studies noted above[52,156] demonstrated benefit for combination treatment (CBT + fluoxetine), this finding was inconsistent with a British RCT (excluded from the AHRQ/RTI-UNC review because of ineligible population) that failed to find benefit of combination treatment (fluoxetine + CBT) over monotherapy in the context of routine specialist care of adolescents with MDD.[182] Although week 12 findings from the TORDIA study[178] demonstrated superiority of combination treatment (CBT + SSRI or SNRI) over medication alone, in a follow-up study the initial treatment assignment

did not affect rates of remission.[183] In the United States, expert consensus generally (but not universally) supports the prioritization of combination treatment, particularly if there is a need for acute symptom reduction in a severe, functionally impairing disorder, or partial response to either treatment alone.

Combination treatment typically involves concurrent administration of psychotherapy (CBT in the AHRQ-included study) and medication (fluoxetine in the AHRQ-included study). Optimally, combination treatment would be delivered in the same facility to enhance convenience for patient and family as well as communication between treatment providers. Typically, combination treatment would be more intense in the first months (eg, weekly psychotherapy visits for 3 to 4 months followed by booster sessions at variable intervals; weekly medication visits or contacts in the first month tapering to bi-monthly in the second month and monthly to quarterly thereafter). Parents would be involved initially in psychoeducation and intermittently thereafter as indicated.

4. **AACAP suggests (2C) that continued fluoxetine alone or cognitive-behavioral therapy plus continued fluoxetine could be offered to adolescents and children responding to acute treatment with fluoxetine to prevent relapse/recurrence of major depressive disorder.**

Five RCTS in children and adolescents of MDD relapse prevention from the same investigator group (2 RCTs for fluoxetine continuation,[184,185] and 2 RCTs and one follow-on study for CBT + continued fluoxetine)[186-188] were included in the AHRQ/RTI-UNC review (see the review for study summaries[51]).

Differences of Opinion. None. The Guideline Writing Group voted unanimously in favor of this suggestion.

Benefits and Harms. Among children and adolescents with MDD responding to treatment with fluoxetine in the acute phase, compared to placebo, continued fluoxetine prevented relapse/recurrence (low SOE); evidence was insufficient for harms.

Among children and adolescents with MDD responding to treatment with fluoxetine in the acute phase, compared to fluoxetine alone, CBT + continued fluoxetine prevented relapse/recurrence (low SOE); evidence was insufficient for harms.

Additional Support. No recent meta-analyses of RCTs were available to support or refute this suggestion.

Implementation. Relapse prevention intervention in children and adolescents with MDD derives from the high likelihood of relapse or recurrence of the disorder, most often occurring within 6 to 12 months of remission.[189,190] The 2 studies noted above[184,185] of continued fluoxetine among children and adolescents with single or recurrent MDD responding to acute fluoxetine treatment demonstrated lower risk of and longer time to relapse/recurrence compared to those in participants assigned to placebo, when observed for up to 8 months post acute treatment. These findings are consistent with a clinical recommendation of continued antidepressant treatment of youth with MDD for 6 to 12 months post remission (continuation treatment).[8]

The studies noted above[186-188] of continued fluoxetine + CBT among children and adolescents with single or recurrent MDD responding to acute fluoxetine treatment demonstrated lower risk of and longer time to relapse/recurrence compared to those in participants assigned to fluoxetine alone, when observed for up to 20 months post acute treatment.

Although the optimal timing for the introduction of CBT to the treatment of MDD in youth is not known with certainty, for youth responding to acute treatment with medication alone, relapse prevention CBT (RP-CBT) introduced in the continuation treatment phase may effectively address residual symptoms and optimize treatment gains. A typical implementation may comprise 8 to 12 sessions in 3 stages: weekly for the first month, bi-monthly for the next 2 months, and every 4 to 6 weeks for the last 3 months, for a total treatment length approximating 6 to 8 weeks. However, the number and frequency of sessions can be individualized in accordance with patient needs.

In the first stage, the aims of treatment are as follows: reducing residual symptoms through core skills; assessing and identifying core beliefs; and identifying and increasing areas of strength and wellness. Techniques used in this stage include psychoeducation, case conceptualization, and mood monitoring, and training in behavioral coping, cognitive restructuring, positive self-schema, problem solving, and family communication skills. In the second stage, the aims of treatment are consolidation and further practice of core skills and relapse prevention. Techniques used in this stage are introduction to wellness, practice and application of core and wellness skills for relapse prevention, and creation of a relapse prevention and wellness plan. In the third stage, the aims of treatment are consolidation of treatment gains, and evaluation and revision of the relapse prevention and wellness plans as needed. Techniques used in this stage depend upon the patient's needs. Most implementations have included a family component averaging 3 sessions.

Areas for Additional Treatment Research

For many important domains of treatment for depression (listed in part below), the AHRQ/RTI-UNC 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[e]
- Preferential sequencing of SSRIs and CBT[f]
- Treatment effect modifiers (eg, child and family characteristics, treatment setting, disorder severity, comorbidities, delivery methods)[g]
- Effects of other psychotherapies (eg, attachment-based therapy, family therapy, psychodynamic therapy, parent−child interaction therapy, mindfulness therapy)[h]
- Effects of other antidepressant medications and combinations of medications[i]
- Use of complementary and alternative interventions (eg, exercise, spirituality, yoga, sleep, omega-3 fatty acid supplementation)[j]
- Use of interventional treatments (eg, neurofeedback, transcranial magnetic stimulation, electroconvulsive therapy) and novel psychopharmacologic agents (eg, ketamine)[k]
- Long-term safety risks of pharmacologic treatment[l]
- Effectiveness of psychosocial and pharmacologic treatments in underserved and minority populations[m]
- Effectiveness of psychosocial and pharmacologic treatments in populations with comorbid psychiatric and developmental disorders[n]
- Interventions for treatment-resistant, recurrent, persistent, and bipolar depression[o]
- Interventions for subsyndromal depression[p]

LIMITATIONS

The limitations[191] of the Treatment section of this guideline reflect the following limitations of the AHRQ review:

- Small body of evidence
- Brief follow-up of most studies
- Variable methods for reporting benefit outcomes
- Variable methods for reporting treatment emergent adverse events and serious adverse events
- Insufficient data to assess risk of suicidal behavior
- Inability to disaggregate findings for children and adolescents in studies with mixed populations
- Inability to disaggregate findings for study populations with mixed disorders (eg, MDD, PDD, DD NOS)
- Lacking or sparse descriptions and analyses of potentially mediating and moderating variables (eg, intervention components, participant demographics, comorbidities, symptom severity)
- Insufficient data to assess effectiveness of collaborative care
- Poor representation of young children in study populations
- Poor representation of non-Caucasian or other minority group youth in study populations
- Paucity of studies addressing persistent depressive disorder as the primary disorder
- Paucity of studies addressing subsyndromal depression (DD NOS) as the primary disorder

The limitations of the Assessment and Implementation sections of this guideline reflect their primary derivation from expert opinion and consensus rather than rigorous, critically appraised empirical research.

CONCLUSIONS

As noted in this guideline, there are significant limitations in the quality and quantity of rigorous empirical support for the etiology, assessment, and treatment of depression in children and adolescents. The paucity of depression research in youth is disturbingly out of proportion to the magnitude of the personal and public health impact of the illness. Nonetheless, congruent with national and international guidelines,[8,60-62] in this guideline psychotherapy (specifically CBT and interpersonal therapy) and psychopharmacology (specifically selective serotonin reuptake inhibitor [SSRI] medication [except paroxetine]) have some rigorous (RCT/meta-analysis) empirical support as well as strong expert consensus as treatment options. Because of the compelling contribution of psychological and social−environmental factors to the onset of depression, consideration of supportive interventions as a first-line treatment for mild presentations of depression in children and adolescents is warranted. Empirically validated psychotherapies and SSRI medications, alone or in combination, can be considered for moderate-to-severe presentations, with continuation of treatment for a sufficient period of time to reduce the risk of relapse or recurrence. Because effective treatment outcomes are predicated in part

[e]AHRQ review: equivocal head-to-head comparisons of SSRI vs CBT
[f]AHRQ review: no data
[g]AHRQ review: equivocal subgroup analyses
[h]AHRQ review: insufficient evidence
[i]AHRQ review: insufficient evidence
[j]AHRQ review: one study for exercise suggested benefit for adolescents with MDD; otherwise insufficient evidence
[k]AHRQ review: no data
[l]AHRQ review: no data
[m]AHRQ review: no data
[n]AHRQ review: no data
[o]AHRQ review: insufficient data
[p]AHRQ review: insufficient data

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 outcomes.

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 (including telepsychiatry, Web and telephone application-based adaptations of psychotherapy, trained mid-level practitioner- and lay-delivered treatments, collaborative care) for safe and effective treatment of child and adolescent depressive disorders is an urgent priority. Pharmacotherapeutic task sharing with pediatric practitioners, particularly for mild-to-moderate depressive presentations, can greatly expand access to safe and effective care while conserving child and adolescent psychiatrists for more severe and complex presentations and for the delivery of novel interventional and genetically guided treatments as they are developed. The sequencing and comparative effectiveness of depression treatments, delineation of mediators and moderators of effective depression treatments, effective approaches to treatment nonresponders and disorder relapse/recurrence, long-term effects of SSRI use, additional evaluation of the degree of suicide risk associated with SSRIs, and the discovery of novel pharmacologic or interventional treatments remain other key research needs.

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The AACAP Clinical Practice Guidelines critically assess and synthesize scientific and clinical information as an educational service to AACAP members and other interested parties. The treatment statements in the guidelines are primarily based upon information available on the date of publication of the corresponding AHRQ systematic review. The guidelines are not continually updated and may not reflect the most recent evidence. The guidelines should not be considered to be a statement of the standard of care nor exclusive of all proper treatments or methods of care. The guidelines do not account for individual variation among patients. As such, it is not possible to draw conclusions about the effects of not implementing a particular recommendation, either in general or for a specific patient. The ultimate decision regarding a particular assessment, clinical procedure, or treatment plan must be made by the clinician in light of the psychiatric evaluation, other clinical data, the patient's and family's personal preferences and values, and the diagnostic and treatment options available. Use of these guidelines is voluntary. AACAP provides the guidelines on an "as is" basis, and makes no warranty, expressed or implied, regarding them. AACAP assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of the guidelines or for any errors or omissions.

The primary intended audience for the AACAP Clinical Practice Guidelines is child and adolescent psychiatrists; however, the information presented also could be useful for other medical or behavioral health clinicians.

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