

**PRACTICE PARAMETER FOR THE ASSESSMENT AND TREATMENT OF
CHILDREN AND ADOLESCENTS WITH DEPRESSIVE DISORDERS**

ABSTRACT

This practice parameter describes the epidemiology, clinical picture, differential diagnosis, course, risk factors, and pharmacological and psychotherapy treatments of children and adolescents with major depressive or dysthymic disorders. Side effects of the antidepressants, particularly the risk for suicidal ideation and behaviors are discussed. Recommendations regarding the assessment and the acute, continuation, and maintenance treatment of these disorders are based on the existent scientific evidence as well as the current clinical practice. **Key Words:** major depressive disorder, dysthymic disorder, children, adolescents, evaluation, treatment, antidepressants, selective serotonin reuptake inhibitors, psychotherapy, practice parameter.

ATTRIBUTION

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INTRODUCTION

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Depressive disorders are often familial recurrent illnesses associated with increased psychosocial morbidity and mortality. Early identification and effective treatment may reduce the impact of depression on the family, social, and academic functioning in youth and may reduce the risk for suicide, substance abuse, and persistence of depressive disorders into adulthood. Evidence-supported treatment interventions have emerged in psychotherapy and medication treatment of childhood depressive disorders that can guide clinicians to improve outcomes in this population.

METHODOLOGY

The list of references for this parameter was developed by searching *PsycINFO*, *MedLine*, and *Psychological Abstracts*; by reviewing the bibliographies of book chapters and review articles; by asking colleagues for suggested source materials; and from the previous version of this parameter (American Academy of Child and Adolescent Psychiatry, 1998), the recent American Psychiatric Association/AACAP guidelines “The Use of Medication in Treating Childhood and Adolescent Depression: Information for Physicians” published by ParentsMedGuide.org, the American Psychiatric Association guidelines for the treatment of adults with MDD (American Psychiatric Association, 2000a; Fochtman and Gelenberg, 2005), the Texas algorithms for the treatment of children and adolescents with MDD (Hughes et al., 2007), and the National Institute of Health and Clinical Excellence (NICE) guidelines for the treatment of depressed youth (2004). The searches, conducted in 2005, used the following text words: major depressive disorder, dysthymia, antidepressants, and psychotherapy (e.g., interpersonal, psychodynamic, and cognitive) combined with the word child. The searches covered the period 1990 to January 2007, and only articles that included depressive *disorders* were included. Given space limitations, we mainly cited review articles published in refereed journals and added new relevant articles not included in the reviews.

DEFINITIONS

The terminology in this practice parameter is consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* (American Psychiatric Association, 2000b). Unless it is specified, the term “depression” encompasses both major depressive (MDD) and dysthymic (DD) disorders. Impairment means reduced functioning in one or more major areas of life (academic performance, family relationships, and peer interactions).

The information included in this parameter pertains mainly to MDD. There are few clinical studies and no controlled trials for the treatment of DD in youth. However, based on the limited adult literature (American Psychiatric Association, 2000a), efficacious treatments for MDD may also be useful for the management of DD.

In this parameter, unless otherwise specified, the terms “child” and “youth” will refer to children and adolescents. “Parent” refers to parent or legal guardian.

EPIDEMIOLOGY

The prevalence of MDD is estimated to be approximately 2% in children and 4% to 8% in adolescents, with a male/female ratio of 1:1 during childhood and 1:2 during adolescence

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(Birmaher et al., 1996). The risk for depression increases by a factor of 2 to 4 after puberty, particularly in females (Angold et al., 1998), and the cumulative incidence by age 18 is approximately 20% in community samples (Lewinsohn et al., 1998).

Approximately 5% to 10% of children and adolescents have subsyndromal symptoms of MDD. These youth have considerable psychosocial impairment, high family loading for depression, and an increased risk for suicide and developing MDD (Fergusson et al., 2005; Gonzales-Tejera et al., 2005; Lewinsohn et al., 2000; Pine et al., 1998).

The few epidemiological studies on DD have reported a prevalence of 0.6% to 1.7% in children and 1.6% to 8.0% in adolescents (Birmaher et al., 1996).

Studies in adults and one study in youth have suggested that each successive generation since 1940 is at greater risk for developing depressive disorders and that these disorders have their onset at a younger age (Birmaher et al., 1996).

CLINICAL PRESENTATION

Clinical depression manifests as a spectrum disorder with symptoms ranging from subsyndromal to syndromal. To be diagnosed with a syndromal disorder (MDD), a child or adolescent must have at least 2 weeks of persistent change in mood manifested by either depressed or irritable mood and/or loss of interest and pleasure plus a group of other symptoms including wishing to be dead, suicidal ideation or attempts; increased or decreased appetite, weight, or sleep; and decreased activity, concentration, energy, or self-worth, or exaggerated guilt (American Psychiatric Association, 2000b; World Health Organization, 1992). These symptoms must represent a change from previous functioning and produce impairment in relationships or in performance of activities. Furthermore, symptoms must not be attributable only to substance abuse, use of medications, other psychiatric illness, bereavement, or medical illness.

Overall, the clinical picture of MDD in children and adolescents is similar to the clinical picture in adults, but there are some differences that can be attributed to the child's physical, emotional, cognitive, and social developmental stage (Birmaher et al., 1996; Fergusson et al., 2005; Kaufman et al., 2001; Klein et al., 2005; Lewinsohn et al., 2003a; Luby et al., 2004; Yorbik et al., 2004). For example, children may have mood lability, irritability, low frustration tolerance, temper tantrums, somatic complaints, and/or social withdrawal instead of verbalizing feelings of depression. Also, children tend to have fewer melancholic symptoms, delusions, and suicide attempts than depressed adults.

There are different subtypes of MDD, which may have prognostic and treatment implications. Psychotic depression has been associated with family history of bipolar and psychotic depression (Haley et al., 1988; Strober et al., 1993), more severe depression, greater long-term morbidity, resistance to antidepressant monotherapy, and, most notably, increased risk of bipolar disorder (Strober and Carlson, 1982). MDD can be manifested with atypical symptoms such as increased reactivity to rejection, lethargy (leaden paralysis), increased appetite, craving for carbohydrates, and hypersomnia (for a review see Stewart et al., 1993; Williamson et al., 2000). Youth with seasonal affective disorder (SAD) (Swedo et al., 1995) mainly have symptoms of depression during the season with less daylight. However, SAD should be differentiated from depression triggered by school stress, because both usually coincide with the school calendar.

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DD consists of a persistent, long-term change in mood that generally is less intense but more chronic than in MDD. As a consequence, DD is often overlooked or misdiagnosed. Although the symptoms of dysthymia are not as severe as in MDD, they cause as much, or more, psychosocial impairment (Kovacs et al., 1994; Masi et al., 2001). For a *DSM-IV* diagnosis of DD, a child must have depressed mood or irritability on most days for most of the day for a period of 1 year, as well as two other symptoms from a group including changes in appetite or weight and changes in sleep; problems with decision-making or concentration; and low self-esteem, energy, and hope (American Psychiatric Association, 2000b).

COMORBIDITY

Both MDD and DD are usually accompanied by other psychiatric and medical conditions, and often they occur together (the so-called “double depression”). Depending on the setting and source of referral, 40% to 90% of youth with depressive disorder also have other psychiatric disorders, with up to 50% having two or more comorbid diagnoses. The most frequent comorbid diagnoses are anxiety disorders, followed by disruptive disorders, attention-deficit/hyperactivity disorder (ADHD), and, in adolescents, substance use disorders. MDD and DD usually manifest after the onset of other psychiatric disorders (e.g., anxiety), but depression also increases the risk for the development of non-mood psychiatric problems such as conduct and substance abuse disorders (Angold et al., 1999; Birmaher et al., 1996; Fombonne et al., 2001a, b; Lewinsohn et al., 1998, 2003a; Rohde et al., 1991).

DIFFERENTIAL DIAGNOSIS

Several psychiatric (e.g., anxiety, dysthymia, ADHD, ODD, PDD, substance abuse) and medical disorders (e.g., hypothyroidism, mononucleosis, anemia, certain cancers, autoimmune diseases, premenstrual dysphoric disorder, and chronic fatigue syndrome) as well as conditions such as bereavement and depressive reactions to stressors (adjustment disorder) may co-occur with or mimic MDD or DD. These conditions may cause poor self-esteem or demoralization, but should not be diagnosed as MDD or DD unless they meet criteria for these disorders. Moreover, the symptoms of the above-noted conditions may overlap with the symptoms of depression (e.g., tiredness, poor concentration, and sleep and appetite disturbances), making the differential diagnosis complicated. Also, medications (e.g., stimulants, corticosteroids, and contraceptives) can induce depression-like symptomatology. The diagnosis of MDD or DD can be made if depressive symptoms are not due solely to the illnesses or the medications and if the child fulfills the criteria for these depressive disorders.

Since most children and adolescents presenting to treatment are experiencing their first episode of depression, it is difficult to differentiate whether their depression is part of unipolar major depression or the depressive phase of bipolar disorder. Certain indicators such as high family loading for bipolar disorder, psychosis, and history of pharmacologically-induced mania or hypomania may herald the development of bipolar disorder (Birmaher et al., 1996). It is important to evaluate carefully for the presence of subtle or short-duration hypomanic symptoms because these symptoms often are overlooked, and these children and adolescents may be more likely to become manic when treated with antidepressant medications (Martin et al., 2004). However, it is also important to note that not all children who become activated or hypomanic while receiving antidepressants have bipolar disorder (Wilens et al., 1998).

CLINICAL COURSE

The median duration of a major depressive episode for clinically referred youth is about 8 months, and for community samples, about 1 to 2 months. Although most children and adolescents recover from their first depressive episode, longitudinal studies of both clinical and community samples of depressed youth have shown that the probability of recurrence reaches 20% to 60% by 1 to 2 years after remission and climbs to 70% after 5 years (Birmaher et al., 2002; Costello et al., 2002). Recurrences can persist through life, and a substantial proportion of children and adolescents with MDD will continue to suffer MDD during adulthood. Moreover, between 20% and 40% will develop bipolar disorder, particularly if they have the risk factors described above (Geller et al., 1994; Strober and Carlson, 1982).

Childhood depression, compared with adult-onset depression, appears to be more heterogeneous. Some children may have a strong family history of mood disorders and high risk for recurrences, whereas others may develop bipolar disorder or be more likely to develop behavior problems and substance abuse than depression (Birmaher et al., 2002; Fombonne et al., 2001a, b; Harrington, 2001; Weissman et al., 1999). Although there are some differences, for the most part the predictors of recovery, relapse, and recurrence overlap. In general, greater severity, chronicity or multiple recurrent episodes, comorbidity, hopelessness, presence of residual subsyndromal symptoms, negative cognitive style, family problems, low socioeconomic status, and exposure to ongoing negative events (abuse, family conflict) are associated with poor outcome (Birmaher et al., 2002; Lewinsohn et al., 1998).

Childhood DD has a protracted course, with a mean episode length of approximately 3 to 4 years for clinical and community samples, and is associated with an increased risk for subsequent MDD and substance use disorders (Klein et al., 1988; Kovacs et al., 1994; Lewinsohn et al., 1991).

COMPLICATIONS

If untreated, MDD may affect the development of a child's emotional, cognitive, and social skills and may interfere considerably with family relationships (Birmaher et al., 1996, 2002; Lewinsohn et al., 2003b). Suicide attempts and completion are among the most significant and devastating sequelae of MDD with approximately 60% report having thought about suicide and 30% actually attempt suicide (American Academy of Child and Adolescent Psychiatry, 2001; Brent et al., 1999; Gould et al., 1998). The risk for suicidal behavior increases if there is a history of suicide attempts, comorbid psychiatric disorders (e.g., disruptive disorders, substance abuse), impulsivity and aggression, availability of lethal agents (e.g., firearms), exposure to negative events (e.g., physical or sexual abuse, violence), and a family history of suicidal behavior (Beautrais, 2000; Brent et al., 1988; Gould et al., 1998).

Children and adolescents with depressive disorders are also at high risk for substance abuse (including nicotine dependence), legal problems, exposure to negative life events, physical illness, early pregnancy, and poor work, academic, and psychosocial functioning. After an acute episode of depression, a slow and gradual improvement in psychosocial functioning may occur unless there are relapses or recurrences. However, psychosocial difficulties frequently persist after the remission of the depressive episode, underscoring the need for continuing treatment for

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the depression as well as treatment that addresses associated psychosocial and contextual issues (Fergusson and Woodward, 2002; Hammen et al., 2003, 2004; Lewinsohn et al., 2003b).

In addition to the depressive disorder, other factors such as comorbid psychopathology, physical illness, poor family functioning, parental psychopathology, low socioeconomic status, and exposure to negative life events may affect the psychosocial functioning of depressed youth (Birmaher et al., 1996; Fergusson and Woodward, 2002; Lewinsohn et al., 1998, 2003b).

RISK FACTORS

High-risk, adoption, and twin studies have shown that MDD is a familial disorder, which is caused by the interaction of genetic and environmental factors (Birmaher et al., 1996; Caspi et al., 2003; Kendler et al., 2005; Pine et al., 1998; Pilowsky et al., 2006; Reinherz et al., 2003; Weissman et al., 2005, 2006b). In fact, the single most predictive factor associated with the risk of developing MDD is high family loading for this disorder (Nomura et al., 2002; Weissman et al., 2005).

The onset and recurrences of major depression may be moderated or mediated by the presence of stressors such as losses, abuse, neglect, and ongoing conflicts and frustrations. However, the effects of these stressors also depend on the child's negative attributional styles for interpreting and coping with stress, support, and genetic factors. Other factors such as the presence of comorbid disorders (e.g., anxiety, substance abuse, ADHD, eating disorders), medical illness (e.g., diabetes), use of medications, biological, and socio-cultural factors have also been related to the development and maintenance of depressive symptomatology (Caspi et al., 2003; Costello et al., 2002; Garber and Hilsman, 1992; Kaufman et al., 2001; Kendler et al., 2005; Lewinsohn et al., 1998; Pine et al., 1998, 2002, 2004; Rey et al., 2004; Weissman et al., 2005; Williamson et al., 1998).

EVIDENCE BASE FOR PRACTICE PARAMETERS

The AACAP develops both patient-oriented and clinician-oriented practice parameters. Patient-oriented parameters provide recommendations to guide clinicians toward the best treatment practices. Treatment recommendations are based both on empirical evidence and clinical consensus, and are graded according to the strength of the empirical and clinical support. Clinician-oriented parameters provide clinicians with the information (stated as principles) needed to develop practice-based skills. Although empirical evidence may be available to support certain principles, principles are primarily based on expert opinion and clinical experience.

In this parameter, recommendations for best treatment practices are stated in accordance with the strength of the underlying empirical and/or clinical support, as follows:

- Minimal Standard [MS] is applied to recommendations that are based on rigorous empirical evidence (e.g., randomized, controlled trials) and/or overwhelming clinical consensus. Minimal standards apply more than 95% of the time (i.e., in almost all cases).
- Clinical Guideline [CG] is applied to recommendations that are based on strong empirical evidence (e.g., non-randomized controlled trials) and/or strong clinical consensus. Clinical guidelines apply approximately 75% of the time (i.e., in most cases).

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- Option [OP] is applied to recommendations that are acceptable based on emerging empirical evidence (e.g., uncontrolled trials or case series/reports) or clinical opinion, but lack strong empirical evidence and/or strong clinical consensus.
- Not Endorsed [NE] is applied to practices that are known to be ineffective or contraindicated.

The strength of the empirical evidence is rated in descending order as follows:

- [rct] Randomized, controlled trial is applied to studies in which subjects are randomly assigned to two or more treatment conditions
- [ct] Controlled trial is applied to studies in which subjects are non-randomly assigned to two or more treatment conditions
- [ut] Uncontrolled trial is applied to studies in which subjects are assigned to one treatment condition
- [cs] Case series/report is applied to a case series or a case report

CONFIDENTIALITY

Recommendation 1. *The clinician should maintain a confidential relationship with the child or adolescent while developing collaborative relationships with parents, medical providers, other mental health professionals, and appropriate school personnel [MS].*

At the outset of the initial contact, the clinician should clarify with the patient and parents the boundaries of the confidential relationship that will be provided. The child's right to a confidential relationship is determined by law that varies by state. Each state has mandatory child abuse reporting requirements. Parents will expect information about the treatment plan, the safety plan, and progress toward goals of treatment. The child should expect that suicide or violence risk issues will be communicated to the parents. The clinician should request permission to communicate with medical providers, other mental health professionals involved in the treatment, and appropriate school personnel. Clinicians should provide a mechanism for parents to communicate concerns about deterioration in function and high-risk behaviors such as suicide threats or substance use.

SCREENING

Recommendation 2. *The psychiatric assessment of children and adolescents should routinely include screening questions about depressive symptomatology [MS].*

Clinicians should screen all children and adolescents for key depressive symptoms including depressive or sad mood, irritability, and anhedonia. A diagnosis of a depressive disorder should be considered if these symptoms are present most of the time, affect the child's psychosocial functioning, and are above and beyond what is expected for the chronological and psychological age of the child. To screen for depressive symptoms, clinicians could use checklists derived from the DSM or ICD-10 criteria for depressive disorders, clinician-based instruments, and/or child and parent depression self-reports (American Academy of Child and Adolescent Psychiatry, 1997; Klein et al., 2005; Myers and Winters, 2002).

EVALUATION

Recommendation 3. *If the screening indicates significant depressive symptomatology, the clinician should perform a thorough evaluation to determine the presence of depressive and other comorbid psychiatric and medical disorders [MS].*

A comprehensive psychiatric diagnostic evaluation is the single most useful tool currently available to diagnose depressive disorders. The psychiatric assessment of depressed children and adolescents must be performed by a developmentally sensitive clinician who is able to achieve good rapport with children. For example, children may either have difficulties verbalizing their feelings or alternatively deny that they are depressed. Thus the clinician should also be attentive to observable manifestations of depression such as irritability, changes in sleep habits, decline in school performance, and withdrawal from previous pleasurable activities.

Clinicians should evaluate the child's and family's strengths. Also, the evaluation should be sensitive to ethnic, cultural, and religious characteristics of the child and her/his family that may influence the presentation, description, or interpretation of symptoms and the approach to treatment.

The evaluation should include direct interviews with the child and parents/caregivers and, ideally, with the adolescent alone. Also, whenever appropriate, other informants including teachers, primary care physicians, social services professionals, and peers should be interviewed. Subtypes of depressive disorders (seasonal, mania/hypomania, psychosis, subsyndromal, symptoms of depression), comorbid psychiatric disorders, medical illnesses, and (as indicated) physical examinations and laboratory tests are among the areas that should be evaluated.

Because of the prognostic and treatment implications, as described under Differential Diagnosis above, it is crucial to evaluate for the presence of lifetime manic or hypomanic symptoms.

Several standardized structured and semi-structured interviews are available for the evaluation of psychiatric symptoms in children older than 7 years old (American Academy of Child and Adolescent Psychiatry, 1997; Klein et al., 2005; Myers and Winters, 2002) and more recently in younger children (Luby et al., 2003). However, many of these interviews are too long to be carried out in clinical settings, require special training, and have low parent-child agreement. Parents' reports also may be influenced by their own psychopathology, highlighting the importance of obtaining information not only from parents, but also from the child and other sources, including teachers.

In the assessment of the onset and course of mood disorders, it is helpful to use a mood diary and a mood timeline that uses school years, birthdays, etc., as anchors. Mood is rated from very happy to very sad, and/or very irritable to non-irritable, and normative and non-normative stressors as well as treatments are noted. The mood timeline can help children and their parents to visualize the course of their mood and comorbid conditions, identify events that may have triggered the depression, and examine the relationship between treatment and response.

At the present time, no biological or imaging tests are clinically available for the diagnosis of depression.

Evaluation of a child's functioning can be done through the use of several rating scales (American Academy of Child and Adolescent Psychiatry, 1997; Winters et al., 2005). Among the shortest and simplest ones are the Children's Global Assessment Scale (Shaffer et al., 1983) and the Global Assessment of Functioning (American Psychiatric Association, 2000b).

Finally, the clinician, together with the child and parents, should evaluate the appropriate intensity and restrictiveness of care (e.g., hospitalization). The decision for the level of care will depend primarily on level of function and safety to self and others, which in turn are determined

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by the severity of depression, presence of suicidal and/or homicidal symptoms, psychosis, substance dependence, agitation, child's and parents' adherence to treatment, parental psychopathology, and family environment.

Recommendation 4. *The evaluation must include assessment for the presence of harm to self or others [MS].*

Suicidal behavior exists along a continuum from passive thoughts of death to a clearly developed plan and intent to carry out that plan (American Academy of Child and Adolescent Psychiatry, 2001; Gould et al., 1998). Because depression is closely associated with suicidal thoughts and behavior, it is imperative to evaluate these symptoms at the initial and subsequent assessments (American Academy of Child and Adolescent Psychiatry, 2001, Gould et al., 1998). For this purpose, low burden tools to track suicidal ideation and behavior such as the Columbia-Suicidal Severity Rating Scale can be used. Also, it is crucial to evaluate the risk (e.g., age, sex, stressors, comorbid conditions, hopelessness, impulsivity) and protective factors (e.g., religious belief, concern not to hurt family) that might influence the desire to attempt suicide. Both current severity of suicidality and the most severe point of suicidality in episode and lifetime should be assessed. The presence of guns in the home should be ascertained, and the clinician should recommend that the parents secure or remove them (Brent et al., 1993b).

Clinicians should also differentiate suicidal behavior from other types of self-harm behaviors, the goal of which is to relieve negative affect. This type of behavior most commonly involves repetitive self-cutting, with clear motivation to relieve anger, sadness, or loneliness rather than to end one's life.

Homicidal behavior follows a continuum similar to suicidality, from fleeting thoughts of homicide to ideas with a plan and intent. It is important to note that suicidal and homicidal ideation can occur in the same individual; fully one third of adolescent suicide victims in one study had homicidal ideation in the week before their suicide (Brent et al., 1993a). The clinician should conduct an assessment similar to that described for suicidal ideation with regard to what factors are influencing, either positively or negatively, the degree of likelihood the patient will carry out a homicidal act. As is the case for patients at risk for suicidal behavior, it is important to restrict access to any lethal agents, particularly guns (Brent et al., 1993b).

Recommendation 5. *The evaluation should assess for the presence of ongoing or past exposure to negative events, the environment in which depression is developing, support, and family psychiatric history [MS].*

As noted above, depression often results from an interaction between depressive diathesis and environmental stressors; thus the need for a careful evaluation of current and past stressors such as physical and sexual abuse, ongoing intra- and extra-familial conflicts, neglect, living in poor neighborhoods, and exposure to violence. If the abuse is current, ensuring the safety of the patient is the first priority of treatment. It is also important to assess the sequelae of the exposure to negative events such as PTSD.

Depression often occurs in a recurring pattern involving conflict with peers, parents, and other adult authority figures such as teachers. The relationship between conflict and depression is often bi-directional because depression can make a person more irritable, which then increases interpersonal tension, causing others to distance themselves from the depressed person, which then leads to an experience on the part of the patient of loneliness and lack of support. An assessment of the key relationships in the patient's social network is a critical component to the

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implementation of one type of psychotherapy for adolescent depression for which there is evidence of efficacy, namely interpersonal psychotherapy (IPT) (Mufson et al., 2004). Involvement in deviant peer groups may lead to antisocial behavior, generating more stressful life events and increasing the likelihood of depression (Fergusson et al., 2003).

Presence of family psychopathology should be evaluated to assist in both diagnosis and treatment, since parental psychopathology can affect the child's ability and willingness to participate in treatment, may be predictive of course (e.g., bipolar family history), and may have an influence on treatment response. The clinician should assess for discord, lack of attachment and support, and a controlling relationship (often referred to as "affectionless control"), as these can be related to risk for other psychiatric conditions such as substance abuse and conduct disorder that can complicate the presentation and course of depression (Nomura et al., 2002). For further information regarding assessment of the family, refer to the Practice Parameter for the Assessment of the Family (American Academy of Child and Adolescent Psychiatry, in press).

TREATMENT

Recommendation 6. *The treatment of depressive disorders should always include an acute and continuation phase. Some children may also require maintenance treatment [MS].*

The treatment of depression is usually divided into three phases: acute, continuation, and maintenance. The main goal of the acute phase is to achieve response and ultimately full symptomatic remission. (For definitions of outcome, see Table 1.) Continuation treatment is required for all depressed youth to consolidate the response during the acute phase and avoid relapses. Finally, maintenance treatment is used to avoid recurrences in some youth who have had a more severe, recurrent, and chronic disorder.

Treatment strategies for each one of these three treatment phases are discussed in detail below. In general, the choice of treatment at each of these phases should be governed by factors such as the subject's age and cognitive development, severity and subtype of depression, chronicity, comorbid conditions, family psychiatric history, family and social environment, family and patient treatment preference and expectations, cultural issues, and availability of expertise in pharmacotherapy and/or psychotherapy.

Table 1. Definitions of Outcome*

Response: No symptoms or a significant reduction in depressive symptoms for at least 2 weeks

Remission: A period of at least 2 weeks and less than 2 months with no or very few depressive symptoms

Recovery: Absence of significant symptoms of depression (e.g., no more than 1-2 symptoms) for ≥ 2 months

Relapse: A DSM episode of depression during the period of remission

Recurrence: The emergence of symptoms of depression during the period of recovery (a new episode)

*(e.g., Birmaher et al., 2000 [ut]; Emslie et al., 1998; Frank et al., 1991)

Recommendation 7. *Each phase of treatment should include psychoeducation, supportive management, and family and school involvement [MS].*

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Psychoeducation. Psychoeducation refers to education of family members and the patient about the causes, symptoms, course, and different treatments of depression and the risks associated with these treatments as well as no treatment at all. Education should make the treatment and decision-making process transparent and should enlist parent and patient as collaborators in their own care. Depression is presented as an illness, not a weakness, which is no one's fault but has genetic and environmental contributions. The difficulties the patient experiences in function are not manipulation, but the manifestations of an illness. The patient and family should be prepared for what is likely to be a recurrent and often chronic illness that may have a prolonged period of recovery. This enables the patient and family not to be overly disappointed if recovery is prolonged, and it prepares them for the necessity of continuation and adherence to treatment. Parents also need guidance about how to parent—when to be strict and when to be lax in light of their child's depression.

Written material and reliable web sites about depression and its treatment can help parents and their child to learn about depression and monitor the child's progress and, if the child is taking medications, potential emerging side effects.

There are no controlled trials of psychoeducation, but psychoeducation seems to improve adherence to treatment and reduce the symptoms of depression (Brent et al., 1993c [ut]; Renaud et al., 1998 [ut]). For families with depressed parents, psychoeducation with or without further interventions have also showed improvement in how families problem solve around parental illness and children's behavior and attitudes (Beardslee et al., 2003).

Supportive Management. In addition to psychoeducation, all subjects require supportive psychotherapeutic management, which may include active listening and reflection, restoration of hope, problem solving, coping skills, and strategies for maintaining participation in treatment.

Family Involvement. Even in the absence of formal family therapy, it is virtually impossible to successfully treat a child or adolescent patient without the close involvement of parents. Firstly, the clinician has to recognize that motivation for treatment comes often from the parents, and so therefore the treatment contract must involve them. Secondly, the parents may observe aspects of the child's functioning or symptoms that the child either is not aware of or does not wish to share, and this information is vital to the development of a realistic and effective treatment contract. Thirdly, the parents are able to monitor their child's progress and serve as a safety net.

As described in the section about psychotherapies (Recommendation 9), despite the scarce and weak empirical evidence, knowledge of risk factors suggests that interventions with families are an important part of clinical management. These interventions should take into account the family's cultural and religious background, and focus on strengthening the relationship between the identified patient and caregiver(s), provide parenting guidance (e.g., management of conflicts), reduce family dysfunction, and facilitate treatment referral for caregivers or siblings with psychiatric disorders and for marital conflict (Asarnow et al., 1993 [rct]; Birmaher et al., 2000 [ut]; Diamond et al., 2002 [ut]; Garber et al., 2002; Hammen et al., 2004; Nomura et al., 2002; Samford et al., 2006). During the acute phase of treatment, especially if both parent and child are depressed, it may be difficult to do much productive family work when multiple family members are depressed and irritable. Family work that is conducted after some symptomatic relief is still important because parent-child conflict is associated not only with prolongation of depressive episodes, but also with relapse and recurrence (Birmaher et al., 2000 [ut]).

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School Involvement. School personnel also need psychoeducation to help them understand the disease model of depression. Issues related to confidentiality also need to be discussed. The clinician, along with the family, should advocate for some accommodations (e.g., schedule, work load) to the patient's current difficulties until recovery has been achieved. However, if after recovery the child continues to have academic difficulties, then one should suspect that there is still some subsyndromal depression or that there are other comorbid conditions (e.g., developmental learning disorders, ADHD, anxiety, substance abuse) or environmental factors that might explain the child's persistent difficulties.

Students with a depressive disorder may qualify for the Emotional Disturbance disability categorization under IDEA and therefore be eligible to receive school-based services (e.g., counseling) and accommodations that enable them to continue to learn (see Practice Parameter for Psychiatric Consultation to Schools, American Academy of Child and Adolescent Psychiatry, 2005).

Recommendation 8. *Education, support, and case management appear to be sufficient treatment for the management of depressed children and adolescents with an uncomplicated or brief depression or with mild psychosocial impairment [CG].*

The current acute randomized controlled trials (RCTs) with psychotherapy or pharmacotherapy have reported that up to 60% of children and adolescents with MDD respond to placebo (Bridge et al., 2007 [rct]; Cheung et al., 2005 [rct]) and 15% to 30% respond to very brief treatment (Goodyer et al., 2007 [rct]; Harrington et al., 1998; Renaud et al., 1998 [ut]). In fact, supportive treatment, compared with either cognitive-behavioral therapy (CBT) or IPT, is equally efficacious for those with mild depression. However, when patients are more severely depressed and have significant melancholic symptoms, hopelessness, or suicidal ideation/behaviors, supportive treatment is inferior to either of these indicated therapies (Barbe et al., 2004a [rct]; Mufson et al., 1999 [rct]; Renaud et al., 1998 [ut]; Treatment of Adolescent Depression Study (TADS) Team, 2004 [rct]). Thus it is reasonable, in a patient with a mild or brief depression, mild psychosocial impairment, and the absence of clinically significant suicidality or psychosis, to begin treatment with education, support, and case management related to environmental stressors in the family and school. It is expected to observe response after 4-6 weeks of supportive therapy.

Recommendation 9. *For children and adolescents who do not respond to supportive psychotherapy or who have more complicated depressions, a trial with specific types of psychotherapy and/or antidepressants is indicated [CG].*

In children and adolescents with moderate to severe depression, chronic or recurrent depression, considerable psychosocial impairment, suicidality, agitation, and psychosis supportive psychotherapy and case management is usually not adequate. For these children and adolescents interventions with more specific types of psychotherapies or pharmacological treatments for depressive disorders are indicated.

As reviewed below, moderate depression may respond to CBT or IPT alone. More severe depressive episodes will generally require treatment with antidepressants. Treatment with antidepressants may be administered alone until the child is amenable to psychotherapy or if appropriate, it can be combined with psychotherapy from the beginning of treatment. Finally, depressed youth who do not respond to prior monotherapy treatment, either psychotherapy or antidepressants, require a combination of these two treatment modalities.

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In general, in addition to considering the severity and chronicity of the depressive symptoms, prior response to treatment, and other familial and environmental factors, the decision about which type of monotherapy to offer may be dictated by availability, patient and family preference. For example, children and/or their families may not wish to participate in psychotherapy or may object to taking any medications; specific types of psychotherapies such as CBT or IPT may not be available; children may not have responded previously to psychotherapy (e.g., 6 to 8 weeks of CBT or IPT); and/or children may be too agitated or psychotic, or have low motivation, poor concentration, or sleep disturbances, to participate in psychotherapy other than supportive treatment plus pharmacotherapy until they are feeling better; or they may have disorders (e.g., autism, mental retardation) for which CBT or IPT may not be appropriate.

The extant literature regarding the acute psychotherapy and pharmacological treatments and their side effects and clinical use for children and adolescents with depressive disorders is summarized below.

Psychotherapy: A recent rigorous meta-analysis of 35 RCTs for depressed youth showed that although some studies demonstrated large effects, overall the effects of psychotherapy for the acute treatment of depressed youth are modest (Weisz et al., 2006). Treatments were equally efficacious for children and adolescents, individual and group psychotherapy, samples identified as having depressive disorders vs. depressive symptomatology, efficacy vs. effectiveness studies, and whether the studies used cognitive techniques (CBT) or other approaches (e.g., IPT, behavior problem solving, relaxation, attachment-based therapy). Outcomes were significantly better when the informant was the youngster when compared with their parents, indicating the importance of interviewing both children and parents. There was no correlation between duration of treatment and response suggesting that brief treatments may be an efficacious and economical way to treat depressed youth. However, the few studies that included follow-up after the acute treatment, showed that the beneficial effects of psychotherapy appear durable for the initial months, but not for one year. Thus, more studies are needed to evaluate the effects of “boosters” and continuation therapy. Only six studies assessed suicidality as an outcome. On average, these studies showed a small reduction in suicidality emphasizing the need for more target techniques to address this worrisome symptom. Finally, the effects of the psychotherapy for depressed youth also improved anxiety, but not externalizing symptoms.

Other meta-analyses have also shown that CBT is effective for the treatment of youth with MDD (Compton et al., 2004; Harrington et al., 1998). CBT appears to be more efficacious even in the face of comorbidity, suicidal ideation, and hopelessness, but when there is a history of sexual abuse or when one of the parents is depressed, CBT does not appear to perform as well (Barbe et al., 2004b [rct]; Brent et al., 1998 [rct]; Lewinsohn et al., 1998; Melvin et al., 2006 [rct]; Rohde et al., 2004 [rct]).

In sharp contrast with most CBT studies (Weisz et al., 2006), a recent large RCT did not find differences between CBT and placebo for adolescents with MDD (Treatment of Adolescent Depression Study (TADS) Team, 2004; March et al., 2006b [rct]). Moreover, while the combination of CBT and fluoxetine showed a more rapid decline in depressive symptom reduction (Kratohvil et al., 2006), rates of clinical improvement and baseline-adjusted symptom ratings at endpoint were not different between combination treatment and medication alone. Also, the combined treatment was better than fluoxetine alone mainly for teens with mild to moderate depressions and for depression with high levels of cognitive distortion, but not for severe depressions (Curry et al., 2006 [rct]). The combination treatment did result in a greater rate of

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remission than in any of the other treatments, but the effects were modest (remission rate 37% in combined treatment) (Kennard, 2006 [rct]). It is unclear why CBT did not differ from placebo in this study with regard to acute treatment. Possible explanations include that the adolescents were not blind to medication assignment in the two CBT cells, treatment delivered a “low dose” of a large number of skills and techniques, whereas some of the more successful treatment studies with CBT used a flexible protocol that focused mainly on cognitive restructuring and behavior activation (Brent, 2006; Brent et al., 1997 [rct]; Weersing and Weisz, 2002 [ct]; Wood et al., 1996 [ct]). While the results of TADS may also suggest that CBT is difficult to disseminate, one quality improvement study suggested that CBT (sometimes delivered in combination with medication) can be delivered effectively in primary care settings to depressed adolescents and results in better outcomes than treatment as usual (Asarnow et al., 2005 [rct]).

It seems to be clinically intuitive and consistent with some studies of adult depressives that the combination of CBT plus medication would be superior to medication alone (Keller et al., 2000). In the TADS study, on the primary outcomes, the differences between combination and medication alone were either non-existent or modest, although all positive contrasts did favor the combination (March et al., 2006b; Vitiello et al., 2006). The rate of remission was higher in combination, but, similar to other studies, was disappointingly low (37% in combination vs. 23% in medication alone). Three other RCTs examining the effects of combined treatment vs. medication alone have also been disappointing. Goodyer and colleagues (2007 [rct]) found that in moderate to severely depressed adolescents who did not respond to a brief psychosocial treatment, the combination of CBT plus an SSRI (mainly fluoxetine) was no better than the SSRI alone in relief of depressive symptoms or improvement in overall outcome. Melvin and colleagues (2006 [rct]) were unable to demonstrate the superiority of combined sertraline and CBT over either treatment alone for adolescents with mild to moderate depression. After acute treatment, CBT was found to be superior to sertraline alone which may suggest an advantage to CBT, but might also be explained by the relatively low sertraline dose. Finally, Clarke and colleagues (2005 [rct]) compared the addition of CBT to SSRI management in primary care and found some modest improvement on quality of life but not on the primary outcome. Moreover, an unexpected result of the combined treatment was that those patients were more likely to discontinue their SSRIs.

IPT is emerging as another efficacious psychotherapy for adolescent depression where it has been shown to be superior to twice a month supportive clinical management, with differences most prominent in those who were moderately or severely depressed and in older teens (Mufson et al., 1999, 2004 [rct]). IPT has been shown to be at least as efficacious as CBT for adolescent depression (Rossello and Bernal, 1999 [rct]). IPT appears to be relatively easy to disseminate insofar as therapists in school-based health clinics with brief training and supervision were able to improve depression using IPT compared with treatment as usual (Mufson et al., 2004).

Most of the above-noted clinical trials in clinically referred populations were carried out with adolescents, rather than in younger children, but some randomized CBT trials for symptomatic volunteers have been successfully used in younger children (Reynolds and Coates, 1986 [rct]; Stark et al., 1987 [rct]; Weisz et al., 1997 [rct]), although in some, but not all studies, CBT was better than wait-list control, but not an alternative treatment. Most clinicians recommend the adaptation of cognitive, interpersonal, and psychodynamic techniques for younger children. In addition, because of the prominent role of family issues in early-onset depression and the greater dependency of the child on parents, some form of family intervention

is recommended. However, no RCTs have been conducted in clinically referred depressed children.

Because family interaction is related to the onset and course of adolescent depression (Asarnow et al., 1993 [rct]; Birmaher et al., 2000 [ut]; Nomura et al., 2002; Pilowsky et al., 2006), the improvement of family interactions is a logical treatment target for of adolescent depression. However, only one RCT has examined the impact of family therapy, and found that CBT was superior to a systemic behavioral family therapy in the short-term reduction of adolescent depression (Brent et al., 1997 [rct]). One form of family treatment termed “attachment therapy” has shown promise as an intervention, and was superior to wait-list control for relief of depressive symptomatology (Diamond et al., 2002 [ut]).

There is a substantial case based literature on the treatment of depression with individual psychodynamic psychotherapy, as well as substantial clinical experience indicating that individual psychodynamic psychotherapy can address a broad range of the comorbidities in depressed youth including: developmental, interpersonal, and intrapersonal factors important to social, peer, and educational functioning. In addition to very close monitoring of medications and symptomatology, psychodynamic interventions can be useful to help change patients’ depressive beliefs, world expectations, and challenge notions of futility and the meaning of life. Recent open trials and a RCT comparing psychodynamic psychotherapy plus parent support vs. family therapy for the treatment of youth with depressive disorders are promising, but further studies with state-of-the-art methodology are necessary (Crits-Christoph et al., 2002 [ut]; Muratori et al., 2003 [ut]; Trowell et al., 2007 [rct]).

It is important to emphasize that, while the above-noted research studies try to isolate specific diagnostic entities for clinical trials, most cases in clinical practice have multiple factors necessitating a multimodal treatment approach including a combination of options such as CBT, IPT interventions, individual psychodynamic psychotherapy, family therapy school/learning interventions, and/or community consultation.

Pharmacotherapy. One way to conceptualize the efficacy of treatment is to calculate the number to treat (NNT) to get one response that it is attributable to active treatment and not placebo. Across all the published and unpublished selective serotonin reuptake inhibitor (SSRI) RCTs, depressed patients treated with SSRIs have a relatively good response rate (40% to 70%), but the placebo response rate is also high (30% to 60%), resulting in an overall NNT of 10 (95% CI 7-14) (Bridge et al., 2007 [rct]; Cheung et al., 2005 [rct]; Wagner, 2005 [rct]). With the exception of the fluoxetine studies (e.g., Emslie et al., 1997 [rct]), due to the high placebo responses significant differences between SSRIs and placebo were only found in depressed adolescents (Bridge et al., 2007). The difference between the response to SSRIs and placebo is inversely related to the number of sites involved in the study (Bridge et al., 2007; Cheung et al., 2005). Fluoxetine is the only medication to be approved by the FDA for the treatment of child and adolescent depression, and it shows a larger difference between medication and placebo than do trials with other antidepressants. It is not clear if this is due to actual differences in the effect of the medication, if it is due to other related properties of the medication (long half-life may lessen the impact of poor adherence to treatment), or whether the studies involving fluoxetine were better designed and conducted or used more severely depressed patients.

Several studies showed small or no differences between the SSRI and placebo, in part because the rates of placebo response were high (e.g., Wagner et al., 2003 [rct]). Thus, it is possible that the depressive symptoms in youth may be highly responsive to supportive management, that these studies included subjects with mild depressions, or that other

methodological issues are responsible for the lack of difference between medication and placebo, such as including subjects with mild to moderate depressions and low medication dosages (for a review of the limitations of current pharmacological trials, see Cheung et al., 2005).

The rate of remission (e.g., Children's Depression Rating Scale-Revised score ≤ 28 - Poznanski and Mokros, 1995), a more stringent and yet more clinically relevant outcome, ranged between 30% and 40% (Emslie et al., 1997, 2002 [rct]; Goodyer et al., 2007 [rct]; Kennard et al., 2006 [rct]; Treatment of Adolescent Depression Study (TADS) Team, 2004 [rct]; Wagner et al., 2003 [rct]). Possible explanations for the low rate of remission are that optimal pharmacological treatment may involve a higher dose or longer duration of treatment, the lack of treatment of comorbid conditions might affect depressive symptoms, and/or some children and adolescents need to receive a combination of both pharmacological and psychosocial interventions.

Few trials have evaluated the effects of other classes of antidepressants for the treatment of depressed youth. So far these RCTs have showed no differences between venlafaxine or mirtazapine and placebo (Bridge et al., 2007; Cheung et al., 2005 [rct]; Emslie et al., submitted [rct]; Wagner, 2005 [rct]). Secondary analysis of the venlafaxine trials showed an age effect, with these medications being better than placebo for depressed adolescents, but not depressed children (Emslie et al., 2007 [rct]). However, children were treated with low venlafaxine dosages. One study showed better response in most measurements between nefazodone and placebo for adolescents with MDD, but a second study including depressed children and adolescents was negative (Cheung et al., 2005). The response rates for the above-noted antidepressants and for placebo are comparable with those of the SSRIs. Small open-label studies have suggested bupropion's effectiveness in treating adolescent MDD with and without ADHD (e.g., Daviss et al., 2001 [ct]), but there are no RCTs. Similarly, no controlled studies using duloxetine have been reported for the treatment of youth with MDD. Finally, RCTs as well as a meta-analysis have shown that tricyclic antidepressants are no more efficacious than placebo for the treatment of child and adolescent depression (Hazell et al., 2006) and should *not* be used as a first-line medication. Moreover, they are associated with more side effects than the SSRIs and can be fatal after an overdose.

Side Effects. Overall, the SSRIs and other novel antidepressants have been well tolerated by both children and adolescents, with few short-term side effects. The side effects of the SSRIs and other serotonergic and/or adrenergic reuptake inhibitors novel antidepressants appear to be similar, dose-dependent, and may subside with time (Cheung et al., 2005; Emslie et al., 2006; Findling et al., 2002; Leonard et al., 1997; Safer and Zito, 2006). The most common side effects include gastrointestinal symptoms, sleep changes (e.g., insomnia or somnolence, vivid dreams, nightmares, impaired sleep), restlessness, diaphoresis, headaches, akathisia, changes in appetite (increase or decrease), and sexual dysfunction. Approximately 3% to 8% of youth, particularly children, also may show increased impulsivity, agitation, irritability, silliness, and "behavioral activation" (Martin et al., 2004; Safer and Zito, 2006; Wilens et al., 1998). These symptoms should be differentiated from mania or hypomania that may appear in children and adolescents with, or predisposed to develop, bipolar disorder (Wilens et al., 1998). More rarely, the use of antidepressants has been associated with serotonin syndrome (Boyer and Shannon, 2005), increased predisposition for bleeding (e.g., easy bruising, epistaxis) (Lake et al., 2000; Weinrieb et al., 2005), and increased suicidality (see below for details). Because of the risk of bleeding, patients treated with SSRIs and other antidepressants who are going to have surgery should inform their physicians, as they may wish to discontinue treatment during the preoperative period. Venlafaxine and perhaps other noradrenergic reuptake inhibitors may elevate the blood pressure

and cause tachycardia. Mirtazapine, a serotonin and adrenergic receptor blocker, may increase appetite, weight, and somnolence. Trazodone, a serotonin 2A receptor blocker and weak serotonin reuptake inhibitor, and mirtazapine are mainly used as adjunctive and transient treatments for insomnia. Trazodone should be used with caution in males because it can induce priapism. Nefazodone, a serotonin 2A receptor blocker and weak serotonin reuptake inhibitor, was taken off the market amid rare reports of hepatic failure being associated with its use. While the rate of serious hepatic involvement is four times higher than in SSRIs, the absolute rate is still extremely low. The use of non-long-acting preparations of bupropion was associated with seizures, particularly if the dosages were above 400 mg/day or if the dosages were increased rapidly, and possible if subjects had bulimia.

The long-term side effects of all antidepressants have not been systematically evaluated in children and adolescents.

Suicidal Ideation/Attempts. The FDA in collaboration with Columbia University evaluated the effects on suicidality of nine antidepressants used in 24 acute RCTs (16 MDD, 4 OCD, 2 GAD, 1 SADS, and 1 ADHD) (Hammad et al., 2006; Posner et al., in press). The primary outcomes were *spontaneously* reported occurrences of suicidal ideation and behavior, “suicidal adverse events,” and using the suicidal items of depressive ratings scales, representing emergence or worsening of suicidality. The suicide adverse events analyses showed that for all disorders and antidepressants an *overall* risk ratio (RR) for suicidality of 1.95 (95% CI: 1.28-2.98). The *overall* RR for suicidal ideation was 1.74 (95% CI: 1.06-2.86) and for suicidal attempts 1.9 (1.0-2.86). When analyses were restricted to MDD trials for SSRIs, the overall RR was 1.66 (95% CI: 1.02-2.68). Among the antidepressants, only the venlafaxine (and more recently fluoxetine in the TADS study) (Hammad et al., 2006) showed a statistically significant association with suicidality. Interestingly, however, the majority of the venlafaxine suicidal events involved ideation and not behavior. In general, these results translate to 1-3 *spontaneously reported* suicide adverse events for every 100 youth treated with one of the antidepressants included in the FDA meta-analyses. There were very few suicidal attempts and *no completions*.

In contrast to the analyses of the suicide adverse events, evaluation of the incidence of suicidal ideation and attempts ascertained through rating scales in 17 studies did not show significant onset or worsening of suicidality (RRs approximately 0.90) (Hammad et al., 2006).

The above results need to be taken in the context of the limitations of the FDA study such as using the metric of relative risk (RR), which is limited to trials with at least one event, inability to generalize the results to populations not included in RCTs, short term data, not including all available RCTs, and multiple comparisons and the methodological limitations of spontaneously generated data (Hammad et al., 2006).

A more recent, thorough meta-analysis extended the FDA analyses by including more published and unpublished antidepressant RCTs (15 MDD, 6 OCD, and 6 anxiety) (Bridge et al., 2007). Using similar statistical methods to those used by the FDA study, this meta-analysis found comparable small, but significant increased *overall* RR for *spontaneously reported* suicidality for all disorders and antidepressants (Bridge et al., 2007). When using pooled random effects analyses of risk differences (RD) instead of RR, both the new analyses of the FDA data and the recent meta-analyses yielded a small, but significant *overall* RD (drug minus placebo) (FDA: 0.8, 95% CI: 0.1-1.5 vs. Bridge et al.: 0.7, 95% CI: 0.1 to 1.3). However, there were no longer significant differences for MDD (Bridge et al., 2007). Moreover, the *overall* number needed to harm (NNH) (number of subjects needed to treat to observe one adverse event that can be attributed to the active treatment) for MDD was 112 (Bridge et al., 2007). As stated above, the

overall NNT for the antidepressants in pediatric depression is 10. Thus, taking into account the limitation of any meta-analysis, nearly 11 times more depressed patients may respond favorably to antidepressants than might *spontaneously report* suicidality.

As stated by the FDA (Hammad et al., 2006), the implications and clinical significance regarding the above-noted findings is uncertain, since, with the increase in usage of SSRIs there has been a dramatic decline in adolescent suicide (Olfson et al., 2003). Moreover, pharmacoepidemiological studies, while correlative rather than causal, support a positive relationship between SSRI use and the reduction in the adolescent and young adult suicide rate (Gibbons et al., 2005, 2006; Olfson et al., 2003; Valuck et al., 2004). Also, two recent studies showed increased suicidal attempts only immediately before the treatment with SSRIs or psychotherapy (Simon and Savarino, 2007), and similarly to the TADS study, improved suicidal ideation after treatment was initiated.

How can we understand that there are increased rates of spontaneously reported SAEs on drug vs. placebo, but not any differences in suicidality on regularly assessed clinical measures? The clue may be in the term “spontaneous” and explanations of the association between drug and suicidality other than causality. One such alternative explanation is subjects on active drug have more side effects (headache, etc.) and as a result providers may have more opportunity/contact with subjects to hear about suicidal occurrences, as opposed to these events being “caused” by antidepressants. Another alternative explanation is improvement from the antidepressant resulting in a subject talking about suicidal thoughts for the first time.

It is possible that, in a subgroup of patients treated with SSRIs, particularly those already agitated and/or suicidal, that treatment causes a disinhibition that leads to worsening of ideation and/or a greater tendency to make suicidal threats. Because this event usually leads to removal of the subject from the study and a change in treatment, analyses that look at the slope of suicidal ideation will not find an effect. In addition, suicidality as measured on rating scales is highly correlated with the severity of depression that is more likely to decline on drug than on placebo.

In conclusion, it appears that *spontaneously* reported events are more common in SSRI treatment. Nevertheless, given the greater number of patients who benefit from SSRIs than who experience these SAEs, the lack of any completed suicides, and the decline in overall suicidality on rating scales, the risk benefit ratio for SSRI use in pediatric depression appears to be favorable, with careful monitoring.

Although the risk benefit ratio favors the use of SSRIs, further work is required (Apter et al., 2006; Bridge et al., 2007; Emslie et al., 2006; March et al., 2006a, b). Also, it remains to be clarified whether certain factors such as sex; subject’s history of suicidality; family history of suicidality; disorder (it appears that the effects are more obvious in depressed youth); severity of depressive symptoms at intake; dosages, half-life, and type of antidepressants; time during treatment; withdrawal side effects (due to non-compliance or medication short-half life); induction of agitation, activation, or hypomania; and/or susceptibility to side effects (e.g., slow metabolizers or variations in genetic polymorphisms) are related to increased risk for suicidality (Apter et al., 2006; Brent, 2004; Bridge et al., 2007; Hammad et al., 2006; Safer and Zito, 2006).

Clinical Use. Except for lower initial doses to avoid unwanted effects, the dosages of the antidepressants in children and adolescents are similar to those used for adult patients (Findling et al., 2002; Leonard et al., 1997). However, some studies have reported that the half-lives of sertraline, citalopram, paroxetine, and bupropion SR are much shorter than reported in adults (Axelson et al., 2002, Daviss et al., 2005; Findling et al., 2006). Therefore, psychiatrists should be alert for the possibility of withdrawal side effects when these medications are prescribed once

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a day. Also, to avoid side effects and improve adherence to treatment, it is recommended to start with a low dosage and increase it slowly until appropriate dosages have been achieved. Patients should be treated with adequate and tolerable doses for at least 4 weeks. Clinical response should be assessed at 4-week intervals, and if the child has tolerated the antidepressant, the dosage may be increased if a complete response has not been obtained (Heiligenstein et al., 2006; Hughes et al., 2007). At each step, adequate time should be allowed for clinical response, and frequent, early dose adjustments should be avoided. However, patients who are showing minimal or no response after 8 weeks of treatment are likely to need alternative treatments. Furthermore, by about 12 weeks of treatment, the goal should be remission of symptoms, and in youth who are not remitted by that time, alternative treatment options may be warranted. Other strategies for non-responders are described in Recommendation 15.

Given the small, but statistically significant, association between the antidepressants and suicidality, it is recommended that all patients receiving these medications be carefully monitored for suicidal thoughts and behavior, as well as other side effects thought to be possibly associated with increased suicidality, such as akathisia, irritability, withdrawal effects, sleep disruption, increased agitation, and induction of mania or a mixed state, particularly during the first weeks of treatment. The FDA recommends that depressed youth should be seen every week for the first 4 weeks and biweekly thereafter. However, it is not always possible to schedule weekly face-to-face appointments. In this case, evaluations should be briefly carried out by phone, but it is important to emphasize that there is no data to suggest that the monitoring schedule proposed by the FDA or telephone calls have any impact on the risk of suicide. Monitoring is important for all patients, but patients at increased risk for suicide (e.g., those with current or prior suicidality, impulsivity, substance abuse, history of sexual abuse, family history of suicide) should be scrutinized particularly closely. Those with a family history of bipolar disorder should be carefully monitored for onset of mania or mixed state. After the continuation or maintenance phases are over, or when the antidepressants need to be discontinued, all antidepressants, except for fluoxetine, should be discontinued slowly. Fluoxetine, because of its long half-life, is the exception and can be stopped at once. Abrupt discontinuation of antidepressants may induce withdrawal symptoms, some of which may mimic a relapse or recurrence of a depressive episode (e.g., tiredness, irritability, and severe somatic symptoms) (Zajecka et al., 1997). Sometimes withdrawal symptoms can be accompanied by worsening or emergent suicidal symptoms. The withdrawal symptoms can appear after as few as 6 to 8 weeks on the antidepressants and within 24 to 48 hours of discontinuation.

Careful attention to possible medication interactions is recommended because most antidepressants inhibit, to varying degrees, the metabolism of several medications that are metabolized by the diverse clusters of hepatic cytochrome P450 isoenzymes. In addition, interactions of antidepressants with other serotonergic and/or noradrenergic medications, in particular monoamine oxidase inhibitors (MAOIs), may induce the serotonergic syndrome, marked by agitation, confusion, and hyperthermia (Boyer and Shannon, 2005).

For further information regarding the management of medication, refer to the Practice Parameter for the Use of Psychotropic Medications in Children and Adolescents (American Academy of Child and Adolescent Psychiatry, submitted).

Recommendation 10. *To consolidate the response to the acute treatment and avoid relapses, treatment should always be continued for 6 to 12 months [MS].*

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In naturalistic studies of depressed patients treated with either CBT or fluoxetine, the rate of relapse is high (Birmaher et al., 2000 [ut]; Emslie et al., 1998 [ut]; Kroll et al., 1996 [ut]), with the highest risk for relapse within 4 months of symptomatic improvement. After a 12-weeks open treatment with fluoxetine, a 6 months randomized controlled fluoxetine discontinuation trial also showed that continued treatment with this SSRI was associated with a much lower rate of relapse (40%) compared to treatment with placebo (69%) (Emslie et al., 2004 [ut]). The high relapse rate on fluoxetine was accounted for, at least in part, by the poor adherence to treatment. Residual depressive symptoms after the open trial were associated with higher rates of relapse during the discontinuation trial indicating the need to seek for remission and not only response to treatment. Monthly continuation therapy with CBT also resulted in a much lower relapse rate than found in a historical control group that received acute treatment followed by no continuation treatment (Kroll et al., 1996 [ct]).

Until further research becomes available, continuation therapy for at least 6 to 12 months is recommended for *all* patients who have responded to the acute treatment. Often, discontinuation can be tried during the summer, so that a relapse would be less disruptive to school function. However, it is important to note that the treatment for depression can also be helping other disorders (e.g., anxiety) and discontinuation may accelerate the symptoms of these other conditions. During the continuation phase, patients typically are seen at least monthly, depending on clinical status, functioning, support systems, environmental stressors, motivation for treatment, and the presence of comorbid psychiatric or medical disorders. In this phase, psychotherapy consolidates the skills learned during the acute phase and helps patients cope with the psychosocial sequelae of the depression, but also addresses the antecedents, contextual factors, environmental stressors, and internal as well as external conflicts that may contribute to a relapse. Moreover, if the patient is taking antidepressants, follow-up sessions should continue to foster medication adherence, optimize the dose, and evaluate for the presence of side effects.

Recommendation 11. To avoid recurrences, some depressed children and adolescents should be maintained in treatment for longer periods of time [CG].

As discussed in the Clinical Course section above, MDD is a recurrent illness. Thus, once the child has been asymptomatic for approximately 6 to 12 months, the clinician must decide whether maintenance therapy is indicated, which therapy, and for how long. The main goal of the maintenance phase is to foster healthy growth and development and prevent recurrences. This phase may extend one year or longer and is typically conducted with visits at a frequency of monthly to quarterly, depending on the patient's clinical status, functioning, support systems, environmental stressors, motivation for treatment, existence of comorbid psychiatric/medical disorders, and availability and skill of the clinician.

There are no treatment studies of youth to guide clinicians as to which patients require a longer period of continuation and maintenance treatment. In adults, those with at least three episodes of recurrent depression require longer periods of treatment (e.g., at least 3 to 5 years) (Kupfer et al., 1992). One general rule of thumb is that the longer it takes for a patient to recover or the higher the number of recurrences, the longer the period of maintenance should be. Specifically, those patients with at least two episodes of depression, or one very severe or chronic episodes of depression, should have maintenance treatment for longer than 1 year. Those with double depression (depression with comorbid dysthymic disorder) who have been depressed "as long as they can remember" may need treatment indefinitely, with an explanation to families that there is no hard and fast rule about this because of a lack of studies in this population.

Moreover, other factors that are related to risk for a prolonged episode or recurrence should also make the clinician consider maintenance treatments. These factors include patient factors of comorbidity, psychosis, suicidality, number of prior episodes, environmental factors such as family disruption due to conditions external to the child (e.g., divorce, illness, job loss, or homelessness), family psychopathology, and lack of community support.

Finally, it is important to treat the youth not only for a certain length of time, but to treat to achieve no or minimal residual symptoms, because children and adolescents who have not recovered fully and still have subsyndromal depression are more vulnerable to have a recurrence (Brent et al., 2001; Lewinsohn et al., 1994; Pine et al., 1998).

Recommendation 12. *Depressed patients with psychosis, seasonal depression, and bipolar disorder may require specific somatic treatments [CG].*

Psychotic Depression. Although there are very few studies in youth (Geller et al., 1985 [ct]), it appears that the combination of antidepressants with antipsychotics may be helpful for patients with psychotic depression. However, vague or mild psychotic symptoms in a depressed child may respond to antidepressants alone. Currently, clinical consensus recommends the atypical antipsychotic medications combined with SSRIs as the treatment of choice for depressed psychotic youth. It is important to be aware of the short- and long-term side effects associated with the use of atypical antipsychotics and possible interactions with the antidepressants. How long these medications should be continued after the psychotic symptoms have improved is a question, but in general the recommendation is to slowly taper off these medications, with the eventual goal of keeping the child on monotherapy with an antidepressant.

In adults, electroconvulsive therapy (ECT) is particularly effective for this subtype of depression. Non-controlled reports suggest that this treatment also may be useful for depressed psychotic adolescents (American Academy of Child and Adolescent Psychiatry, 2004).

Seasonal Affective Disorder (SAD). A small RCT showed that bright light therapy is efficacious for youth with SAD (Swedo et al., 1997 [rct]). It appears that patients may respond better during the morning hours, but morning hours may be difficult on school days and for youth who refuse to wake up early in the morning. Bright light therapy has been associated with some side effects, such as headaches and eye strain. Some authors have recommended an ophthalmological evaluation before initiating light therapy, but this practice has been frequently questioned unless patients have a history of eye illness. Treatment with light may induce episodes of hypomania or mania in vulnerable patients.

Bipolar Disorder. The symptoms of unipolar and bipolar depression are similar; therefore, early in the course of illness it is difficult to determine whether a patient needs only an antidepressant or would benefit from concomitant use of mood stabilizers. As noted above under Differential Diagnosis, some specific symptoms may warn the clinician about the possibility that the child is at risk for the development of a manic or hypomanic episode. Sometimes the child experiences mild recurrent hypomanic symptoms that often are overlooked. If indicators of risk for bipolar disorder are present (see differential diagnosis section), the clinician should discuss with the patient and family the pros and cons of initiating a prophylactic mood-stabilizing agent. Patients with a psychotic depression may be at greater risk for developing bipolar disorder (Geller et al., 1994; Strober and Carlson, 1982).

For mild to moderate unipolar depression in patients with a bipolar diathesis, it may be best to start with psychotherapy because the risk for manic conversion with the use of antidepressants is substantial (Martin et al., 2004). Also, if there is a strong suspicion that the

child has bipolar disorder, a mood stabilizer, such as lithium carbonate, valproate, or lamotrigine may be indicated, particularly if the patient presents with a depressive disorder marked by mood lability (for further discussion of the treatment of bipolar depression see Kowatch et al., 2005).

Recommendation 13. *Treatment should include the management of comorbid conditions [MS].*

It is of prime importance to treat the comorbid conditions that frequently accompany MDD because these conditions may influence the initiation, maintenance, and recurrence of depression; reduce the probability of a complete treatment response; and increase the risk for suicide, other functional impairment in school, and problems with interpersonal relationships associated with MDD (Birmaher et al., 1996, 2002; Curry et al., 2006; Daviss et al., 2001; Fombonne et al., 2001a, b; Hamilton and Bridge, 1999; Hughes et al., 1990, 2007). Likewise, depressive symptoms also may negatively influence the treatment of comorbid disorders. Although there are very few studies (e.g., Daviss et al., 2001 [ct]) to guide the clinician in how to sequence the treatment of depression and other comorbid disorders, we suggest that the clinician make a determination of which condition is causing the greatest distress and functional impairment, and begin treatment with that disorder. Also, if recovery from depression is unlikely until a comorbid condition is addressed (e.g., severe malnutrition in anorexia, or severe substance dependence, such as cocaine or intravenous drug dependence), then the comorbid condition must be addressed first.

Several psychosocial and pharmacological treatments used to treat depression also may be useful for the treatment of comorbid conditions, particularly anxiety disorders (Bridge et al., 2007). For depressed youth with comorbid substance abuse, it is important to treat both disorders because depressive symptomatology increases the risk of persistent substance abuse and vice versa; abuse worsens the prognosis of the depression and depression comorbid with substance abuse is a potent set of risk factors for completed suicide (American Academy of Child and Adolescent Psychiatry, 2001; Gould et al., 1998). One RCT in adults as well as an open trial in adolescents with depression comorbid with alcohol abuse found that fluoxetine was superior to placebo in reduction of both depressive symptoms and alcohol use (Cornelius et al., 2001). However, further studies regarding the use of psychosocial and pharmacological treatments for depressed youth with comorbid substance abuse are necessary.

There are few published studies examining the efficacy of psychopharmacological or psychotherapeutic treatments for depression in medically ill children and adolescents. Studies are necessary, however, because diagnosable depression may occur frequently in children and adolescents with medical diseases, and medical illness and its treatment may change the natural course of depression (Lewinsohn et al., 1996). Furthermore, the pharmacokinetics, pharmacodynamics, and side effects of the antidepressants may be affected by both the medical illnesses and medications used to treat these illnesses. Psychotherapy is useful not only for treating depression in these children, but for helping these patients and their families cope with the medical illness (Kovacs et al., 1996; Szigethy et al., 2004 [ut]).

Recommendation 14. *During all treatment phases, clinicians should arrange frequent follow-up contacts that allow sufficient time to monitor the subject's clinical status, environmental conditions, and, if appropriate, medication side effects [MS].*

Symptoms of depression, suicidal or homicidal ideation, mania or hypomania; development of new comorbid disorders; psychosocial and academic functioning; and

environmental conditions should be reviewed frequently by interviewing the child, parents, and, if appropriate, other informants (e.g., teachers).

Traditionally, treatment response has been determined by the absence of MDD criteria (e.g., no more than one DSM symptom) (Table 1) or, more frequently, by a significant reduction (e.g., $\geq 50\%$) in symptom severity. However, using the latter criterion, patients deemed “responders” may still have considerable residual symptoms. Therefore, an absolute final score on the Beck Depression Inventory ≤ 9 (Beck and Steer, 1987) or Children’s Depression Rating Scale (Poznanski and Mokros, 1995) ≤ 28 together with persistent improvement in patient’s functioning for at least 2 weeks or longer may better reflect a satisfactory response. Overall improvement has also been measured using a score of 1 or 2 (very much or much improvement) in the Clinical Global Impression Scale, Improvement subscale (Guy, 1976).

Since the goal is to restore function and not just reduce symptoms, a lack of progress in functional status is an important clue that the depression is incompletely treated or that impaired functional status is due to a comorbid psychiatric or medical disorder or environmental factors. The functional improvement can be measured using several rating scales such as a score ≥ 70 on the Global Assessment of Functioning (DSM-IV) (American Psychiatric Association, 2000b) or the Children’s Global Assessment Scale (Shaffer et al., 1983).

If a patient is being treated with medications, it is important to evaluate the adherence to medication treatment, presence of side effects, and youth and parent beliefs about the medication benefits and its side effects that may contribute to poor adherence or premature discontinuation of treatment. History of suicidality, homicidal ideation, and somatic symptoms should be evaluated before starting the pharmacological treatment, and during treatment they should be differentiated from symptoms of mood and other psychiatric or medical conditions.

Recommendation 15. *During all treatment phases, for a child or adolescent who is not responding to appropriate pharmacological and/or psychotherapeutic treatments, consider factors associated with poor response [MS].*

When managing patients who are not responding to treatment, the following reasons for treatment failure should be considered: misdiagnosis, unrecognized or untreated comorbid psychiatric or medical disorders (e.g., anxiety, dysthymic, eating, substance use, personality, hypothyroidism), undetected bipolar disorder, inappropriate pharmacotherapy or psychotherapy, inadequate length of treatment or dosage, lack of adherence to treatment, medication side effects, exposure to chronic or severe life events (such as sexual abuse or ongoing family conflicts), personal identity issues (such as concern about same-sex attraction), cultural/ethnic factors, and an inadequate fit with, or skill level of, psychotherapist.

Preliminary results of the NIMH multicenter study, the Treatment of Resistant Depression in Adolescents (TORDIA), showed that in depressed adolescents who have failed to respond to an adequate trial with a SSRI, a switch to another antidepressant plus CBT resulted in a better response than a switch to another antidepressant without additional psychotherapy (Brent et al., 2007 [rct]).

Open small studies using lithium and MAOI augmentation have shown contradictory results (Ryan et al., 1988a [ut], b; Strober et al., 1992 [ut]). Adult studies suggest that augmentation with T3 is efficacious and well-tolerated, but such studies have not been conducted in younger populations (Cooper-Kazaz et al., 2007 [rct]). Sallee et al. (1997 [rct]) found that intravenous clomipramine was superior to placebo for adolescents with treatment-resistant depression. Finally, some reports have suggested that adolescents with treatment-resistant

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depression may respond to ECT (American Academy of Child and Adolescent Psychiatry, 2004), but further research in this area is needed.

Several psychopharmacological strategies have been recommended for adults with resistant depression that may be applicable to youth: optimization (extending the initial medication trial and/or adjusting the dose; addition of CBT or IPT), switching to another agent in the same or a different class of medications, augmentation, or combination (e.g., lithium, T₃) (Hughes et al., 2007). Optimization and augmentation strategies are usually used when patients have shown a partial response to the current regimen and switching is usually used when patients have not responded or cannot tolerate the medications, but no studies have validated these practices in children. In a landmark study of treatment resistant depressed adults, after unsuccessful treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant (Rush et al., 2006 [rct], Trivedi et al., 2006 [rct]). In addition, a combination of medication plus CBT has been shown to be superior to medication management alone for the treatment of partial responders and for the prevention for relapse (Fava et al., 2004 [ut]; Keller et al., 2000 [rct]). A switch from one modality of treatment to another (medication to psychotherapy or vice versa) has been found to be helpful for some chronically depressed adults who have failed one monotherapy (Schatzberg et al., 2005 [ut]). Depressed adolescents and adults with a history of sexual abuse may show a lower likelihood for response to standard treatments and may need a psychotherapeutic approach that deals with interpersonal issues and the after-effects of the trauma (Barbe et al., 2004b [rct]). Also, depressed adolescents randomized to CBT and fluoxetine showed the highest response when compared to monotherapy with CBT, fluoxetine, or placebo, although post hoc comparison between combination and fluoxetine alone was not significantly different, and, for more severe depressions, the combination was not superior to fluoxetine alone (Curry et al., 2006 [rct]). Finally, the use of somatic therapies that have not been well studied in children such as transcranial magnetic stimulation or more intensive somatic therapies for depressed teens such as ECT should be considered.

Each of the above-noted strategies requires implementation in a systematic fashion, education of the patient and family, and support and education to reduce the potential for the patient to become hopeless.

PREVENTION

Recommendation 16. *Children with risk factors associated with development of depressive disorders should have access to early services interventions [CG].*

Several RCTs using psychoeducation, cognitive, coping and social skills, and family therapy have targeted children and adolescents deemed to be at risk for depression, by virtue of having subsyndromal depressive symptoms, a previous episode of depression, and/or a family history of depression (Beardslee et al., 2003; Clarke et al., 1995, 2001, 2002 [rct]; Jaycox et al., 1994 [rct]; Weisz et al., 1997 [rct]).

A recent meta-analysis of the existent literature regarding the prevention of depressive symptoms in youth showed that programs that included populations at risk were more effective than those targeting general populations (universal studies), particularly for females and older subjects. However, the effects of these treatments were small to modest, both immediately post-intervention and at an average follow-up of 6 months (Horowitz and Garber, 2006).

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Successful treatment of mothers with depression was associated with significant less new psychiatric diagnoses and higher remission rates of existing disorders in their children (Weissman et al., 2006a). Maternal depression has also been associated with less response to CBT for depression (Brent et al., 1998). These findings support the importance of early identification and vigorous treatment for depressed mothers in primary care or psychiatric clinics.

Early-onset dysthymia is associated with an increased risk of MDD (Kovacs et al., 1994), indicating the need for early treatment. Also, there is evidence that anxiety disorder is a precursor of depression (Kovacs et al., 1989; Pine et al., 1998; Weissman et al., 2005), and treatment of this disorder may reduce the onset and recurrences of depression (Dadds et al., 1999; Hayward et al., 2000). Since SSRIs appear to have a much greater efficacy for anxiety than for depression, vigorous detection and treatment of anxiety disorders may reduce the risk for subsequent depression.

The strategies for the prevention of onset or of recurrence of depression should include the amelioration of risk factors associated with this disorder. In addition, prevention may also include lifestyle modifications—regular and adequate sleep, exercise, a coping plan for stress (e.g., meditation, yoga, exercise, or social activities), pursuit of enjoyable and meaningful activities, and avoidance of situations that are predictably stressful and nonproductive. For those with recurrent depression, a proactive plan to avoid stressors and a plan for coping with anticipated difficulties may be helpful in relapse and recurrence prevention.

Finally, it is important to educate caregivers, school personnel, pediatricians, and youth about the warning signs of depressive disorder and appropriate sources of assessment and treatment.

PARAMETER LIMITATIONS

AACAP practice parameters are developed to assist clinicians in psychiatric decision-making. These parameters are not intended to define the standard of care; nor should they be deemed inclusive of all proper methods of care or exclusive of other methods of care directed at obtaining the desired results. The ultimate judgment regarding the care of a particular patient must be made by the clinician in light of all the circumstances presented by the patient and his/her family, the diagnostic and treatment options available, and available resources.

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