29 - 31.12a Depressive Disorders and Suicide in Ch

31.12a Depressive Disorders and Suicide in Children and Adolescents

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ideation, and suicide remains the most serious risk of major depression. Nevertheless, many depressed youth do not ever have suicidal ideation, and many children and adolescents who engage in suicidal behavior do not have a depressive disorder. There is epidemiological evidence to suggest that depressed youth with recurrent active suicidal ideation, including a plan, and who have made prior attempts, are at higher risk to complete suicide, compared to youth who express only passive suicidal ideation. Mood disorders in children and adolescents have been studied increasingly over the last two decades, culminating in large sample multisite randomized controlled trials such as the Treatment of Adolescent Depression (TADS) study, which provides evidence

of the efficacy of both cognitive-behavioral therapy as well as selective serotonin reuptake inhibitors (SSRIs). Furthermore, when the preceding modalities are combined, the greatest efficacy is achieved. Increased recognition of depressive disorders in preschool populations has sparked clinicians and researchers to develop psychosocial interventions such as the Parent-Child Interaction Therapy Emotion Development (PCITED), which target treatment specifically for this age group. The expression of disturbed and depressed mood appears to vary with developmental stage. Very young children with major depression are often observed to be sad, listless, or apathetic, even though they may not articulate these feelings verbally. Perhaps surprisingly, mood-congruent auditory hallucinations are not infrequently observed in young children with major depression. Somatic complaints such as headaches and stomachaches, withdrawn and sad appearance, and poor self-esteem are more universal symptoms. Patients in late adolescence with more severe forms of depression often display pervasive anhedonia, severe psychomotor retardation, delusions, and a sense of hopelessness. Symptoms that appear with the same frequency, regardless of age and developmental status, include suicidal ideation, depressed or irritable mood, insomnia, and diminished ability to concentrate. Developmental issues, however, influence the expression of depressive symptoms. For example, unhappy young children who exhibit recurrent suicidal ideation are rarely able to propose a realistic suicide plan or to carry out such a plan. Children’s moods are especially vulnerable to the influences of severe social stressors, such as chronic family discord, abuse and neglect, and academic failure. Many young children with major depressive disorder have histories of abuse, neglect, and families with significant psychosocial burdens such as parental mental illness, substance abuse, or poverty. Children who develop depressive disorders in the midst of acute toxic family stressors may have remission of depressive symptoms when the stressors diminish or when a more nurturing family environment is introduced. Depressive disorders are generally episodic, albeit typically lasting close to a year; however, their onset may be insidious and remain unidentified until significant impairment in peer relationships, deterioration in academic function, or withdrawal from activities emerges. Attentiondeficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder are not infrequently comorbid with a major depressive episode. In some cases, conduct disturbances or disorders occur in the context of a major depressive episode and resolve with the resolution of the depressive episode. Clinicians must clarify the chronology of the symptoms to determine whether a given behavior (e.g., poor concentration, defiance, or temper tantrums) was present before the depressive episode and is unrelated to it or whether the behavior is occurring for the first time and is related to the depressive episode. EPIDEMIOLOGY Depressive disorders increase in frequency with increasing age in the general population. Mood disorders among preschool-age children are estimated to occur in

about 0.3 percent of community samples, and 0.9 percent in clinic settings. The prevalence of major depression in school age children is 2 to 3 percent. Depression in referred samples of school-age children is found to be the same frequency in boys as in girls, with some surveys indicating a slightly increased rate among boys. In adolescents, prevalence rate of major depression is from 4 to 8 percent and two to three times more likely in females than males. By age 18 years, the cumulative incidence of major depression is 20 percent. Children with a family history of major depression in a firstdegree relative are about three times more likely to develop the disorder than in those without family histories of affective disorders. The prevalence of persistent depressive disorder in children ranges from 0.6 to 4.6 percent and in adolescence increases to 1.6 to 8 percent. Children and adolescents with persistent depressive disorder have a high likelihood of developing major depressive disorder at some point after 1 year of the persistent depressive disorder. The rate of developing a major depression on top of persistent depressive disorder (double depression) within a 6-month period of persistent depressive disorder is estimated to be about 9.9 percent. Among psychiatrically hospitalized children and adolescents, the rates of major depressive disorder have been estimated to be close to 20 percent for children and 40 percent for adolescents. ETIOLOGY Considerable evidence indicates that major depression in youth is the same fundamental disorder experienced by adults, and that its neurobiology is likely to be an interaction of genetic vulnerability and environmental stressors. Genetic Studies Converging evidence suggests that an interaction between genetic susceptibility and environmental stressors contributes to an emerging major depression and is associated with brain volume, especially in the hippocampal region. The serotonin transporter gene and, in particular, the serotonin transporter promoter polymorphism (5-HTTLPR) have become a focus of investigation. Patients with the short S-allele of the serotonin polymorphism who also experienced a significant environmental adverse event such as neglect, developed smaller hippocampal volumes compared to patients with only one of the above risk factors. The S-allele of the polymorphism leads to decreased serotonin (5HT) reuptake and thus potentially to decreased uptake of serotonin into the brain. A large longitudinal study in New Zealand found that the S-allele of the serotonin transporter gene was associated with early environmental stress and subsequent depression. This study demonstrated a relationship between early environmental stress and subsequent depression in children with one or two short alleles, but not in children with two long alleles. Because the short alleles are less efficient in transcription, this finding suggests that the availability of the transporter gene may provide a marker for vulnerability to depression. The findings that the combination of a decreased volume in the hippocampus is associated with the S-allele of the serotonin transporter gene

polymorphism and early adverse events in depression, may represent a mechanism by which the risk of major depression is mediated by both genetics and environmental stressors. Familiality Twin studies have demonstrated that major depression is approximately 40 to 50 percent heritable. There is an increased risk of depression in the children of parents with the disorder, and this risk is further increased for the child when the parents developed depressive disorders at an early age. Studies suggest age-related differences in the heritability of major depression such that in younger children, environmental influences appear to be more dominant and in first episodes in adolescence, heritability may play a larger role. Family studies suggest that for children with a parent with a history of major depressive disorder, the risk of developing an episode of major depressive disorder is doubled, whereas with two depressed parents, the risk of an episode of major depressive disorder quadruples in the offspring before age 18 years. Similarly, children with the largest number of severe episodes starting at younger ages exhibit the densest family histories

of major depressive disorder. Neurobiology Neuroendocrine studies have examined the hypothalamic-pituitary-adrenal axis, the hypothalamic growth hormone, the hypothalamic-pituitary-thyroid, and the hypothalamic-pituitary-gonadal axes, seeking to demonstrate consistent markers in depressed youth. These studies have yielded inconsistent results. For example, depressed prepubertal children secrete significantly more growth hormone during sleep than nondepressed children or youth with other psychiatric disorders. In addition, depressed children secrete significantly less growth hormone in response to insulin-induced hypoglycemia than do nondepressed patients. Both findings appear to persist for months after partial or full remission. Thyroid hormone studies have found lower free total thyroxine (FT4) levels in depressed adolescents than in a matched control group. These values were associated with normal thyroid-stimulating hormone (TSH). This finding suggests that, although values of thyroid function remain in the normative range, FT4 levels have shifted downward. These downward shifts in thyroid hormone possibly contribute to the clinical manifestations of depression. Sleep studies are also inconclusive in depressed children and adolescents. Polysomnography in depressed children have only occasionally shown characteristic sleep markers of adults with major depressive disorder: reduced rapid eye movement (REM) latency and an increased number of REM periods. Magnetic Resonance Imaging Neuroimaging studies of depressed youth demonstrate smaller frontal white matter

volumes, larger frontal gray matter volumes, and larger lateral ventricle volumes. Depressed youth have been found to have a blunted amygdala response to fearful faces compared to non-depressed children and depressed children have been found to have smaller amygdale volumes compared to healthy controls. Because twin studies and adoption studies have demonstrated that depression appears to be only 40 to 50 percent heritable, with environmental contributions more predominant in younger children, family and environmental contributions must be examined. Adverse events during childhood such as maltreatment, abuse or neglect, parental death, parental psychiatric illness, substance abuse, parent–child conflict, and lack of family cohesion are all risk factors for childhood depression. Data from twin and genetic studies support the conclusion that the interaction of genetic and environmental factors plays a critical role in depressive disorders, since correlation of adverse life events and depression is stronger in children and adolescents with known genetic susceptibility. Once a child or adolescent has experienced one major depressive episode, the psychosocial “scars” increase his or her vulnerability for a subsequent episode. The psychosocial impairments in depressed children remain far after recovery from the episode. Among depressed preschoolers, the sooner that adverse life events promoting the depression are identified, the more rapidly interventions may be administered to treat the depression. DIAGNOSIS AND CLINICAL FEATURES Major Depressive Disorder Major depressive disorder in children is diagnosed most easily when it is acute and occurs in a child without previous psychiatric symptoms. Often, however, the onset is insidious, and the disorder occurs in a child who has had several years of difficulties with hyperactivity, separation anxiety disorder, or intermittent depressive symptoms. According to the DSM-5, diagnostic criteria for a major depressive episode consist of at least five symptoms, for a period of 2 weeks, including either (1) depressed or irritable mood, or (2) a loss of interest or pleasure. Additional symptoms may include failure to make expected weight gains, daily insomnia or hypersomnia, psychomotor agitation or retardation, daily fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death. These symptoms must produce social or academic impairment. To meet the diagnostic criteria for major depressive disorder, the symptoms cannot be

due to the direct effects of a substance (e.g., alcohol) or a general medical condition. In contrast to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), in which a diagnosis of major depressive disorder was not made within 2 months of the loss of a loved one, except when marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation was present, in DSM-5, a diagnosis of major depressive disorder can be made at any time following a loss, even without the preceding

symptoms. This change reflects the understanding that grief typically lasts 1 to 2 years, rather than 2 months, and that major depressive disorder may occur in the presence of grief at any time after a loss. A major depressive episode in a prepubertal child is likely to be manifest by somatic complaints, psychomotor agitation, and mood-congruent hallucinations. Anhedonia is also frequent, but anhedonia, as well as hopelessness, psychomotor retardation, and delusions, are more common in adolescent and adult major depressive episodes than in those of young children. Adults have more problems than depressed children and adolescents with sleep and appetite. In adolescence, negativistic or frankly antisocial behavior and the use of alcohol or illicit substances can occur and may justify the additional diagnoses of oppositional defiant disorder, conduct disorder, and substance abuse or dependence. Feelings of restlessness, irritability, aggression, reluctance to cooperate in family ventures, withdrawal from social activities, and isolation from peers often occur in adolescents. School difficulties are likely. Depressed adolescents may become less attentive to personal appearance and show increased sensitivity to rejection by peers, and in romantic relationships. Children can be reliable reporters about their emotions, relationships, and difficulties in psychosocial functions. They may, however, refer to depressive feelings in terms of anger, or feeling “mad” rather than sad. Clinicians should assess the duration and periodicity of the depressive mood to differentiate relatively universal, short-lived, and sometimes frequent periods of sadness, usually after a frustrating event, from a true, persistent depressive mood. The younger the child, the more imprecise his or her time estimates are likely to be. Mood disorders tend to be chronic if they begin early. Childhood onset may be the most severe form of mood disorder and tends to appear in families with a high incidence of mood disorders and alcohol abuse. The children are likely to have such secondary complications as conduct disorder, alcohol and other substance abuse, and antisocial behavior. Functional impairment associated with a depressive disorder in childhood extends to practically all areas of a child’s psychosocial world; school performance and behavior, peer relationships, and family relationships all suffer. Only highly intelligent and academically oriented children with no more than a moderate depression can compensate for their difficulties in learning by substantially increasing their time and effort. Otherwise, school performance is invariably affected by a combination of difficulty concentrating, slowed thinking, lack of interest and motivation, fatigue, sleepiness, depressive ruminations, and preoccupations. Depression in a child may be misdiagnosed as a learning disorder. Learning problems secondary to depression, even when long-standing, are corrected rapidly after a child’s recovery from the depressive episode. Children and adolescents with severe forms of major depressive disorder may have hallucinations and/or delusions. Usually, these psychotic symptoms are thematically consistent with the depressed mood, occur with the depressive episode (usually at its worst), and do not include certain types of hallucinations (such as conversing voices and a commenting voice, which are specific to schizophrenia). Depressive hallucinations

usually consist of a single voice speaking to the person from outside his or her head, with derogatory or suicidal content. Depressive delusions center on themes of guilt, physical disease, death, nihilism, deserved punishment, personal inadequacy, and (sometimes) persecution. These delusions are rare in prepuberty, probably because of cognitive immaturity, but are present in about half of psychotically depressed adolescents. Adolescent onset of a mood disorder can be complicated by use of alcohol or drugs. One study found that up to 17 percent of adolescents with depressive disorder received an initial evaluation due to substance abuse. Persistent Depressive Disorder (Dysthymia) Persistent depressive disorder, in DSM-5, represents a consolidation of chronic major depressive disorder and what DSM-IV-TR termed dysthymic disorder. In children and adolescents it consists of a depressed or irritable mood for most of the day, for more days than not, over a period of at least 1 year. DSM-5 notes that in children and adolescents, irritable mood can replace the depressed mood criterion for adults and that the duration criterion is not 2 years but 1 year for children and adolescents. According to the DSM-5 diagnostic criteria, two or more of the following symptoms must accompany the depressed or irritable mood: low self-esteem, hopelessness, poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, or poor concentration or difficulty making decisions. During the year of the disturbance, these symptoms do not resolve for more than 2 months at a time. In addition, the diagnostic criteria for dysthymic disorder specify that during the first year, no major depressive episode emerges. To meet the DSM-5 diagnostic criteria for persistent depressive disorder, a child must not have a history of a manic or hypomanic episode. Persistent depressive disorder is also not diagnosed if the symptoms occur exclusively during a chronic psychotic disorder or if they are the direct effects of a substance or a general medical condition. DSM-5 provides specifiers for early onset (before 21 years of age) or late onset (after 21 years of age). A child or adolescent with persistent depressive disorder may have had a major depressive episode before developing persistent depressive disorder; however, it is much more common for a child with persistent depressive disorder for more than 1 year to develop a concurrent episode of major depressive disorder. In this case, both depressive diagnoses apply (double depression). Persistent depressive disorder in youth is known to have an average age of onset that is several years earlier than the typical onset of major depressive disorder. Occasionally, youth fulfill the criteria for persistent depressive disorder, except that their episode does not last for a whole year, or they experience remission from symptoms for more than a 2-month period. These mood presentations in youth may predict additional mood disorder episodes in the future. Current knowledge suggests that the longer, more recurrent, and less directly related to social stress these episodes are, the greater the likelihood of future severe mood disorder. When minor depressive episodes follow a significant stressful life event by less than 3 months, it may

be classified as an adjustment disorder. Cyclothymic Disorder Cyclothymia is a chronic and fluctuating mood disturbance of hypomanic symptoms and periods of depressive symptoms that do not meet diagnostic criteria for major depressive disorder. The difference in the DSM-5 diagnostic criteria for youth with cyclothymic disorder compared to adults is that a period of 1 year, rather than 2 years, of numerous mood swings is applied. Bipolar II disorder is distinguished from cyclothymia by a history of episodes of major depressive disorder. When an episode of major depressive disorder occurs after a diagnosis of cyclothymia has been present for at least 2 years, a concurrent diagnosis of Bipolar II disorder is made. Bereavement Bereavement is a state of grief related to the death of a loved one, which presents with an overlap of symptoms characteristic of a major depressive episode. Typical depressive symptoms associated with bereavement include feelings of sadness, insomnia, diminished appetite, and, in some cases, weight loss. Grieving

children may become withdrawn and appear sad, and they are not easily drawn into even favorite activities. In DSM-5, bereavement is not a mental disorder; however, uncomplicated bereavement is included as a category documented with a v code, indicating that a normal grief reaction to the loss of a loved one has become a focus of clinical attention. Children in the midst of a typical bereavement period may also meet the criteria for major depressive disorder. Symptoms indicating major depressive disorder exceeding typical bereavement include intense guilt related to issues beyond those surrounding the death of the loved one, preoccupation with death other than thoughts about being dead to be with the deceased person, morbid preoccupation with worthlessness, marked psychomotor retardation, prolonged serious functional impairment, and hallucinations other than transient perceptions of the voice of the deceased person. The duration of bereavement varies; in children, the duration may depend partly on the support system in place. For example, a child who must be removed from home because of the death of the only parent in the home may feel devastated and abandoned for a long period. Children who lose loved ones may feel a sense of guilt, that the death may have occurred because they were “bad” or did not perform as expected. Ryan was a 12-year-old 7th grader in middle school who was brought to the emergency room in handcuffs by police after walking into oncoming traffic right after school. Ryan walked in front of a city bus; the driver began honking at the boy who kept walking slowly into the traffic. Two police stationed in their car across the street from the school heard the bus honking and noticed Ryan and confronted him. The police were about to issue the boy a citation for crossing against the red light; however, when they inquired as to why he had crossed against the traffic light he

informed them that he was trying to kill himself. The police handcuffed Ryan, placed him in the police car without a struggle and brought him to the local hospital’s emergency room. Ryan’s mother was contacted and met her son in the emergency room. Ryan was found to be physically intact, without injury, by the emergency room doctors, and psychiatric evaluation was initiated by a team of child psychiatrists including an attending child psychiatrist and two child and adolescent psychiatry residents. Ryan became tearful when asked what had happened, and reported that he had purposefully walked in front of the bus in the hope of being hit by the bus in order to die. Ryan reported that he has been bullied by numerous peers over the last 2 years and is picked on because he is short and overweight. Ryan reported that on this day, a girl in his class had pushed him down and started hitting him and laughing at him. Ryan reported that he had been teased and physically assaulted repeatedly by peers in his grade and that they call him stupid and fat. Ryan has some friends, who usually defend him, but on this day, his friends were not close by and he became desperate. Ryan disclosed, however, that even before this day, he has been consistently sad in school for the past year, and that he has thought about suicide recurrently over the last year, mainly due to feeling ostracized and worthless after being picked on and bullied. Ryan continues to be actively suicidal, disclosing his strong feeling that for him, life is not worth living. Ryan is a relatively good student, earning good grades, especially in math, although he is currently failing history. Upon separate interview with Ryan’s mother, she reports that she has no knowledge of any problems that Ryan has been struggling with, and that she feels that Ryan is not depressed, not severely bullied, or seriously unhappy in school, and reports that this must have been a mistake and that she is ready to take him home. Ryan reported that he had previously seen a counselor in school a few times last year when he was bullied, but that he has received no intervention for his depression or his suicidality and that he has not shared these feeling with his family and that he is generally content at home. Ryan has an older brother and a younger brother

who are well adjusted. When Ryan and his mother were interviewed together, Ryan was able with some encouragement to let his mother know how depressed, hopeless, and suicidal he feels, and why. Ryan's mother burst into tears and Ryan tried to comfort his mother, although he was crying as well. Ryan was placed on a 72-hour hold for "danger to self," and referred to a children's psychiatric inpatient unit for further evaluation and treatment. A trial of an SSRI antidepressant was recommended as well as psychoeducation and family sessions so that Ryan and his family would reach an understanding about his current psychiatric disorder, and that together they could work on a safe and productive plan for Ryan. Ongoing psychosocial intervention was recommended for Ryan and his family after hospitalization. PATHOLOGY AND LABORATORY EXAMINATION No laboratory test is useful in making a diagnosis of a major depression. If a child or

adolescent also complains of symptoms of hypothyroidism, that is, dry skin, coldness, lethargy, and so on, then a screening test for thyroid function may be indicated. Rating scales for depressive symptoms administered by the clinician to the child and parent may be helpful in the evaluation. The Children's Depression Rating Scale-Revised (CDRS-R) is a 17-item instrument administered by the clinician separately to the parent and child or adolescent. The clinician scores a rating for each item using the information from both the parent and the child. The scale assesses affective, somatic, cognitive, and psychomotor symptoms. A cumulative score of 40 is a marker for moderate depression and a score of 45 or greater for significant depression. DIFFERENTIAL DIAGNOSIS Substance-induced mood disorder may be difficult to differentiate from other mood disorders until detoxification occurs. Anxiety symptoms and disorders often coexist with depressive disorders. Of particular importance in the differential diagnosis is the distinction between agitated depressive or manic episodes and ADHD, in which the persistent excessive activity and restlessness can cause confusion. Prepubertal children generally do not show classic forms of agitated depression, such as hand-wringing and pacing. Instead, an inability to sit still, irritability, and frequent temper tantrums are the most common symptoms. Sometimes, the correct diagnosis becomes evident only after remission of the depressive episode. COURSE AND PROGNOSIS The course and prognosis of major depression in children and adolescents depends on the severity of illness, the rapidity of interventions, and the degree of response to the interventions. In general, 90 percent of youth recover from a first episode of moderate to severe major depressive disorder within 1 to 2 years. The age of onset, episode severity, and the presence of comorbid disorders also influence course and prognosis. In general, the younger the age of onset, the greater the recurrence of multiple episodes, and the presence of comorbid disorders predict a poorer prognosis. The mean length of an untreated episode of major depression in children and adolescents is about 8 to 12 months; the cumulative probability of recurrence is 20 to 60 percent within 2 years and 70 percent by 5 years. The greatest risk for relapse is in the 6 months to 1 year after treatment is discontinued. Depressed children who live in families with high levels of chronic conflict are more likely to have relapses. The relapse rates for childhood major depression into adulthood are also high. In a community sample, 45 percent of adolescents with a history of major depression developed another episode of major depression in early adulthood. Youth with major depression are at higher risk for the development of future bipolar disorder, compared to adults. Overall estimates of children with an episode of major depression developing bipolar disorder are about 20 to 40 percent. Clinical characteristics of a depressive episode in youth, suggesting the highest risk of developing bipolar I disorder include hallucinations and delusions, psychomotor

retardation, and a family history of bipolar illness. In a longitudinal study of prepubertal children with major depression, 33 percent developed bipolar I disorder, whereas 48 percent went on to develop bipolar II or bipolar disorder not otherwise specified by early adulthood. Depressive disorders are associated with short-term and long-term peer relationship difficulties and complications, compromised academic achievement, and persistently low self-esteem. Persistent depressive disorder has an even more protracted recovery than major depressive disorder; the mean episode length is about 4 years. Early onset persistent depressive disorder is associated with significant risks of comorbidity with major depressive disorder (70 percent), bipolar disorder (13 percent), and future substance abuse (15 percent). The risk of suicide, which accounts for about 12 percent of adolescent mortalities, is significant among adolescents with depressive disorders. TREATMENT The American Academy of Child and Adolescent Psychiatry practice parameters, as well as a consensus of experts who developed the Texas Children's Medication Algorithm Project (TMAP) made evidence-based recommendations for the treatment of children and adolescents with depressive disorders. These include psychoeducation and supportive interventions for youth with mild forms of depression. For youth with moderate to severe depression or recurrent episodes of major depression, with significant impairment and with active suicidal thoughts or behaviors, or psychosis, optimal intervention includes both psychopharmacological and CBT. CBT or interpersonal therapy (IPT) alone may be effective for moderate depression, especially when treatment is continued for 6 months or longer. Psychiatric Hospitalization Assessment of suicidal thoughts, behaviors, and past history of suicidal behavior is indicated in evaluating every child or adolescent with major depression. Safety is the most immediate consideration in assessing depression in youth, that is, a determination as to whether immediate psychiatric hospitalization is necessary. Depressed children and adolescents who express suicidal thoughts or behaviors most often require some extended evaluation in the safety of the psychiatric hospital to provide maximal protection from self-destructive impulses and behaviors.

EVIDENCE-BASED TREATMENT STUDIES The Treatment for Adolescents with Depression Study (TADS) divided 439 adolescents between 12 years and 17 years of age into three treatment groups of 12 weeks, composed of either fluoxetine (Prozac) alone (10 to 40 mg per day), fluoxetine with the same dose range in combination with CBT, or CBT alone. Based on ratings of the Children's Depression Rating Scale-Revised (CDRS-R) combination treatment had significantly superior response rates compared with either treatment alone. Based on CGI scores, at 12 weeks, rates of much or very much improved were 71 percent for the combined treatment group, 60.6 percent for the fluoxetine group, and 43.2 percent for the CBT alone group; and 34.4 percent for the placebo group. At 12 weeks, combination treatment was rated the optimal strategy in the treatment of adolescent depression. By the end of 9 months of treatment, however, response rates for each group had converged so that response for the combination group was 86 percent, fluoxetine group response was about 81 percent, and CBT-alone group response rate was 81 percent. The long-term effectiveness of treatments for adolescent depression demonstrates that for moderately ill adolescents, fluoxetine, CBT, or the combination is efficacious. However, the addition of CBT to fluoxetine decreased persistent suicidal ideation and potential treatment-related emergence of suicidal ideation. A second large multicenter randomized placebo controlled trial, Treatment of SSRIResistant Depression in Adolescents (TORDIA), included adolescents with major depression, who had not responded to a 2-month trial with an SSRI antidepressant. In this study, 334 adolescents between 12 and 18 years of age were randomly assigned to a different SSRI agent (either citalopram, paroxetine, citalopram, or another antidepressant class, venlafaxine) with or

without concurrent CBT. The SSRI plus CBT group and the venlafaxine plus CBT group had higher response rates of improvement (54.8 percent) than the group on medications alone (40.5 percent). There were no differences found in the response rates between antidepressant agents. Psychosocial Interventions CBT is widely recognized as an efficacious intervention for the treatment of moderately severe depression in children and adolescents. CBT aims to challenge maladaptive beliefs and enhance problem-solving abilities and social competence. A review of controlled cognitive-behavioral studies in children and adolescents revealed that, as with adults, both children and adolescents showed consistent improvement with these methods. Other “active” treatments, including relaxation techniques, were also shown to be helpful as adjunctive treatment for mild to moderate depression. Findings from one large controlled study comparing cognitive-behavioral interventions with nondirective supportive psychotherapy and systemic behavioral family therapy showed that 70 percent of adolescents had some improvement with each of the interventions; cognitivebehavioral intervention had the most rapid effect. Another controlled study comparing a brief course of CBT with relaxation therapy favored the cognitive-behavioral

intervention. At a 3- to 6-month follow-up, however, no significant differences existed between the two treatment groups. This effect resulted from relapse in the cognitivebehavioral group, along with continued recovery in some patients in the relaxation group. Factors that seem to interfere with treatment responsiveness include the presence of comorbid anxiety disorder that probably was present before the depressive episode. It has been shown, however, that longer term CBT is efficacious in the treatment of depression, and has the advantage of mitigating suicidal ideation. Interpersonal psychotherapy (IPT) focuses on improving depression through a focus on ways in which depression interferes with interpersonal relationships and overcoming these challenges. The four main areas of focus with interpersonal psychotherapy include loss, interpersonal disputes, role transition, and interpersonal deficits. A modification of interpersonal therapy to more specifically address depression for adolescents (IPT-A) includes a focus on separation from parents, authority figures, peer pressures, and dyadic relationships. IPT-A has been studied on an outpatient basis as well as in a school-based clinic setting. A 12-week study of 48 adolescents with major depression randomly assigned to IPT-A or clinical monitoring found that the group receiving IPT-A showed decreased depressive symptoms, increased social functioning, and improved problem solving compared to the other group. In the school-based health clinic, depressed adolescents were randomly assigned to IPT-A or treatment as usual for a period of 16 weeks. Clinic staff were trained and administered the treatment. At the end of 16 weeks, those adolescents receiving IPT-A had greater symptom reduction and improved overall functioning; especially older and more severely depressed adolescents seemed to benefit most significantly. Parent-Child Interaction Therapy Emotion Development (PCIT-ED) for preschool depression, a modification of Parent-Child Interaction Therapy (PCIT) historically used in the treatment of disruptive disorders for children, was piloted in a randomized controlled trial for 54 depressed preschoolers. Fifty-four depressed young children from age 3 to 7 years were randomly assigned to either PCIT-ED or psych-education with their caregivers. PCIT-ED was manualized and consists of three modules conducted over 14 sessions in 12 weeks. The core modules of PCIT—Child-Directed Interaction (CDI) and Parent-Directed Interaction (PDI)—were utilized and limited to four sessions each. The focus of these modules is to strengthen the parent–child relationship by coaching parents in positive play techniques, giving effective directives to the child, and responding to disruptive behavior in firm but not punitive ways. The novel portion of the treatment targeting the preschool depression consisted of a 6-week Emotion Development (ED) module, which focused on helping the parent to be a more effective

emotion guide and affect regulator for the child. As part of the ED module, the parent learned to accurately recognize his or her own emotions as well as the child's and serves to help regulate the child's emotions. A psychoeducation control condition, Developmental Education and Parenting Intervention (DEPI) was developed and administered to parents in small group sessions. The DEPI condition was designed to educate parents about child development and emphasized emotional and social development without individual coaching or practice with behavioral techniques as

provided in the PCIT-ED group. Primary outcome measures included parent's report of the child's symptoms of depression using a structured instrument, the Preschool Age Psychiatric Assessment (PAPA), and depression severity was measured pretreatment and posttreatment using parent ratings on the Preschool Reelings Checklist Scale Version (PFC-S) a 20-item checklist. Results revealed that both groups showed significant improvement with particular improvement in the PCIT-ED group with respect to emotion recognition, child executive functioning, and parenting stress. This pilot study indicates that PCIT-ED is a promising novel intervention for preschool depression that deserves further investigation. Pharmacotherapy Fluoxetine (Prozac) and escitalopram (Lexapro) have Food and Drug Administration (FDA) approval in the treatment of major depression in adolescents. Three randomized controlled trials (RCTs) using fluoxetine with depressed children and adolescents demonstrate its efficacy. Common side effects observed with fluoxetine include headache, gastrointestinal symptoms, sedation, and insomnia. Short-term randomized clinical trials have demonstrated efficacy of citalopram (Celexa), and sertraline (Zoloft) compared with placebo in the treatment of major depression in children and adolescents. Sertraline has been shown to provide efficacy in two multicenter, double-blind, placebo-controlled trials of 376 children and adolescents who were treated with sertraline at doses ranging from 50 mg to 200 mg a day, or placebo. greater than 40 percent decrease in depression rating scale scores were found in nearly 70 percent of the patients treated with sertraline, compared with 56 percent in the placebo group. Most common side effects are anorexia, vomiting, diarrhea, and agitation. Citalopram has been demonstrated in one RCT in the United States to be efficacious in 174 children and adolescents treated with citalopram at doses of 20 to 40 mg a day or placebo for 8 weeks. Significantly more of the group on citalopram showed improvement compared with placebo on the depression rating scale (CDRS-R). A significantly increased response rate (response defined as less than 28 on CDRS-R) of 35 percent was found in the citalopram group, compared with 24 percent of the placebo group. Common side effects that emerged included headache, nausea, insomnia, rhinitis, abdominal pain, dizziness fatigue, and flu-like symptoms. Similar to the literature for adult depression, as many negative as positive study findings have emerged in RCTs of the treatment of childhood and adolescent depression. RCTs to date that have not shown efficacy on primary outcome measures include those using mirtazapine (Remeron), and tricyclic antidepressants. A meta-analysis of SSRI trials in depressed children and adolescents found efficacy of SSRIs compared to placebo with an average response rate of 60 percent for the SSRI compared to 49 percent for placebo. Starting doses of SSRIs for prepubertal children are lower than doses recommended for adults, and adolescents are generally treated at the same doses recommended for

adults. Venlafaxine (Effexor), which blocks both serotonin and norepinephrine uptake, has been found to be effective in the TORDIA study; however, adverse effects including increased blood pressure have made this agent a second-line choice compared to the SSRIs. Tricyclic antidepressants are not generally recommended for the treatment of depression in children and

adolescents due to a lack of proved efficacy along with the potential risk of cardiac arrhythmia associated with their use. A potential side effect of selective serotonin reuptake inhibitors (SSRIs) in depressed children is behavioral activation, or induction of hypomanic symptoms. In such situations, the medication should be discontinued to determine whether the activation resolves with discontinuation of the medication, or evolves into a hypomanic or manic episode. Activation due to SSRIs, however, do not necessarily predict a diagnosis of bipolar disorder. FDA Warning and Suicidality In September 2004, the FDA received information from their Psychopharmacologic Drug and Pediatric Advisory Committee indicating, based on their review of reported suicidal thoughts and behavior among depressed children and adolescents who participated in randomized clinical trials with nine different antidepressants, an increased risk of suicidality in those children who were on active antidepressant medications. Although no suicides were reported, the rates of suicidal thinking and behaviors were 2 percent for patients on placebo, versus 4 percent among patients on antidepressant medications. The FDA, in accordance with the recommendation of their advisory committees, instituted a “black-box” warning to the health professional label of all antidepressant medication indicating the increased risk of suicidal thoughts and behaviors in children and adolescents being treated with antidepressant medications, and the need for close monitoring for these symptoms. Several reviews since 2004, however, concluded that the data do not indicate a significant increase in the risk of suicide or serious suicide attempts after starting treatment with antidepressant drugs. Duration of Treatment Based on available longitudinal data and the natural history of major depression in children and adolescents, current recommendations include maintaining antidepressant treatment for 1 year in a depressed child who has achieved a good response, and to then discontinue the medication at a time of relatively low stress for a medication-free period. Pharmacologic Treatment Strategies for Resistant Depression Pharmacological recommendations, in accordance with an expert consensus panel that developed the Texas Children’s Medication Algorithm Project (TMAP), as well as the Treatment of SSRI-resistant Adolescents with Depression study (TORDIA) in the

treatment of children or adolescents who have not responded to treatment with an SSRI agent is to change to another SSRI medication. If a child is not responsive to the second SSRI medication, then either a combination of antidepressants or augmentation strategies may be reasonable choices as well as an antidepressant from another class of medications. Electroconvulsive Therapy Electroconvulsive therapy (ECT) has been used for a variety of psychiatric illnesses in adults, primarily severe depressive and manic mood disorders and catatonia. ECT is used rarely for adolescents, although published case reports indicate its efficacy in adolescents with depression and mania. Currently case reports suggest that ECT may be a relatively safe and useful treatment for adolescents who have persistent severe affective disorders, particularly with psychotic features, catatonic symptoms, or persistent suicidality. SUICIDE In the United States, suicide is the third leading cause of death among adolescents, after accidental death and homicide. Throughout the world, suicide rarely occurs in children who have not reached puberty. In the last 15 years, the rates of both completed suicide and suicidal ideation rates have decreased among adolescents. This decrease appears to coincide with the increase in SSRI medications prescribed to adolescents with mood and behavioral disturbance. Suicidal Ideation and Behavior Suicidal ideation, gestures, and attempts are frequently, but not always, associated with depressive disorders. Reports indicate that as many as half of suicidal individuals express suicidal intentions to a friend or a relative within 24 hours before enacting suicidal behavior. Suicidal ideation occurs in all age groups and with greatest frequency in children and adolescents with severe mood disorders. More than 12,000

children and adolescents are hospitalized in the United States each year because of suicidal threats or behavior, but completed suicide is rare in children younger than 12 years of age. A young child is hardly capable of designing and carrying out a realistic suicide plan. Cognitive immaturity seems to play a protective role in preventing even children who wish they were dead from committing suicide. Completed suicide occurs about five times more often in adolescent boys than in girls, although the rate of suicide attempts is at least three times higher among adolescent girls than among boys. Suicidal ideation is not a static phenomenon; it can wax and wane with time. The decision to engage in suicidal behavior may be made impulsively without much forethought, or the decision may be the culmination of prolonged rumination. The method of the suicide attempt influences the morbidity and completion rates,

independent of the severity of the intent to die at the time of the suicidal behavior. The most common method of completed suicide in children and adolescents is the use of firearms, which accounts for about two thirds of all suicides in boys and almost one half of suicides in girls. The second most common method of suicide in boys, occurring in about one fourth of all cases, is hanging; in girls, about one fourth commit suicide through ingestion of toxic substances. Carbon monoxide poisoning is the next most common method of suicide in boys, but it occurs in less than 10 percent; suicide by hanging and carbon monoxide poisoning are equally frequent among girls and account for about 10 percent each. Additional risk factors in suicide include a family history of suicidal behavior, exposure to family violence, impulsivity, substance abuse, and availability of lethal methods. Gender differences in nonfatal suicidal behavior among 9th grade adolescents in a recent survey of students in 100 high schools found that serious suicidal thoughts were reported in 19.8 percent of female students and 10.8 percent of females had made an attempt. In male students, 9.3 percent had a history of suicidal thoughts and 4.9 percent had made an attempt. In this study, female students showed evidence of higher levels of mood and anxiety problems, whereas males had a slightly higher level of disruptive behavior problems. Female students reported higher levels of depression, anxiety, somatic complaints, and increased levels of emotional and behavioral problems than males. In young adolescents, even without meeting full criteria for psychiatric disorders, females report more psychopathology along with higher likelihood of nonfatal suicidal behavior. Epidemiology In a study of 9- to 16-year-olds in a 3-month period. passive suicidal thoughts were approximately 1 percent, suicidal ideation with a plan was 0.3 percent, and suicide attempt was 0.25 percent. In adolescents 14 to 18 years, the current rate of suicidal ideation was found to be 2.7 percent and annual incidence was 4.3 percent. Among this population of adolescents, lifetime prevalence of suicide attempt was 7.1 percent with a much higher rate of suicidal behavior for girls than for boys: 10.1 percent compared to 3.8 percent. Completed suicide rates in youth are much less common in children and younger teens 10 to 14 years, with a slighter lower rate of 0.95 per 100,000 for females compared to 1.71 per 100,000 for males. In older adolescents 15 to 19 years of age, completed suicide is considerably lower for females, 3.52 per 100,000 compared to males, 12.65 per 100,000 in the United States in 2004. Etiology Universal features in adolescents who resort to suicidal behaviors are the inability to synthesize viable solutions to ongoing problems and the lack of coping strategies to deal with immediate crises. Therefore, a narrow view of the options available to deal with recurrent family discord, rejection, or failure contributes to a decision to commit suicide.

Genetic Factors. Completed suicide and suicidal behavior is two to four times more likely to occur in individuals with a first-degree family member with similar behavior. Evidence of a genetic

contribution to suicidal behavior is based on family suicide risk studies and the higher concordance for suicide among monozygotic twins compared to dizygotic twins. Recent studies have investigated the possible contributions of the short allele of the serotonin transporter promoter polymorphism (5-HTTLPT) to suicidal behaviors, although to date, the evidence has not been consistent. Current studies are seeking to investigate correlations between genetic vulnerability and environment and timing interactions as multiple variables that may interact to increase the risk of suicidal behavior. Biological Factors. A relationship between altered central serotonin with suicide as well as impulsive aggression has been found in children and adolescents, and has been demonstrated in adults. Studies have documented a reduction in the density of serotonin transporter receptors in the prefrontal cortex, and serotonin receptors among individuals with suicidal behaviors. Postmortem studies in adolescents who have completed suicide show the most significant alterations in the prefrontal cortex and hippocampus, brain regions that are also associated with emotion regulation and problem solving. These studies have found altered serotonin metabolites, alteration in 5HT2a binding and decreased activity of protein kinase A and C. Decreased levels of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have also been found in the cerebrospinal fluid of depressed adults who attempted suicide by violent methods. Metaanalyses suggest an association between the short S-allele of the serotonin transporter promoter gene and depression as well as suicidal behavior, particularly when combined with adverse life events. Psychosocial Factors. Although severe major depressive illness is the most significant risk factor for suicide, increasing its risk by 20 percent, many severely depressed individuals are not suicidal. A sense of hopelessness, impulsivity, recurrent substance use, and a history of aggressive behavior, have been associated with an increased risk of suicide. A wide range of psychopathological symptoms are associated with exposure to violent and abusive homes. Aggressive, self-destructive, and suicidal behaviors seem to occur with greatest frequency among youth who have endured chronically stressful family lives. The most significant family risk factor for suicidal behavior is maltreatment, including physical and sexual abuse and neglect. The single largest association is between sexual abuse and suicidal behavior. Large community studies have provided data suggesting that youth at risk for suicidal behavior include those who feel disconnected, isolated, or alienated from peers. Sexual orientation is a risk factor, with increased rates of suicidal behavior of two to six times among youth who identify themselves as gay, lesbian, or bisexual. Protective factors mitigating the risk of suicidal behavior are youth who have a strong connection to school and peers even in the face of other risk factors.

Diagnosis and Clinical Features The characteristics of adolescents who attempt suicide and those who complete suicide are similar and up to 40 percent of suicidal persons have made a previous attempt. Direct questioning of children and adolescents about suicidal thoughts is necessary, because studies have consistently shown that caregivers are frequently unaware of these ideas in their children. Suicidal thoughts (i.e., children talking about wanting to harm themselves) and suicidal threats (e.g., children stating that they want to jump in front of a car) are more common than suicide completion. Most older adolescents with suicidal behavior meet criteria for one or more psychiatric disorders, often including major depressive disorder, bipolar disorder, and psychotic disorders. Youth with mood disorders in combination with substance abuse and a history of aggressive behavior are at particularly high risk for suicide. The most common precipitating factors in younger adolescent suicide completers appear to be impending disciplinary actions, impulsive behavioral histories, and access to loaded guns, particularly in the home. Adolescents without mood disorders with histories of disruptive and violent, aggressive, and impulsive behavior

may be susceptible to suicide during family or peer conflicts. High levels of hopelessness, poor problem-solving skills, and a history of aggressive behavior are risk factors for suicide. A less common profile of an adolescent who completes suicide is one of high achievement and perfectionistic character traits facing a perceived failure, such an academically proficient adolescent humiliated by a poor grade on an exam. Findings from a World Health Organization mental health survey reveals that a range of psychiatric disorders increase the risk of suicidal ideation across the lifespan. Youth with psychiatric disorders characterized by severe anxiety and poor impulse control are at higher risk to act on suicidal ideation. In psychiatrically disturbed and vulnerable adolescents, suicide behavior may represent impulsive responses to recent stressors. Typical precipitants of suicidal behavior include conflicts and arguments with family members and boyfriends or girlfriends. Alcohol and other substance use can further predispose an already vulnerable adolescent to suicidal behavior. In other cases, an adolescent attempts suicide in anticipation of punishment after being caught by the police or other authority figures for a forbidden behavior. About 40 percent of youth who complete suicide had previous psychiatric treatment, and about 40 percent had made a previous suicide attempt. A child who has lost a parent by any means before age 13 is at higher risk for mood disorders and suicide. The precipitating factors include loss of face with peers, a broken romance, school difficulties, unemployment, bereavement, separation, and rejection. Clusters of suicides among adolescents who know one another and go to the same school have been reported. Suicidal behavior can precipitate other such attempts within a peer group through identification—so-called copycat suicides. Some studies have found a transient increase in adolescent suicides after television programs in which the main theme was the suicide of a teenager.

The tendency of disturbed young persons to imitate highly publicized suicides has been referred to as Werther syndrome, after the protagonist in Johann Wolfgang von Goethe’s novel, The Sorrows of Young Werther. The novel, in which the hero kills himself, was banned in some European countries after its publication more than 200 years ago because of a rash of suicides by young men who read it; some dressed like Werther before killing themselves or left the book open at the passage describing his death. In general, although imitation may play a role in the timing of suicide attempts by vulnerable adolescents, the overall suicide rate does not seem to increase when media exposure increases. In contrast, direct exposure to peer suicide is associated with increased risk of depression and posttraumatic stress disorder rather than suicide. Treatment The prognostic significance of suicidal ideation and behaviors in adolescents ranges from relatively low lethality, to high risk for completion. One of the challenges in addressing suicide is to identify children and adolescents with suicidal ideation, and particularly to treat those who have untreated psychiatric disorders, as the risk of completed suicide increases with age, as does the onset of an untreated psychiatric disorder. Adolescents who come to medical attention because of suicidal attempts must be evaluated before determining whether hospitalization is necessary. Pediatric patients who present to the emergency room with suicidal ideation benefit from an intervention that occurs in the emergency room to ensure that the patient is transitioned to outpatient care when hospitalization is not necessary. Those who fall into high-risk groups should be hospitalized until the acute suicidality is no longer present. Adolescents at higher risk include those who have made previous suicide attempts, especially with a lethal method, males older than 12 years of age with histories of aggressive behavior or substance abuse, use of a lethal method, and severe major depressive disorder with social withdrawal, hopelessness, and persistent suicidal ideation. Relatively few adolescents evaluated for suicidal behavior in a hospital emergency room

subsequently receive ongoing psychiatric treatment. Factors that may increase the probability of psychiatric treatment include psychoeducation for the family in the emergency room, diffusing acute family conflict, and setting up an outpatient follow-up during the emergency room visit. Emergency room discharge plans often include providing an alternative if suicidal ideation reoccurs, and a telephone hot-line number provided to the adolescent and the family in case suicidal ideation reappears. Scant data exist to evaluate the efficacy of various interventions in reducing suicidal behavior among adolescents. CBT alone and in combination with SSRIs have been shown to decrease suicidal ideation in depressed adolescents over time in the Treatment of Adolescent Depression (TADS) study, a large multisite study; however, these interventions do not work immediately, so safety precautions must be taken for highrisk situations. Dialectical behavior therapy (DBT), a long-term behavioral intervention that can be applied to individuals or groups of patients, has been shown to reduce suicidal behavior in adults, but has yet to be investigated in adolescents. Components of DBT include mindfulness training to improve self-acceptance, assertiveness training, instruction on avoiding situations that may trigger self-destructive behavior, and increasing the ability to tolerate psychological distress. This approach warrants

investigation among adolescents. Given the reduction in completed suicide among adolescents over the last decade, during the same period in which SSRI treatment in the adolescent population has markedly risen, it is possible that SSRIs have been instrumental in this effect. Given the risk of increased rate of suicidal thoughts and behaviors among depressed children and adolescents (indicated in randomized clinical trials with antidepressant medications and leading to the “black-box” warning for all antidepressants for depressed youth), close monitoring for suicidality is mandatory for any child or adolescent being treated with antidepressants. REFERENCES Bayer JK, Rapee RM, Hiscock H, Ukoumunne OC, Mihalopoulos C, Wake M. Translational research to prevent internalizing problems in early childhood. Depress Anxiety. 2011;28:50–57. Brent D, Emslie E, Clarke G, Wagner KD, Asarnow JR, Keller M, Ritz, L, Iyengar S, Abebe K, Birmaher B, Ryan N, Kennard B, Hughers C, DeBar L, McCracken J, Strober M, Suddath R, Spirito A, Leonard H, Meham N, Pora G, Onorato M, Zelazny J. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORIDA Randomized Controlled Trial. JAMA. 2008:299:901–913. Correll CU, Kratocvil CJ, March J. Developments in pediatric psychopharmacology: Focus on stimulants, antidepressants and antipsychotics. J Clin Psychiatry. 2011;72:655–670. Christiansen E, Larsen KJ. Young people’s risk of suicide attempts after contact with a psychiatric department—A nested case-control design using Danish register data. J Child Psychol Psychiatry. 2011;52:102. Field T. Prenatal depression effects on early development: A review. Infant Behav Dev. 2011;34:1–14. Frodl T, Reinhold E, Koutsoulieris N, Donohoe G, Bondy B, Reiser M, Moller Hj, Meisenzahl EM. Childhood stress, serotonin transporter gene and brain structures in major depression. Neuropsychopharmacology. 2010;35:1383–1390. Gould MS, Greenberg T, Velting DM, Shaffer D. Youth suicide risk and preventive interventions: A review of the past ten years. J Am Acad Child Adolesc Psychiatry. 2003;42:386. Hall WD. How have the SSRI antidepressants affected suicide risk? Lancet. 2006;367(9527):1959. Harro J, Kiive E. Droplets of black bile? Development of vulnerability and resilience to depression in young age. Psychoneuroendocrinology. 2011;36:380–392. Heiligenstein JH, Hoog SL, Wagner KD, Findling RL, Galil N, Kaplan S, Busner J, Nilsson ME, Brown EB, Jacobson JG. Fluoxetine 40–60 mg versus fluoxetine 20 mg in the treatment of children and adolescents with a less-than-complete response to nine-week treatment with fluoxetine 10–20 mg: A pilot study. J Child Adolesc Psychopharmacol. 2006;1/2:207. Hughes CW, Emslie GJ, Crimson ML, Posner K, Birmaher B, Ryan N, Jensen P, Curry J, Vitiello B, Lopez M, Shon SP, Piszka SR, Trivedi MH, and The Texas Consensus Conference Panel on

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