# The Relationship Between Menarche and Depression in Adolescence

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# ABSTRACT

Prior to adolescence, the rates of depression are similar in girls and boys, or are slightly higher in boys. However, with the onset of puberty, the gender proportion of depression dramatically shifts to a 2:1 female to male ratio. What is the relationship between menarche and the onset of major depression in early adolescence? A recent theoretical model proposes that vulnerability to depression may be rooted in normal female hormonal maturational processes and gender socialization. Information regarding the management of depression in adolescent and young adult women is provided, including gender differences in the presentation of depressive symptoms, instruments to facilitate assessment, and treatment options. Pubertal and other hormonal changes should be monitored prospectively along with individual, genetic, constitutional, and psychological characteristics. The burden of illness associated with onset of depression following menarche reinforces the importance of expeditious recognition and intervention.

CNS Spectrums 2001;6(2):126-138

# **INTRODUCTION**

Beginning at menarche, epidemiologic studies consistently show that mood disorders are at least twice as common in women than in men (Figure 1).<sup>14</sup> Why these gender differences exist and why they start at puberty are perhaps the most intriguing and least understood phenomena in clinical psychiatry.<sup>1</sup> Gender is relevant in this context because of the known relationship between female reproductive milestones and psychiatric illness. The association of mood disorders (eg, premenstrual dysphoria) with the menstrual cycle, pregnancy, the postpartum period, and perimenopause continues to be the focus of ongoing research in North America and around the world. Menarche seems to be the forgotten milestone.

A host of new literature on depression in adolescence has appeared in the last decade. In addition to a surge of research in pediatric psychopharmacology, there is increasing awareness of the risks for early onset depression, and recent research has yielded some encouraging preventive intervention strategies.<sup>5</sup> In this article, we summarize the characteristics associated with the onset of depressive illness—in particular, major depression—around the time of menarche, as well as those factors that may predict response to treatment.

# <u>EPIDEMIOLOGY</u>

# Lifetime Prevalence

The lifetime prevalence of major depression in adolescents and young adults (15–24 years of age) in the United States general population has been reported as 20.6% for females and 10.5% for males.<sup>4</sup> There is conflicting opinion regarding the age at which gender differences in rates of major depression emerge: Researchers are divided between the age brackets of 12–14 years and 15–19 years.<sup>6–12</sup> Almost three quarters of those with major depression report recurrent episodes. The lifetime prevalence of dysthymia is also significantly higher in females than in males (estimates range from 4.0% to 5.3% vs 1.5% to 2.3%, respectively), with an average age of onset between 10 and 11 years of age.<sup>13,14</sup>

#### Comorbidity

In the US National Comorbidity Survey, 76.7% of those with major depression<sup>4</sup> and all individuals diagnosed with bipolar disorder<sup>15</sup> reported comorbid lifetime disorders. It has been suggested that anxiety symptoms tend to predate depressive symptoms in adolescents.<sup>16</sup> In the survey, more than 58% of female respondents with major depression reported having an anxiety disorder prior to the onset of depression.<sup>4</sup> Some researchers have posited that a higher rate of anxiety disorders in girls compared with boys prior to puberty may contribute to the higher female risk for major depression.<sup>617,18</sup>

#### Cross-cultural Differences

There are limited data on the prevalence of female adolescent depression in populations outside of the US, or even among various cultural groups within North America. Moreover, explicit comparisons are hampered by methodologic differences. Several studies, however, merit some attention. Significantly higher levels of depressive symptoms were found in Hispanic/Latino and Asian groups than Caucasian and African-American groups in a nationally representative sample of 6,943 US students (9–20 years of age).<sup>19</sup>

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Disclosure: An expanded/modified version of this paper has recently also been published as Chapter 15 in Steiner M, Yonkers KA, Eriksson E, eds. Mood Disorders in Women. London, UK: Martin Dunitz, Ltd; 2000:247-268.

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In addition, in a national sample of 10–14-year-old female students, the 10- and 11-year-old postmenarcheal girls in Caucasian and Hispanic/Latino (but not African-American) groups had higher mean depression scores than premenarcheal students of the same age. Furthermore, in the Caucasian group, the mean depression scores of postmenarcheal girls remained higher than the scores of premenarcheal girls with increasing age. This consistent divergence between postmenarche and premenarche depression scores across age groups, however, was not apparent in the Hispanic/Latino and African-American groups.<sup>20</sup>

The results of a large community-based US study of adolescent girls and young adults (14–26 years of age) suggest ethnic differences in correlates of moderate to severe depression. Among whites, depressive symptoms were correlated with having dropped out of high school, unemployment, binge drinking, and having a mother with less than a high school education. Hispanic females were more likely to report physical assault and nicotine use. Among African-Americans, depressive symptoms were correlated with nicotine use and unemployment.<sup>21</sup>

# Suicidal Behavior

Suicidal ideation and attempts in female adolescents are usually linked with psychiatric morbidity. A history of suicide attempt has been associated with risk for the onset of major depression in older adolescents.<sup>22</sup> Conversely, being female and having a diagnosis of affective disorder have been identified as risk factors for suicide attempt.<sup>23,24</sup> A link between adolescent suicide attempts and major depression with melancholic features has been suggested; additional associated characteristics may include perfectionism, being overly conscientious, sensitivity to criticism, and despair.<sup>25</sup>

In Britain, investigators have found that the frequency of suicidal behavior (suicidal ideation, attempt, or threat) in female subjects climbed sharply after age 9 years, rising from 3.6% at age 8 years to 24.6% by age 17 years (Figure 2).<sup>26</sup> A US national survey of high school students found that female students were significantly more likely to report suicidal ideation, plan-making, or attempt. Also, a slightly higher percentage of female students reported having made a suicide attempt that required medical attention.<sup>27</sup> Others have





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distinguished deliberate self-harm from "true" suicide attempts (ie, self-harm plus serious intent). In a survey of Australian high school students, the young women were more likely to self-harm and more frequently employed self-poisoning and self-laceration.<sup>28</sup>

# SYMPTOM PRESENTATION

There is general agreement that the clinical features of depression are more similar than different in adolescents and adults, with the exception of a higher frequency of irritable mood in the adolescent presentation. Research suggests that women more frequently present with somatic symptoms of depression (ie, fatigue, appetite and sleep disturbance, and body aches), which has been linked to the onset of major depression in early adolescence and to the presence of a concurrent anxiety disorder.<sup>20</sup> Female gender and the presence of a concurrent anxiety disorder.<sup>20</sup> Female gender the severity of the initial depressive episode.<sup>30</sup>

Negative body image, low self-esteem, and recent stressful events have been highly correlated with depression in samples of high school students.<sup>19,31-33</sup> Compared with depressed boys, depressed girls more frequently exhibit problems with poor self-esteem, worthlessness, guilt feelings, and suicidal ideation.<sup>1,34,35</sup> Low social support has also been correlated with depression in girls.<sup>19</sup> Maladaptive cognitions have been significantly correlated with greater severity of depressive symptoms in depressed adolescents, although neither gender nor type of depressive illness (major depression or dysthymia) were found to contribute to this association.<sup>36</sup>

# **ETIOLOGY**

The onset of puberty is heralded by a growth spurt, which begins with rapid growth in height and weight typically between 7.5 and 11.5 years of age. Following this initial burst, the physical growth and changes associated with puberty take an average of 4–5 years. Menstruation begins after these changes occur. However, considerable variation exists in the sequence and tempo of these events. In North America, menarche occurs at an average age of about 12.5 years.<sup>37</sup>

# Pubertal Status and Pubertal Timing

The relationship between psychosocial development and physical maturation has been widely examined. Girls undergoing pubertal change are thought to experience



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greater distress and to be more vulnerable to stress than pre- or postpubertal girls.<sup>38</sup> Two parameters of pubertal change in particular have received much attention: pubertal status and pubertal timing.

Pubertal status is defined as the current level of physical development of an adolescent relative to the overall process of pubertal change (a biologic factor), usually denoted by a series of stages from prepubertal (Stage I) to adult (Stage V) according to Tanner.<sup>39</sup> Adolescent girls are less optimistic than their prepubescent peers. It has been suggested that these attitudinal differences are a result of the cooccurrence of change in pubertal status and psychosocial stressors that affect youngstersespecially girls-at this developmental stage, such as the transition to a more senior school and the changing expectations regarding social and sexual behavior.40 At puberty, girls' attitudes about their physical appearance, particularly the appearance of secondary sex characteristics, become more negative and may be closely associated with negative affect.<sup>41</sup> In addition, negative attitudes towards menstruation may be found in premenarchal girls-an association that may not decrease until several years postmenarche.42

There appears to be a relatively sharply

demarcated period in mid-puberty when girls become more vulnerable to depression than boys. The onset of menarche may signal an increased but latent biologic vulnerability to mood dysregulation in women. This is suggested by a recent study<sup>43</sup> that found that depression rates in girls rose significantly with the transition to Tanner Stage III (the stage just prior to the first menstrual period peak, characterized by height growth, appearance of sparse pubic hair, and slight enlargement of the breasts), whereas the prevalence of depression in boys declined from Tanner Stage II (Figure 3). Furthermore, it has been determined that in girls pubertal status (vs the age at puberty per se) is a better predictor of the emergence of the sex ratio in depression rates.

Pubertal timing, on the other hand, is defined as the maturation of an adolescent relative to her peers (a psychosocial factor). Girls who mature earlier manifest more emotional and behavioral problems, specifically related to poorer body image, and have poorer psychological adjustment.<sup>41,44,45</sup> With this group, there is an increased likelihood of problem or delinquent behavior or substance use early in adolescence.<sup>44,46</sup> Similarly, females who experienced later pubertal "Girls who mature earlier manifest more emotional and behavioral problems, specifically related to poorer body image, and have poorer psychological adjustment."



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"There is accumulating evidence on the role of family dynamics and familial interpersonal relationships in adolescent health. Less supportive and more conflictual family environments are associated with greater depressive symptomatology and impaired social functioning in adolescents." development, particularly during school transitional times, had more dysphoria and negative attitudes about menstruation compared with peers who were not experiencing pubertal change.<sup>47,48</sup> Girls who perceive that they have been "on time" have a more positive body image and feel more physically attractive than early or late maturers; this relationship has been shown to be relevant to girls from diverse ethnic groups.<sup>44</sup>

There is some debate over whether poor psychological adjustment in precocious puberty is a magnification of preexisting emotional/behavioral issues during childhood or rather a *de novo* event.<sup>38</sup> Early maturation affects psychological functioning when the early maturers represent a noticeable minority within a group.<sup>49</sup>

# **Psychosocial Stressors**

Significant changes in social functioning (eg, peer interactions, lack of connectedness with school), the adolescent's environment (including perceived student prejudice and exposure to violence and poverty<sup>46</sup>), and gender-differentiated social support concerning sexuality<sup>50</sup> challenge the coping skills of young girls during the peripubertal period and beyond. These factors, as well as the experience of a severe life event (eg, physical assault, conflicted romantic relationships, or family or personal illness),<sup>51,52</sup> have been significantly related to the onset of major depression in adolescence.

Similarly, there is also increasing attention to the prevalence of child physical and sexual abuse and its association with psychiatric morbidity. In a large, national school-based survey, investigators found that childhood physical and sexual abuse were significantly correlated with depression in both male and female students.<sup>19</sup> There is mounting evidence that childhood neglect or abuse, particularly sexual abuse, is a risk factor for both adolescent- and adult-onset depression in women.<sup>53455</sup>

# Family Psychiatric History and Genetic Factors

There is evidence for a strong association between a parental or familial history of psychiatric disorders and onset of major depression in adolescence. In a review of longitudinal data it was estimated that, by the age of 20 years, a child with an affectively ill parent has a 40% chance of experiencing an episode of major depression.<sup>56</sup> Based on a study of pubertal twins, there is evidence of increased heritability for depression in adolescent girls.<sup>57</sup> The presence or history of maternal depression significantly increases the likelihood of depression in female children and adolescents.<sup>58,59</sup>

There is also some evidence of an increased risk for major depression in the offspring of probands who have onset of major depression before 20 years of age,<sup>60</sup> as well as in the offspring of parents with alcohol abuse or dependence<sup>61</sup> and in families with a recent history of suicidality.<sup>40</sup> Moreover, significant associations between depression and medical problems (including hospitalization) were found for those offspring with a depressed parent.<sup>62</sup>

# Family Support

There is accumulating evidence on the role of family dynamics and familial interpersonal relationships in adolescent health. Less supportive and more conflictual family environments are associated with greater depressive symptomatology and impaired social functioning in adolescents.<sup>30,32,63,64</sup> Contrary to expectations, however, no gender differences in the association between family characteristics and adolescent depressive symptomatology have been pinpointed. Parental "connectedness" (ie, feelings of warmth, love, and caring from parents) has been identified as a significant protective factor against health risk behaviors,<sup>46</sup> whereas a poor perception by children of their role in the family has been identified as a latent risk factor for the onset of major depression in female adolescence.<sup>33</sup> There is some evidence based on retrospective, population-based studies to support an association between depression in women and a disturbed mother-child relationship."

### Hormones and Neuromodulators

In general, changes in affect, mood, and behavior are considered to be related to cyclic hormonal changes, yet studies of female adolescents and premenstrual syndrome are inconclusive.<sup>65,66</sup> Notwithstanding, relationships between changes in pubertal hormones and negative affect in adolescent girls have been observed. For example, negative affect in healthy girls has been correlated with a rapid increase in estradiol levels,<sup>67</sup> with higher levels of testosterone and cortisol, and with lower levels of dehydroepiandrosterone sulphate.<sup>68</sup>

There is limited direct and indirect evi-

dence for the involvement of the serotonergic system in the etiology of depressive disorders in children and adolescents. Levels of wholeblood serotonin were lowest in a small group of adolescent inpatients diagnosed with mood disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised, compared with those who were diagnosed with disruptive behavior disorder or disruptive behavior disorder and mood disorder, or with normal controls.69 Serotonergic dysregulation in adolescent major depression is further evidenced by a blunted prolactin response to parenteral clomipramine challenge, but no gender effects in major depression subjects were found.70

There is growing evidence for the responsiveness of children and adolescents with major depression to serotonergic-related, but not to noradrenergic-related antidepressants. Researchers have hypothesized that in childhood the serotonergic systems may mature at an earlier rate than the noradrenergic systems.<sup>71</sup> Gonadal hormones affect the production of serotonin receptors at the transcriptional level, and the altered distribution or function of serotonin receptor subtypes brought on by changes in the hormonal milieu at menarche may increase vulnerability to mood disorders.

Several neurobiologic variables, including other hormonal systems that might identify individuals at high risk before they develop the depressive illness, have been examined. On the whole, the overall results of studies in this area are not very encouraging. While one study found that nocturnal hypersecretion of growth hormone significantly differentiated depressed adolescents from controls,<sup>72</sup> the 24-hour pattern of prolactin and growth hormone secretion, as well as findings on the dexamethasone suppression test failed to differentiate between depressed and control groups.<sup>73-75</sup>

Altered hypothalamic-pituitary-adrenal (HPA) system function has been observed both in persons diagnosed with major depression and in their otherwise healthy firstdegree relatives.<sup>76</sup> In addition, a greater susceptibility to stress-induced HPA-axis dysregulation has been linked with enhanced vulnerability to depression in women.<sup>55</sup> Investigators have shown that early physical and emotional stress in animals is associated with altered HPA-axis function and suppression of reproductive function (including delayed puberty); similar associations have been posited in young women.<sup>77</sup> Pituitary hyporesponsiveness is suggested by significantly decreased plasma adrenocorticotropicreleasing hormone stimulation in childhood sexually abused girls (aged 7–15 years) compared with controls. The sexually abused group in this study also had a significantly greater incidence of suicidal ideation/attempts and dysthymia.<sup>78</sup> The longer-term ramifications of HPA-axis dysregulation in female children and adolescents, however, have yet to be determined.

Studies of sleep disturbances in major depression and associated biologic rhythm abnormalities suggest that these are strongly influenced by gender. An influence of gonadal hormone regulation on sleep has been posited in women of childbearing age.<sup>70</sup> In addition, menstrual cycle phase effects on sleep have been observed, but the impact of specific endogenous sex hormones (particularly estrogen and progesterone) on sleep is not yet clear.

Shorter rapid eye movement (REM) latency, long known to be a neurobiologic marker of depression in adults, has also been found in adolescents with major depression compared with healthy controls.<sup>80-82</sup> These observations have led to two paths of investigation. One hypothesis has focused on shorter REM latency as a potential predictor of major depression in female adolescents. In a comparison of adolescents deemed to be at risk for major depression (ie, female sex and having a mother with major depression) and controls (no family psychiatric history in first-degree relatives), baseline REM latency measures together with depressive symptom measures did not differentiate between the two groups.<sup>83</sup> The utility of REM latency as a potential biologic predictor of the onset of major depression in adolescent girls, therefore, is doubtful.

Another postulate has centered on sleep electroencephalography (EEG) and temporal interhemispheric coherence. In a pilot study, about 25% of 21 never mentally ill offspring from families with a history of depression showed significant sleep EEG differences, suggesting a vulnerability to depression.<sup>64</sup> Sex differences in sleep EEG were found in adolescents but not in children with major depression. Adolescent girls with major depression displayed low interhemispheric temporal coherence of EEG rhythms during sleep compared with healthy girls or "Shorter rapid eye movement (REM) latency, long known to be a neurobiologic marker of depression in adults, has also been found in adolescents with major depression compared with healthy controls." depressed adolescent boys. This suggests a disruption in the fundamental brain rest-activity cycle (ie, organization of sleep cycles, physiology, mood, and behavior) that is strongly influenced by age and gender.<sup>85</sup>

It is, nevertheless, still unclear how the dramatic changes in the hormonal milieu associated with menarche and a host of psychosocial stressors combine to produce depressive symptoms. One possible unifying hypothesis suggests that disruption of biologic rhythms (such as disturbed sleep patterns or irregular menstrual cycles) together with psychosocial losses causing the disruption of social rhythms (also known as "social zeitgebers") could trigger the onset of a major depressive episode in vulnerable individuals.<sup>86</sup> Another complementary theory emphasizes the neurobiology of stress and the dysregulation of affect during female biologic transitions such as menarche, a transition that may be associated with changes in the reactivity of the stress system.<sup>87</sup> A more recent model pinpoints normal female hormonal maturational processes and gender socialization. In essence, a vulnerability to depression is rooted in the contradiction of a high need for affiliation together with low attachment security, high anxiety, and coping skills inadequate for dealing with negative life stressors.<sup>88</sup>

In conclusion, it is suggested that pubertal and other hormonal changes should be monitored prospectively along with individual, genetic, constitutional, and psychological characteristics in our efforts to predict the development of negative affect during puberty. The characteristics associated with the onset of mood disorders in female adolescents around the time of menarche are summarized in Table 1.

#### ASSESSMENT

Depression is often underrecognized and



undertreated in adolescents and young adults.<sup>89,90</sup> Adolescents are accurate in reporting their own feelings and emotional problems; therefore, it is important to emphasize that direct interview is essential. It has been observed, however, that parent-adolescent agreement for diagnoses of emotional disturbance, including major depression, dysthymia, and anxiety, is poor<sup>1,91</sup>; this may be particularly relevant to girls in early adolescence (12–16 years of age).<sup>2</sup>

A two-step process for the assessment of mood disorders in adolescents has been suggested: a depression screen to identify putative cases and specific problem areas, followed by a standardized, comprehensive interview to diagnose mood, as well as comorbid disorders.<sup>1</sup> Examples of these instruments are provided in Table 2.<sup>92-97</sup> As an alternative to the standardized diagnostic interviews (usually developed for research settings), the American Academy of Child and Adolescent Psychiatry has recommended a psychiatric symptom checklist derived from *DSM-IV* symptom categories.<sup>98</sup>

The DSM-IV has been advocated as the clinical standard for the diagnosis of mood disorders in adolescents. However, the clinical picture of mood disorders can vary widely across developmental stages and ethnic groups.<sup>98</sup> In general, compared with adults, adolescents with major depression may manifest fewer neurovegetative symptoms and more frequent irritability. High levels of depression, hopelessness, socially prescribed perfectionism, and anger expression are strongly associated with suicidal ideation.<sup>99</sup> Substance-use coping strategies have been significantly associated with higher levels of depressive symptoms in both genders.<sup>19</sup>

The "context" of the depression may play an important role in the assessment and treatment of adolescents. These factors can include family psychiatric history, parent-child relationship(s), familial or home environment, cultural milieu, academic functioning, social (especially peer) relationships, and recent stressful life events.<sup>100</sup> A summary of key questions for parents and adolescents pertaining to adolescent psychosocial functioning has been recently published.<sup>101</sup>

#### <u>TREATMENT</u>

Until recently, persons under the age of 18 years were excluded from clinical drug trials and mostly ignored in psychotherapy studies. This situation is now changing, but empirically based treatment options for this age group are still very scarce. The most frequently used form of treatment for adolescent depression is outpatient psychotherapy, and only a very small percentage of these young patients are prescribed antidepressants. In fact, a disturbingly high proportion of adolescents with serious mood disorders receive less than optimal treatment relative to the seriousness of their illness.<sup>102</sup>

The path to treatment planning that incorporates an adolescent's context is not clearcut. Parental involvement in the treatment process is advocated to enhance communication skills between parent(s) and child and to facilitate parental understanding of the mental health intervention(s). This may be particularly relevant for treating youths in families in which a parent is depressed,<sup>1</sup> or in cases where family interaction is posited to contribute to the maintenance of illness.<sup>103</sup>

Research has shown that the severity of a depressive episode and the life circumstances surrounding the episode strongly influence adolescent treatment-seeking behavior.<sup>1</sup> Additional factors related to treatment utilization include female gender, prior history of depression, history of suicide attempt, and current comorbid nonaffective disorder.<sup>18</sup> Patient characteristics that may predict poorer treatment response are displayed in Table 3.<sup>1,104,105</sup>

#### Psychotherapy

Psychotherapy has been recommended as a first-line intervention for adolescents with mild to moderate depression.<sup>106</sup> In general, the literature supports the use of cognitivebehavioral therapy (CBT) for the acute treatment of depression, either in an individual or group format.<sup>107,108</sup> The aim of CBT is to identify and replace negative cognitions and attributions. The cognitive techniques are usually accompanied by reinforcing behavioral tasks. In research studies, acute (individual or group) psychotherapy for depressive disorders typically lasts for 8-16 sessions. For participants who may still be depressed at the end of the acute phase of treatment, researchers have advocated "booster" sessions or continuation of therapy in order to facilitate recovery. The effectiveness of CBT over the longer term in the prevention of relapse has yet to be demonstrated.

There is early evidence of the effectiveness of interpersonal psychotherapy in the treatment of adolescents with mild to moderate depression (known as IPT-A).<sup>109-112</sup> IPT-A may be particularly beneficial in improving social functioning and interpersonal problem-solving skills. However, further investigations are required with larger and more diverse samples.

It has been suggested that, regardless of psychotherapy mode, approximately one third of adolescents with mild to moderate depression may show a significant reduction in depressive symptoms within one to two sessions.<sup>113</sup> Some data on longer-term (ie, longer than 1 year) follow-up of adolescents have recently become available. Two years following the end of acute treatment, investigators found that, regardless of the type of psychotherapy utilized, subsyndromal depressive symptoms, behavorial problems, or family difficulties were predictive of the need for added treatment. The supplementary treatment included booster psychotherapy sessions and/or medication.114

### Psychopharmacologic Treatment

In general, and compared with studies of psychopharmacotherapy in adults, controlled studies of medication for mood disorders in adolescents are few, and there are little longterm safety data. Researchers have cautioned that response to medication in adolescents should not be solely inferred from similarity in psychopathologic features to adults.<sup>115</sup> Gender differences in pharmacokinetics may be relevant in adolescence as girls' body fat increases more during this period, perhaps influencing drug distribution and the halflives of medication. Moreover, it is postulated that central nervous system neurotransmitter

#### TABLE 2. ASSESSMENT OF MOOD AND COMORBID DISORDERS IN ADOLESCENTS.

Screening

Children's Depression Inventory (CDI)<sup>92</sup>

Children's Interview for Psychiatric Syndromes (ChIPS)\*93

#### Diagnosis

National Institute of Mental Health Diagnostic Interview Schedule for Children, Version IV, (NIMH DISC-IV)<sup>794</sup> Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)<sup>795</sup> Diagnostic Interview for Children and Adolescents (DICA)<sup>\*96</sup> The Child and Adolescent Psychiatric Assessment (CAPA)<sup>\*97</sup> \*Diagnoses according to *DSM-IV* criteria. *DSM-IV=Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Born L, Steiner M. *CNS Spectrums*. Vol 6, No 2. 2001. systems undergo differential development from childhood to adulthood, in part explaining age differences in response to some psychotropic medications.<sup>115</sup> One noticeable example of this age-related difference is the poor response of adolescents to tricyclic antidepressants.

To date, the focus of pharmacologic treatment studies in childhood and adolescence has been on major depression, and there have been no published controlled studies of pharmacotherapy for dysthymic disorder or bipolar disorder in this age group. In addition, the gender differences in adolescent responses to psychopharmacologic treatments have yet to be fully explored.

#### **Major Depressive Disorder**

There is evidence from controlled studies that fluoxetine<sup>116,117</sup> and venlafaxine<sup>118</sup> are efficacious in the treatment of major depression in adolescents. It should be noted that these trials have not exceeded 8 weeks in length. The efficacy and safety of sertraline,<sup>119,120</sup> fluvoxamine,<sup>121</sup> and paroxetine<sup>122,123</sup> for the treatment of depression in children and adolescents are being explored. Detailed descriptions (including dosing, safety and tolerability, costs, drug-drug interactions, etc) of the use of these selective serotonin reuptake inhibitors in adolescents have recently been published.<sup>124-127</sup>

In general, the efficacy of tricyclic antidepressants has not been demonstrated in the treatment of major depression in children and adolescents,<sup>128-131</sup> and the evidence (or lack of evidence) for the use of monoamine oxidase inhibitors is only anecdotal. The efficacy and effectiveness of atypical and novel antidepressants (eg, trazodone, nefazodone, bupropion, venlafaxine, buspirone, and mirtazapine) in youth have yet to be explored in large-scale clinical trials.

#### **Dysthymic Disorder**

At present, medical opinion advocates for the treatment of dysthymia using principles

TABLE 3. PATIENT CHARACTERISTICS THAT MAY PREDICT POOR RESPONSE TO TREATMENT.	
Younger age	
High levels of cognitive distortion and hopelessness at intake	
Comorbid anxiety or conduct disorders	
Family psychiatric history	
Greater externalizing problems (eg, aggression, delinquency)	
Academic problems	
Nonvoluntary treatment referral	
Lack of cohesion with treatment group	
Born L, Steiner M. CNS Spectrums. Vol 6, No 2. 2001.	

applied in the treatment of major depression.<sup>127</sup>

#### **BURDEN OF ILLNESS**

The burden of depressive illness in adolescents is potentially pervasive and disabling. Depressed children and teenagers are at high risk for recurrence and for suicide attempt.<sup>132</sup> In a comparative study of young adults with or without major depression in adolescence, 45% of the adolescents with a history of major depression developed a new episode, 1.7% developed dysthymia, and 0.8% developed bipolar disorder between the ages of 19-24 years. The average annual recurrence rate for major depression was 9% over a 5-year period. Overall, subjects with adolescent major depression were significantly more likely to develop a DSM-IV Axis I disorder in young adulthood.<sup>133</sup> Opinion remains divided, however, about the influence of gender as a risk factor for future recurrence of major depression.132-134

Similarly, adolescents with subclinical depressive symptoms are at greater risk for an adult episode of major depression.<sup>133</sup> The like-lihood of recurrence of a major depressive episode or the occurrence of a first episode within 5 years following early onset of dys-thymia has been shown to be as high as 70%, regardless of treatment utilization.<sup>135</sup> For this reason, dysthymia has been conceptualized as a "gateway" to major depression and recurrent affective illness.<sup>1,136</sup>

Depression in young adolescent girls has been strongly associated with inconsistent use of birth control<sup>21</sup> and teenage pregnancy.<sup>137</sup> It has also been associated with higher rates of marriage and subsequent marital dissatisfaction,<sup>138</sup> increased risk for the initiation of tobacco smoking and dependence, alcohol abuse, and more medical problems.<sup>21,139,140</sup>

#### **CONCLUSION**

Following menarche, adolescent girls are at significantly greater risk for an episode of major depression. More than two thirds of those with a unipolar depressive illness have a comorbid mental disorder, frequently in the form of an anxiety disorder. Assessment using direct interviews and a depression screen is recommended, paying special attention to the context of adolescent depression, including recent stressful life events, personal and family psychiatric history, and interpersonal relationships. While treatment efficacy and long-term follow-up studies in this population are sparse, there is early convincing evidence of the efficacy of both psychotherapy (CBT and IPT-A) and psychopharmacotherapy (selective serotonin reuptake inhibitors) in the more immediate treatment of mild and more severe unipolar depression. The burden of depressive illness with onset in adolescence is staggering, with widespread and long-lasting ramifications. The increased risk for the onset of depression in young women following menarche, therefore, reinforces the importance of early recognition and intervention.<sup>141</sup>

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"Following menarche,

adolescent girls are at

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for an episode of major

depression. More

than two thirds of

those with a unipolar

depressive illness have

a comorbid mental

disorder, frequently

in the form of an

anxiety disorder."

"...there is early

convincing evidence

of the efficacy of both

- psychotherapy (CBT
- and IPT-A) and

psychopharmacotherapy

(selective serotonin

reuptake inhibitors)

in the more immediate

treatment of mild

and more severe

unipolar depression."

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"The burden

of depressive

illness with onset

in adolescence is

staggering, with

widespread and

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