Major Depressive Disorder in Children and Adolescents: Clinical Trial Design and Antidepressant Efficacy

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Major depressive disorder is a common, chronic, recurring, and disabling illness in children and adolescents. Epidemiologic data suggest that the mean age at onset for depression is becoming younger. Antidepressants are widely used in pediatric patients despite a relatively small evidence base from randomized, controlled studies. Compared with the adult population, there are very few controlled studies of antidepressants in children and adolescents, and the studies that have been conducted do not unambiguously demonstrate efficacy. These findings in general are contrary to clinicians' experiences with antidepressants in this population. The different factors associated with the outcome of antidepressant studies in children and adolescents are reviewed. Developmental issues in pediatric patients, such as age of puberty and maturity of neural circuitry, are considered in the context of failed clinical trials. Review of existing controlled trials demonstrates a wide variety in study methodology. Factors such as the study location, methods of patient recruitment, small sample sizes, inclusion/exclusion criteria, study design, and choice of outcome measures all influence the ability of a study to detect differences between an antidepressant and placebo. In the current atmosphere of increased concern about antidepressant side effects, including suicidality, it is increasingly important that clinicians who treat depressed children and adolescents make informed therapeutic decisions based on data from well-controlled clinical trials. *(J Clin Psychiatry 2005;66[suppl 7]:14–20)*

Major depressive disorder is a common illness in children and adolescents, and secular rates are believed to be increasing.[1–3] Prevalence rates of major depressive disorder in children range from 0.4% to 2.5%.[4] The lifetime prevalence rate of 15.3% for adolescents is similar to the lifetime prevalence rate of 16.2% in adults,[1,5] which suggests that major depressive disorder may begin in adolescence. The mean age at onset of major depressive disorder has become progressively younger. In a study conducted over 10 years ago, the age at onset was 11.6 years for children born in 1969 or 1970, but 9.9 years for children born from 1973 to 1975.[6]

Major depressive disorder in children and adolescents is a chronic disorder. Episodes of major depressive disorder often persist for up to 9 months, which is the duration of a single school year.[7] As in adults, child and adolescent depression is frequently recurrent, with 70% of patients experiencing a recurrence of major depressive disorder within 5 years of the initial episode.[8,9] A substantial minority of patients with major depressive disorder (20% to 40%) eventually are diagnosed with bipolar disorder.[9,10]

Major depressive disorder is a serious illness and is associated with increased suicide risk, dysfunctional social and family relationships, underachievement or failure in school, comorbid anxiety disorders, tobacco use, substance/alcohol abuse, and teen pregnancy.[11] Development of newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, and others, has broadened the choices of pharmacologic treatment for children and adolescents with major depressive disorder. However, evidence from clinical studies of efficacy in this population falls far short of ideal.[12] This article reviews the developmental processes in major depressive disorder and examines the available data from clinical studies of antidepressant treat-

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ment of major depressive disorder in children and adolescents. Factors contributing to the outcome of antidepressant studies in this population are considered.

CHILDHOOD DEVELOPMENT AND MAJOR DEPRESSIVE DISORDER

There is relative phenomenological continuity of major depressive disorder with development. Depression in children and adolescents is genetically and familially transmitted and appears to be similar to depression in adults with regard to clinical presentation and longitudinal course.[13,14] One particularly salient issue pertaining to developmental processes and major depressive disorder relates to puberty. Rates of depression in prepubertal boys and girls are equivalent and increase with age for both sexes. However, the relative rates of depression change dramatically at puberty and beyond, when girls are twice as likely to have depression as boys, with a female:male ratio of 2:1 at this stage of the life cycle.[15]

The increased prevalence of major depressive disorder in girls is related to puberty (i.e., Tanner stage), not to chronological age, which has implications for the presentation and course of the disorder.[16] Increased rates of depression in pubertal girls are very probably related to changes in levels of reproductive hormones as has been suggested by Angold and associates[17] and others. However, changes in the hormonal milieu, including fluctuating levels of gonadal hormones and growth hormone, may not be the only factors that contribute to increased rates of depression in pubertal girls.

The mean age at menarche is decreasing, particularly in developed countries.[18,19] A review of large cross-sectional studies in the United States reported that 50% of girls achieve Tanner breast stage 2 by 9 to 10 years of age.[19] Ethnic differences are important in the age at onset of puberty. The findings of a cross-sectional study of more than 17,000 girls demonstrated that 48.3% of African American girls reach Tanner stage 2 by 8 years of age compared with 14.7% of white girls of the same age.[20] The severity of depressive symptoms may also be related to menarche. Young, sexually mature girls experience more pronounced dysphoric symptoms compared with girls who are older at menarche.[21,22] An 8-year-old girl who is physically mature may be less well equipped to cope with the social and interpersonal pressures associated with sexual maturity than a 14-year-old girl. There is a general increase in risk-taking and novelty-seeking with sexual maturation.[23] Earlier puberty also is associated with an earlier age at onset of tobacco use, alcohol use, and sensation-seeking.[23,24] Thus, vulnerability to depression in adolescents, particularly girls, is probably related to the combined influences of heritable traits, sexual maturation, neuroendocrine effects of fluctuating reproductive hormones, support systems, life stressors, and gender socialization.[25,26]

Correlates of neurobiological function also demonstrate developmental pathways. Despite similarities in the course of illness, clinical presentation, and some neurobiological findings, there are significant discrepancies between the depression that occurs in children and adolescents and that observed in adults. For example, some neurobiological correlates in children and adolescents differ from those in adults, as do the patterns of response to antidepressant treatment. Depressed children and adolescents differ from adults with depression on a number of neurobiological measures of hypothalamic-pituitary-adrenal axis function, as reviewed by Kaufman and colleagues.[27] Depressed adults often demonstrate basal cortisol hypersecretion, but studies of children and adolescents with depression[27] have not reported this finding. Similarly, depressed adults have been shown to exhibit basal cortisol hypersecretion and blunted corticotropin secretion following administration of corticotropin-releasing hormone.[27] However, studies in depressed children and adolescents failed to reproduce the findings from adult populations.[27]

The tricyclic antidepressants (TCAs) are not effective in the treatment of depression in children and adolescents.[28–30] In contrast, the SSRIs, which primarily exert activity on the serotonergic system, have been shown to have somewhat greater efficacy than the TCAs in children and adolescents.[28,29] Nonetheless, high rates of treatment response to the SSRIs have not been demonstrated consistently across studies.

Neural pathways that are implicated in the pathophysiology of depression mature at different rates. For example, maturation of serotonergic systems in the prefrontal cortex reaches adult levels by 6 months of age in nonhuman primates,[31] which translates to approximately 6 years of age for human children.[27] However, maturation of noradrenergic and dopaminergic synthesis and circuits occurs at a slower rate, continuing through puberty for noradrenergic systems and adulthood for dopaminergic systems.[32] There are complex interactions between neural systems, reproductive hormones, and stress-related hormones that regulate behavioral affect. The developmental trajectory of these important neurobiological systems may underlie the failure of noradrenergic therapies (e.g., TCAs) as antidepressant treatments and the somewhat greater, albeit still suboptimal, responses seen with serotonergic agents.[32] Longitudinal studies that include measures of neurobiological correlates and treatment response in depressed children and adolescents will enable a better understanding of the role of these developmental processes in the differences between depression in youngsters and adults.

ANTIDEPRESSANT TRIALS IN CHILDREN AND ADOLESCENTS

Progress in the treatment of depression in adults has far outpaced that in children and adolescents. In the last 2

decades of the 20th century, there were more than 200 placebo-controlled trials of antidepressants in adults with depression. However, during that same period of time, only 12 placebo-controlled trials in depressed children and adolescents were published,[27] and a substantial majority of trials did not demonstrate high rates of efficacy.

Why is it that the controlled studies of antidepressants in children and adolescents with major depressive disorder have failed to show efficacy? For purposes of this discussion, efficacy is defined as statistically significant separation from placebo. Antidepressant trials are associated with high rates of placebo response.[33] It has been suggested that the methodologies used in clinical trials are inadequate to ensure unbiased double-blind conditions, which results in an inability to detect true differences between antidepressants and placebo.[34]

Double-blind, placebo-controlled trials[30,35–41] of TCAs in the treatment of depressed youths have not demonstrated superiority of TCAs over placebo. To date, the only class of antidepressant medications that has demonstrated superiority to placebo in the treatment of depression in children and adolescents is the SSRIs. Therefore, SSRIs are considered first-line treatment for depression in youths.[42]

Positive Trials

Fluoxetine is the only antidepressant medication that has U.S. Food and Drug Administration (FDA) approval for the treatment of depression in youths.[43] There have been 3 double-blind, placebo-controlled trials[44–46] that demonstrated the superiority of fluoxetine to placebo in the treatment of youths with major depression. There is 1 positive study[47] of citalopram for the treatment of major depression in 174 child and adolescent outpatients. As early as week 1, significantly more of the citalopram-treated patients compared with placebo-treated patients showed improvement in the Children's Depression Rating Scale-Revised (CDRS-R) score.[47] The efficacy of sertraline was evaluated in a prospectively defined combined analysis of 2 identical multicenter, double-blind, placebo-controlled studies of 376 children and adolescent outpatients with major depression.[48] There was a statistically significant difference between the sertraline and placebo groups in change in CDRS-R score from baseline to endpoint.

Negative Trials

There have been 3 multicenter studies[36,49,50] (275, 206, and 286 youths, respectively) of the efficacy and safety of paroxetine for the treatment of youths with major depression, all of which were negative on the primary outcome measure. In a European double-blind, placebo-controlled trial that included both inpatient and outpatient adolescents with major depression, citalopram was not statistically superior to placebo.[51] Escitalopram was shown not to be significantly superior to placebo in a multicenter, double-blind, placebo-controlled trial of 264 children and adolescents with major depression.[52]

There have been 2 multicenter, double-blind, placebo-controlled studies of venlafaxine for the treatment of major depression in 165 and 201 child and adolescent outpatients, respectively, both of which were negative on the primary outcome measure of change in CDRS-R scores from baseline to endpoint.[53] Two multicenter trials of nefazodone for the treatment of major depression, 1 in adolescents and 1 in children and adolescents, did not demonstrate the superiority of nefazodone to placebo in the primary outcome measure of change from baseline to endpoint in the CDRS-R score.[54] There have been 2 multicenter, double-blind, placebo-controlled trials of mirtazapine for the treatment of 126 and 133 youths, respectively.[51] There was no statistically significant difference between mirtazapine and placebo in the primary efficacy measure of change from baseline to endpoint in the CDRS-R score for either of these studies.

Suicidality and Antidepressants

The FDA issued a Public Health Advisory[55] based on a combined analysis of short-term, placebo-controlled trials of 9 antidepressant medications in children and adolescents with major depressive disorder, obsessive-compulsive disorder, or other psychiatric disorders. It was found that the risk of suicidality (suicidal thinking and behavior) was 4%, which was twice the placebo risk of 2%. There were no suicides in any of these studies. The FDA directed manufacturers to add a black box warning to the health professional label of antidepressant medications to describe the increased risk of suicidal thoughts and behavior in children and adolescents treated with antidepressant medications and to emphasize the need for close monitoring of these patients.[56] This black box warning applies to all antidepressants, whether or not they have been studied in children and adolescents.

Both the American Psychiatric Association[57] and the American Academy of Child and Adolescent Psychiatry[58] raised objections to the black box warning because of concern that it may result in a reduction of appropriate prescribing for youths who would benefit from antidepressant treatment. Recently, the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry in consultation with a national coalition of concerned parents, providers, and professional associations published information for patients and families as well as for physicians on the use of medications in treating childhood and adolescent depression.[59] The ParentsMedGuide provides advice to parents regarding treatment decisions for their children with depression, and the PhysiciansMedGuide provides clinical data about the FDA's black box warning regarding antidepressants in youths.

Methodological Issues in Antidepressant Trials

Researchers and clinicians who treat children and adolescents with major depressive disorder are frustrated by the findings of the existing antidepressant trials. Based on clinicians' experience in the field, the SSRIs offer many benefits to depressed pediatric patients, but the trials do not, thus far, provide unequivocal support for the use of these agents. In the current environment of caution about antidepressant side effects, there is a real need to base treatment decisions on data from well-designed studies. The discrepancy between clinical experience and findings of randomized, controlled studies provides a rationale for a reexamination of the existing clinical trials and consideration of possible reasons why some non-tricyclic antidepressants have not been shown to be effective treatment of major depressive disorder in children and adolescents.

There are some issues of semantics that are important to consider when discussing trial outcome. A failed trial is one that, for a variety of methodological reasons, is not able to show differences between treatment arms when in fact actual differences exist. In other words, the trial fails to demonstrate real differences between treatments. A failed trial is distinct from a negative trial. In a negative trial, study design is adequate to show between-group differences, and the investigational drug is proven to be no more effective than placebo and/or less effective than standard therapy. Because of the high placebo response rates in a disorder such as major depressive disorder, a valid design for testing efficacy of a new antidepressant is a 3-arm, active-comparator study.[60] In a 3-arm study, the new drug is compared with both placebo and an antidepressant of proven efficacy (i.e., an active comparator). If an active comparator arm is not included in the study and the new drug is not shown to be superior to placebo, it cannot be concluded that the drug is ineffective, particularly when rates of placebo response are high.

There are a number of methodological features that could be altered to maximize antidepressant-placebo differences and avoid a failed trial. For purposes of this discussion, it is assumed that the SSRIs are effective treatments of major depressive disorder in children and adolescents. Clinical trial methods are not standardized, and factors such as site selection, patient recruitment, inclusion/exclusion criteria, study design, and outcome measures all affect the findings.

Site selection. The selection of the clinical sites where studies are conducted can be an important contributor to outcome. Some of the relevant variables associated with site selection include the overall number of sites, the number of patients per site, the nature of the site (e.g., academic center, commercial trial organization, community or general hospital), and the expertise of the staff at the sites. Examination of the fluoxetine,[44–46] paroxetine,[36,49,50] and sertraline[48] studies reveals that the number of patients per site and the type of site may have contributed to the overall drug-placebo differences. For example, the fluoxetine study by Emslie and associates[44] of 96 patients was conducted at a single academic medical center (i.e., 96 patients/site), and the SSRI-placebo difference in the percentage of patients with Clinical Global Impressions-Improvement scale (CGI-I) scores of 1 or 2 was 23%. The paroxetine study by Keller and colleagues[36] of 275 patients was conducted at 12 academic sites in the United States and Canada (i.e., 23 patients/site), and the SSRI-placebo difference in the percentage of patients with CGI-I scores of 1 or 2 was 17%. The sertraline study by Wagner et al.[48] enrolled 376 patients at 53 academic and community practice settings in the United States, Canada, and Central America (i.e., 7 patients/site) and showed a drug-placebo difference in percentage of patients achieving a CGI score of 1 or 2 of 10%.

Patient recruitment. Selection bias is another important factor that can influence the outcome of a clinical trial. Adolescent patients who are recruited from advertisements have been shown to achieve higher response rates to psychosocial treatment of depression than patients who were recruited by clinician referral,[61] possibly because the latter group may represent a subpopulation with more complicated, chronic, or treatment-refractory illness.

Inclusion/exclusion criteria. There is a strong clinical impression that the characteristics of the patient sample in antidepressant trials influence the observed response to treatment. Unfortunately, this hypothesis has not been studied. There is a suggestion in the literature that children and adolescents with less severe depression and shorter depressive episodes may have higher rates of placebo response than those with more severe or more persistent depression. Secondary analyses of existing databases in which treatment response is compared with severity or chronicity would be informative. It remains to be determined if clinical trials that limit enrollment to patients with more chronic or severe forms of illness (i.e., a baseline CDRS-R score of 45 or greater) will demonstrate a more robust difference between drug and placebo.

One important way in which clinical trials vary is the exclusion of certain comorbid disorders. Patients with suicidal behavior or serious psychiatric comorbidities, including bipolar disorder, substance use disorders, attention-deficit/hyperactivity disorder (ADHD), and personality disorders, are typically excluded from most randomized, controlled trials. There is greater variability among trials in patients with other, less serious disorders, such as anxiety disorders, eating disorders, and ADHD. A secondary analysis of the adolescent study of paroxetine, imipramine, and placebo[36] was conducted to determine the association of comorbid ADHD and placebo response. The findings of this post hoc analysis revealed that adolescents in this sample with comorbid ADHD had lower rates of response regardless of treatment assignment. In this population, ADHD was not associated with a higher rate of placebo

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response.[62] In addition, patients who are currently being treated with psychoactive agents or psychotherapy are often excluded from enrollment.

Study design. As would be expected, a number of elements of clinical study design affect the ability of the trial to minimize placebo response and uncover differences between treatments. One factor that has been employed, albeit inconsistently, across studies in an attempt to decrease rates of placebo response is the pre-trial placebo run-in period during which eligible patients receive placebo in an open or blinded fashion. In the positive fluoxetine studies,[44,45] the duration of the observation period was 3 weeks, which included a 1-week, single-blind placebo run-in. Patients who continued to fulfill diagnostic criteria for depression and did not exhibit evidence suggestive of a placebo response at the end of the 3-week period were randomly assigned to the trial.[44,45] The diagnostic observation period lasted 1 to 2 weeks in the paroxetine study, but no placebo run-in was employed.[36] In the 2 negative venlafaxine studies, patients underwent a 1- or 2-week, single-blind placebo run-in without a diagnostic observation period.[53]

The duration of the treatment period is another important element of study design. Studies that are of an insufficient duration will fail to detect between-group differences because patients may not have fully responded. The second fluoxetine study[45] assessed remission, which was defined as a CDRS-R score of 28 or lower, at the 8-week endpoint. Although the rates of remission for fluoxetine (41%) were significantly greater than for placebo (20%; $p < .01$) at endpoint, many patients remained ill.[45] It is not known if a longer period of treatment would have resulted in greater rates of remission. The optimal duration of therapy needed to determine differences between drug and placebo in depressed children and adolescents is not known.

There are no randomized, controlled, fixed-dose studies of SSRIs in depressed children and adolescents. The available studies either evaluate a single dosage level or titrate the dose to a predetermined maximum level. Thus, it is not known if the SSRIs are being administered in optimal doses, particularly for children. Fixed-dose studies that compare low doses, such as 5 mg of paroxetine or 50 mg of sertraline, with higher doses would also be valuable in assessing the relationship between negative trial outcome and premature study discontinuation due to adverse effects. In the sertraline trial,[48] dropout rates due to adverse effects were 9% for patients in the sertraline group and 3% for placebo-treated patients. Of the 17 patients in the sertraline group who were withdrawn from the trial because of side effects, 13 were children,[48] suggesting that the dose may have been too high for this age group. Dose-finding studies that would inform the design of future trials as well as clinical practice are clearly needed.

Outcome measures. Outcome measures should be child-based. Studies that have been designed in recent years generally use the CDRS-R, which has become the standard rating scale for studies of child and adolescent depression. In contrast, the Hamilton Rating Scale for Depression (HAM-D) was developed for use in an adult population. The paroxetine study,[36] which was designed before the CDRS-R became accepted as the standard, utilized the HAM-D. In this study, the percentage of patients who were responders on the CGI-I was significantly higher in the paroxetine group (67%) than in the placebo group (48%; $p = .02$), but mean HAM-D total scores at endpoint were not significantly different ($p = .13$).[36] In addition, the second fluoxetine study[45] demonstrated significant differences between fluoxetine and placebo on the CDRS-R ($p < .001$) and Montgomery-Asberg Depression Rating Scale ($p = .02$), but no differences on the Hamilton Rating Scale for Anxiety ($p = .115$).[45] These findings suggest that the Hamilton rating scales may be less sensitive than other outcome measures in children and adolescents. Other factors that may affect the ability of a study to demonstrate differences between treatments include the use of cutoff scores versus change-from-baseline scores and the definition of criteria for response and remission.

CONCLUSION

Childhood and adolescent depression is a serious illness with possible long-term sequelae. The introduction of the SSRIs has resulted in some degree of improvement in the treatment of depression in this population, but response rates are far less than ideal. Overall, the results of available clinical trials are disappointing. There are many different and valid reasons why the literature does not reflect what many clinicians recognize, which is that the SSRIs and other newer antidepressants are of benefit to many children and adolescents with depression.

Children and adolescents can be a difficult population to recruit and retain in clinical studies. Generally, studies that have failed to demonstrate a difference between drug and placebo have had high placebo response rates. This appears to be more evident in children than in adolescents. Dose-finding studies are urgently needed. In addition, studies should include comparisons with both active treatment and placebo arms. A sufficient number of patients should be enrolled in order to detect a difference between drug and placebo. In the future, studies should include age-appropriate and developmentally appropriate rating scales as well as measures of quality of life, school performance, peer and family relationships, and effect on comorbid conditions and substance use and abuse.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nefazodone (Serzone and

others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–3105
2. Kovacs M. Depressive disorders in childhood: an impressionistic landscape. J Child Psychol Psychiatry 1997;38:287–298
3. Ryan ND, Williamson DE, Iyengar S, et al. A secular increase in child and adolescent onset affective disorder. J Am Acad Child Adolesc Psychiatry 1992;31:600–605
4. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years, pt 1. J Am Acad Child Adolesc Psychiatry 1996;35:1427–1439
5. Kessler RC, Walters EE. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. Depress Anxiety 1998;7:3–14
6. Kovacs M, Gatsonis C. Secular trends in age at onset of major depressive disorder in a clinical sample of children. J Psychiatr Res 1994;28:319–329
7. McCauley E, Myers K, Mitchell J, et al. Depression in young people: initial presentation and clinical course. J Am Acad Child Adolesc Psychiatry 1993;32:714–722
8. Kovacs M, Feinberg TL, Crouse-Novak M, et al. Depressive disorders in childhood, 2: a longitudinal study of the risk for a subsequent major depression. Arch Gen Psychiatry 1984;41:643–649
9. Rao U, Ryan ND, Birmaher B, et al. Unipolar depression in adolescents: clinical outcome in adulthood. J Am Acad Child Adolesc Psychiatry 1995;34:566–578
10. Strober M, Lampert C, Schmidt S, et al. The course of major depressive disorder in adolescents, 1: recovery and risk of manic switching in a follow-up of psychotic and nonpsychotic subtypes. J Am Acad Child Adolesc Psychiatry 1993;32:34–42
11. Fergusson DM, Woodward LJ. Mental health, educational, and social role outcomes of adolescents with depression. Arch Gen Psychiatry 2002;59:225–231
12. Whittington CJ, Kendall T, Fonagy P, et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341–1345
13. Kovacs M. Presentation and course of major depressive disorder during childhood and later years of the life span. J Am Acad Child Adolesc Psychiatry 1996;35:705–715
14. Weissman MM, Wolk S, Goldstein RB, et al. Depressed adolescents grown up. JAMA 1999;281:1707–1713
15. Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey, 1: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29:85–96
16. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychol Med 1998;28:51–61
17. Angold A, Costello EJ, Erkanli A, et al. Pubertal changes in hormone levels and depression in girls. Psychol Med 1999;29:1043–1053
18. Karlberg J. Secular trends in pubertal development. Horm Res 2002;57 (suppl 2):19–30
19. Lee PA, Guo SS, Kulin HE. Age of puberty: data from the United States of America. APMIS 2001;109:81–88
20. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99:505–512
21. Ge X, Kim IJ, Brody GH, et al. It's about timing and change: pubertal transition effects on symptoms of major depression among African American youths. Dev Psychol 2003;39:430–439
22. Kaltiala-Heino R, Marttunen M, Rantanen P, et al. Early puberty is associated with mental health problems in middle adolescence. Soc Sci Med 2003;57:1055–1064
23. Martin CA, Kelly TH, Rayens MK, et al. Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. J Am Acad Child Adolesc Psychiatry 2002;41:1495–1502
24. Wilson DM, Killen JD, Hayward C, et al. Timing and rate of sexual maturation and the onset of cigarette and alcohol use among teenage girls. Arch Pediatr Adolesc Med 1994;148:789–795
25. Born L, Shea A, Steiner M. The roots of depression in adolescent girls: is menarche the key? Curr Psychiatry Rep 2002;4:449–460
26. Steiner M, Dunn E, Born L. Hormones and mood: from menarche to menopause and beyond. J Affect Disord 2003;74:67–83
27. Kaufman J, Martin A, King RA, et al. Are child-, adolescent-, and adult-onset depression one and the same disorder? Biol Psychiatry 2001;49:980–1001
28. Cohen D, Gerardin P, Mazet P, et al. Pharmacological treatment of adolescent major depression. J Child Adolesc Psychopharmacol 2004;14:19–31
29. Ryan ND. Medication treatment for depression in children and adolescents. CNS Spectr 2003;8:283–287
30. Kye CH, Waterman GS, Ryan ND, et al. A randomized, controlled trial of amitriptyline in the acute treatment of adolescent major depression. J Am Acad Child Adolesc Psychiatry 1996;35:1139–1144
31. Goldman-Rakic PS, Brown RM. Postnatal development of monoamine content and synthesis in the cerebral cortex of rhesus monkeys. Brain Res 1982;256:339–349
32. Ryan ND, Varma V. Child and adolescent mood disorders: experience with serotonin-based therapies. Biol Psychiatry 1998;44:336–340
33. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 2002;287:1840–1847
34. Stolk P, Ten Berg MJ, Hemels ME, et al. Meta-analysis of placebo rates in major depressive disorder trials. Ann Pharmacother 2003;37:1891–1899
35. Kashani JH, Shekim WO, Reid JC. Amitriptyline in children with major depressive disorder: a double-blind crossover pilot study. J Am Acad Child Psychiatry 1984;23:348–351
36. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001;40:762–772
37. Preskorn SH, Weller EB, Hughes CW, et al. Depression in prepubertal children: dexamethasone nonsuppression predicts differential response to imipramine vs placebo. Psychopharmacol Bull 1987;23:128–133
38. Puig-Antich J, Perel JM, Lupatkin W, et al. Imipramine in prepubertal major depressive disorders. Arch Gen Psychiatry 1987;44:81–89
39. Kramer AD, Feiguine RJ. Clinical effects of amitriptyline in adolescent depression: a pilot study. J Am Acad Child Psychiatry 1981;20:636–644
40. Geller B, Cooper TB, Graham DL, et al. Double-blind placebo-controlled study of nortriptyline in depressed adolescents using a "fixed plasma level" design. Psychopharmacol Bull 1990;26:85–90
41. Kutcher S, Boulos C, Ward B, et al. Response to desipramine treatment in adolescent depression: a fixed-dose, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 1994;33:686–694
42. Hughes CW, Emslie GJ, Crismon MJ, et al. The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. J Am Acad Child Adolesc Psychiatry 1999;38:1442–1454
43. Food and Drug Administration (FDA). FDA Approves Prozac for Pediatric Use to Treat Depression and OCD. January 3, 2003. Talk Paper T03-01. Available at: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01187.html. Accessibility verified June 14, 2005
44. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031–1037
45. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41:1205–1215
46. Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: TADS randomized controlled trial. JAMA 2004;292:807–820
47. Wagner KD, Robb AS, Findling RL, et al. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. Am J Psychiatry 2004;161:1079–1083
48. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. JAMA 2003;290:1033–1041
49. Emslie G, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder [poster]. Presented at the 51st annual meeting of the American Academy of Child and Adolescent Psychiatry; October 19–24, 2004; Washington, DC
50. Milin R, Simeon J, Spenst W. Double-blind study of paroxetine in adoles-

cents with unipolar major depression [abstract]. American Academy of Child and Adolescent Psychiatry and Canadian Academy of Child Psychiatry Joint Annual Meeting; October 19–24, 1999; Chicago, Ill
51. Food and Drug Administration (FDA). Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Pediatric Advisory Committee. September 13–14, 2004. Available at: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm. Accessibility verified June 14, 2005
52. Wagner KD, Jonas J, Bose A, et al. Controlled trial of escitalopram in the treatment of pediatric depression [poster]. Presented at the 51st annual meeting of the American Academy of Child and Adolescent Psychiatry; October 19–24, 2004; Washington, DC
53. Emslie GJ, Findling RL, Yeung PP, et al. Efficacy and safety of venlafaxine ER in children and adolescents with major depressive disorder [poster]. Presented at the 157th annual meeting of the American Psychiatric Association; May 1–6, 2004; New York, NY
54. Rynn MA, Findling RL, Emslie GJ, et al. Efficacy and safety of nefazodone in adolescents with MDD [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
55. Food and Drug Administration (FDA). FDA Public Health Advisory. Suicidality in children and adolescents being treated with antidepressant medications. October 15, 2004. Available at: http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm. Accessibility verified June 14, 2005
56. Food and Drug Administration (FDA). News. FDA launches a multipronged strategy to strengthen safeguards for children treated with antidepressant medications. October 15, 2004. Available at: http://www. fda.gov/bbs/topics/news/2004/NEW01124.html. Accessibility verified June 14, 2005
57. American Psychiatric Association (APA). News release. APA responds to FDA's new warning on antidepressants. October 15, 2004. Available at: http://www.psych.org/news_room/press_releases/04-55apaonfdablackboxwarning.pdf. Accessibility verified June 14, 2005
58. American Academy of Child and Adolescent Psychiatry (AACAP). Comment on pending pediatric antidepressants warning. Joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee. September 28, 2004. Available at: http://www.aacap.org/announcements/AACAP_Comment.htm. Accessibility verified June 14, 2005
59. ParentsMedGuide.org. Available at: http://www.parentsmedguide.org. Accessibility verified June 14, 2005
60. Charney DS, Nemeroff CB, Lewis L, et al. National Depressive and Manic-Depressive Association consensus statement on the use of placebo in clinical trials of mood disorders. Arch Gen Psychiatry 2002; 59:262–270
61. Brent DA, Kolko DJ, Birmaher B, et al. Predictors of treatment efficacy in a clinical trial of three psychosocial treatments for adolescent depression. J Am Acad Child Adolesc Psychiatry 1998;27:906–914
62. Birmaher B, McCafferty JM, Bellew KM, et al. Comorbid ADHD and other disruptive behavior disorders as predictors of response in adolescents treated for major depression. Presented at the 153rd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill