# A Review of Pharmacotherapy of Major Depression in Children and Adolescents

Paul J. Ambrosini, M.D.

***Objective:*** **The review examined the historical progression and current status of pharmacotherapy of child and adolescent major affective disorder.** ***Methods:*** **A MEDLINE search was used to identify double-blind, placebo-controlled studies of child and adolescent major depression. Only studies that used reliable diagnostic and recovery parameters were included.** ***Results:*** **Few well-designed studies have compared placebo and tricyclic antidepressants in the treatment of major depressive disorder in children and adolescents. However, results consistently suggest that tricyclic antidepressants are not efficacious. Early results of double-blind placebo-controlled trials with fluoxetine and paroxetine have shown a significant drug effect. However, the results are inconsistent, which could reflect the ways that response to medication is defined, the ways that rating scales measure recovery, and uncertainties of dosing strategies with second-generation antidepressants. Hypothesized reasons for the unique response pattern in youths include the changing hormonal status of children, the differential maturation of the noradrenergic versus serotonergic neurotransmitter systems, and the possibility that a large proportion of depressed youths are in the early stages of bipolar disorder, which is not effectively treated by these medications.** ***Conclusions:*** **Tricyclic antidepressants are not superior to placebo for the treatment of child and adolescent major depressive disorder. Although two of three trials of second-generation antidepressants in this age group have had negative results, data suggest that these drugs may be more promising. It is too early in our investigation to know whether these agents will be effective in treating major depressive disorder in children and adolescents. (*Psychiatric Services* 51:627–633, 2000)**

The proliferation of newer classes of antidepressants with a wider margin of safety than the tricyclic antidepressants has led to increased use of these agents among children and adolescents, not only for affective disorders but also for anxiety and behavioral disorders. Their benefit in obsessive-compulsive disorder is based on relatively consistent results (1,2), which is not the case for management of behavior disorders in youths (3). The clinical efficacy studies of newer antidepressants for affective disorders in children and adolescents have had negative or marginal results.

The use of antidepressants for depressed children and adolescents, regardless of their limited benefit, continues because of the known morbidity associated with depressive illness, which includes an increased suicide rate (4), poorer psychosocial outcomes (5,6), and the potential chronic morbidity of the disorder (7–9), with few alternative modalities of care. Use of these medications for childhood affective disorders is also based on the premise of the similarity and continuity of major depressive disorder across age groups. However, this conceptualization may be a simplistic theory of affective disorders in youths. The phenotypic similarity noted in depressive symptoms between adults and children may not necessarily imply a genotypic concordance. This issue may be reflected in the variable efficacy of antidepressants among depressed children compared with their superiority to placebo for most adults with depression.

This review assesses the therapeutic benefits of antidepressants in child and adolescent major depression. It contrasts the therapeutic efficacy and characteristics of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) and discusses the future directions of antidepressant treatment of childhood and adolescent major depressive disorder. Nonpharmacological interventions such as interpersonal or cognitive-behavioral therapies are not addressed because few well-designed investigations in this area have been done (10), and no study comparing pharmacotherapy with cognitive therapeutic interventions has been undertaken.

## Methods

Articles pertaining to the pharmacotherapy of child and adolescent major depression were found in the

***Dr. Ambrosini*** *is associate professor of psychiatry at MCP–Hahnemann University and Eastern Pennsylvania Psychiatric Institute, 3200 Henry Avenue, Philadelphia, Pennsylvania 19129 (e-mail, paul.ambrosini@drexel.edu).*

MEDLINE database from the 1960s through 1999. The references from these articles were also used as a collateral source of previous studies. Studies were included in this review only if they were double-blind, placebo-controlled trials among either children or adolescents. Included were studies that used diagnostic assessments of proven reliability and those in which recovery was measured in a clinically acceptable manner with standardized rating instruments. Studies with samples of fewer than ten subjects were excluded.

## Results

The point prevalence rate of early-onset affective disorders in the general adolescent population is approximately 3 percent; it is less than 1 percent among preadolescents depending on the stringency of ascertainment methods (11,12). These rates approach adult patterns and also reflect the more traditional female predominance of depression by the later adolescent years. No direct concordance of psychological changes between adult and child depression has been found. However, general agreement exists that the onset of depression in childhood predicts future affective disturbances (7,8,13).

Of particular note is the disparity in the success of pharmacotherapy of depression between children and adolescents and adults. However, this finding is based on a paucity of well-designed drug treatment studies of affective disorders among children and adolescents. Over the past 30 years, the investigation of pharmacotherapy of child and adolescent affective disorders has generally progressed through three phases. These periods can be viewed as the early studies, the tricyclic antidepressant phase, and the second-generation antidepressant phase. Each has added a distinct understanding to our knowledge base.

### *The early studies*

The first studies, in the 1960s, investigating the pharmacotherapy of depressed children were quite flawed for several reasons. First, these reports described antidepressant response in a mixed diagnostic group of children with heterogeneous symptoms. Second, no consistent measurements were used to assess response, and well-designed treatment protocols were lacking. Finally, a mixed group of drugs was given, from minor tranquilizers to antidepressants (14). In fairness to these investigators, however, they began their work before the establishment of *DSM* criteria and the publication of *DSM* diagnostic interview schedules for children, such as the Diagnostic Interview for Children and Adolescents (DICA), the Diagnostic Interview Schedule for Children, and the childhood version of the Schedule for Affective Disorders and Schizophrenia (K-SADS). These early studies nonetheless established the fact that children and adolescents could tolerate adult pharmaceuticals safely if they were medically monitored.

***Editor's Note:*** This is the first in an occasional series of articles on use of psychopharmacology in the treatment of specific disorders and with specific populations. The articles were solicited by George M. Simpson, M.D., editor of the journal's Psychopharmacology column, who has found that some notable topics require more expansive treatment than is possible in the relatively short space of a column. Other articles in this series will focus on herbal medicines and on attention-deficit hyperactivity disorder across the life span.

### *The tricyclic phase*

The first well-designed, double-blind, placebo-controlled study of tricyclic antidepressants for childhood depression was reported in 1987 by Puig-Antich and associates (15). It examined use of imipramine for preadolescents. Earlier reports frequently had small sample sizes and used unvalidated response measures (14). Over the next decade additional double-blind studies using amitriptyline, desipramine, and nortriptyline were published. The results were consistently discouraging as tricyclic antidepressants were not found superior to placebo for treating prepubertal or adolescent major depression. These studies are summarized in Table 1. Meta-analyses of most of the studies further supported the marginal efficacy of these medications (16,17).

Although the outcomes of these studies were relatively consistent, the treatment designs varied considerably. Each used a structured interview (K-SADS) to ascertain initial depression status, but the entry criteria subsequently used for the randomization phase differed. Studies by Puig-Antich and colleagues (15), Kye and associates (18), and Birmaher and coworkers (19) required that each subject meet diagnostic criteria for major depressive disorder after placebo washout and at the time that they were randomly assigned to treatment. Geller and associates (20,21) and Kutcher and colleagues (22) required only that scores on depression severity scales remain persistently elevated before randomization.

Earlier studies excluded obviously inappropriate subjects with comorbid disorders, such as those with major depressive disorder who were psychotic and those with active substance abuse. However, only the most recently completed trials have excluded those with family histories of bipolar disorder in an attempt to exclude the bipolar genotype. These differences in sample selection could theoretically have some bearing on response patterns.

Each research group used a well-designed, aggressive pharmacotherapeutic strategy, most tracking plasma levels of tricyclic antidepressants. The length of treatment, which was relatively short in the earlier studies (about five weeks), was extended to ten weeks in successive studies in an attempt to maximize response (23). Criteria to measure response to the medication were based on a variety of depression rating scales or *DSM* symptom severity scores. However,

***Table 1***

Summary of double-blind, placebo-controlled studies of tricyclic antidepressants in the treatment of major depressive disorder among children and adolescents

| First author and year | Drug | Dose range | Duration (weeks) | Sample size | Patient characteristics | | | | Response rate (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age | Males | Females | Inpatient or outpatient | Placebo | Tricyclic |
| Puig-Antich, 1987 | Imipramine | 5 mg per kg | 5 | 38 | Prepubescent | 23 | 15 | Mixed | 68.2 (15/22) | 56.3 (9/16) |
| Geller, 1989 | Nortriptyline plasma level | Fixed | 8 | 50 | Prepubescent | 35 | 15 | Outpatient | 16.6 (4/24) | 30.8 (8/26) |
| Geller, 1990 | Nortriptyline plasma level | Fixed | 8 | 31 | Adolescent | 17 | 14 | Outpatient | 21.1 (4/19) | 8.3 (1/12) |
| Kutcher, 1994 | Desipramine | 200 mg | 6 | 42 | Adolescent | 15 | 27 | Outpatient | 36 (9/25) | 47.1 (8/17) |
| Kye, 1996[1] | Amitriptyline | 5 mg per kg | 8 | 31 | Adolescent | 22 | 9 | Outpatient | 56–72 | 15–85 |
| Birmaher, 1998[1] | Amitriptyline | 5 mg per kg | 10 | 27 | Adolescent | 8 | 19 | Inpatient | 77–78 | 57–86 |

[1] The response rates in these studies were ranges because they used multiple measures to assess response.

the variability in these parameters was quite extensive. For example, Puig-Antich and colleagues (15) and Geller and associates (20,21) used a relatively conservative definition of response—a score of less than 2 (indicating minimal symptoms)—on the K-SADS interview on most of the questions about *DSM* criteria for a major depressive disorder. The studies by Kutcher and associates (22), Kye and coworkers (18), and Birmaher and colleagues (19) used a wider definition of response, which included improvement rates on depression severity scales and analyses of response-remission status either among subjects who left the study—with the last observation carried forward—or among subjects who completed the study. These methodologies are frequently used in adult pharmacotherapy reports.

With the exception of the study by Birmaher and associates (19) that examined chronically depressed inpatients, the later studies noted some trends suggesting response as measured by scores on the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI), and the Clinical Global Impressions–Severity (CGI-S).

The investigation of the efficacy of tricyclic antidepressants for treating child and adolescent affective disorder is most likely at an end because of the mediocre response profile of these drugs. The cardiotoxicity of the tricyclic antidepressants, which makes them particularly lethal in overdoses, is also problematic (24). The toxicity is most striking when compared with the wide margin of safety in overdoses of SSRIs. However, this phase of investigation advanced the methodological implementation of pharmacotherapy of depressed children by standardizing diagnostic ascertainment and operationalizing response measurements.

Also, these investigations shed light on the drug response characteristics of children and adolescents with major depressive disorders. At the outset, most youths studied have moderate to severe depression as measured by either duration of the disorder or depression severity scores on standardized rating scales. Evidence suggests that those who view themselves as most severely depressed may respond less favorably to tricyclics (19), which implies that self-ratings of depression severity could be a valuable parameter to assess response patterns. The importance of self-ratings is further supported by the fact that clinicians tend to overrate improvement during treatment studies (25). A complementary issue is the finding that a substantial proportion of treated youths still exhibit subsyndromal depressive symptoms, so that partial remission may be more characteristic of treatment with tricyclic antidepressants (19,23).

No substantial evidence was found that comorbid diagnoses influenced recovery in youths treated with tricyclics. However, because comorbid problems are prevalent (26), ratings of recovery and remission from depression may be influenced by impairment resulting from comorbid disorders (27). The characteristics of the rating scales used to assess depression severity and response with the tricyclic antidepressants were infrequently analyzed. Although the BDI and the HDRS are validated indicators of affective disorder in adolescent samples (28,29) and the Children's Depression Rating Scale (CDRS) has been validated in child samples (30), only three instruments have been shown to be sensitive to pharmacotherapy in adolescents: the BDI, K-SADS-derived symptom severity scales (23), and the HDRS (Ambrosini and Tan, unpublished data, 1998). These instruments have not been reported to be sensitive to treatment effects in prepubertal children. Furthermore, the Children's Depression Inventory (CDI), which is used frequently for preadolescents, is not a sensitive scale for identifying major

***Table 2***

Summary of double-blind, placebo-controlled studies of selective serotonin reuptake inhibitors and new antidepressants in the treatment of major depressive disorder among children and adolescents

| First author and year | Drug | Dose range | Duration (weeks) | Sample size | Scale[1] | Patient characteristics | | | | Response rate (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age | Males | Females | Inpatient or outpatient | Placebo | Drug |
| Simeon, 1990 | Fluoxetine | 60 mg | 7 | 40 | HDRS<br>CGI-I | 13–18 | 18 | 22 | Mixed | 63<br>63 | 71<br>76 |
| Emslie, 1997 | Fluoxetine | 20 mg | 8 | 96 | CGI-I at exit<br>CDI-I at completion | 7–17 | 52 | 44 | Outpatient | 33<br>58 | 58<br>74 |
| Mandoki, 1997 | Venlafaxine | 37.5–75 mg | 6 | 33 | HDRS<br>CDRS | 8–18 | 25 | 8 | Outpatient | ns<br>ns | ns<br>ns |

[1] HDRS, Hamilton Depression Rating Scale; CGI-I, Clinical Global Impression–Improvement; CDRS, Children's Depression Rating Scale

depressive disorder in outpatient samples (31), nor has it been shown to be sensitive to pharmacotherapy.

### *The second-generation antidepressant studies*

Even though the selective serotonin reuptake inhibitors have been available for about a decade, few double-blind, placebo-controlled trials of their efficacy in depressed youths have been conducted. The lack of studies primarily reflects the general difficulty of introducing new pharmaceuticals in child populations. Secondly, the pharmaceutical industry has been reluctant to introduce antidepressant drug trials in an age group that was shown to be nonresponsive in previous trials of antidepressants. The proper methodological requirements for these studies also were debated for the reasons noted above.

Nonetheless, studies using fluoxetine, paroxetine, and venlafaxine have been completed. The overall results from these studies are more encouraging than those reported for the tricyclic antidepressants, as indications have been found of their superiority to placebo. However, these early findings must be viewed cautiously, as the outcomes are inconsistent either within or across studies. The results from the fluoxetine (32) and venlafaxine (33) studies, the only reports currently published, are summarized in Table 2.

Of the two fluoxetine studies (32,34), only that by Emslie and associates (32) noted a significant drug effect. The study investigated use of a fixed-dose paradigm (20 mg a day) in a mixed sample of 96 depressed children and adolescents. Subjects were treated for eight weeks following a three-week assessment and a one-week placebo lead-in. Diagnoses were ascertained with K-SADS and DICA interviews. At the time of random assignment to fluoxetine or placebo, each subject had a CDRS score greater than 40, indicating persistence of depressive symptoms, and continued to meet diagnostic inclusion and exclusion criteria. Primary response measures were weekly scores on the Clinical Global Impressions–Improvement (CGI-I) and CDRS scores.

At study exit, responses of subjects on fluoxetine were significantly superior to those on placebo. Fifty-six percent improved much or very much as measured by the CGI-I, while only 33 percent of placebo-treated youths responded. However, among study completers, no significant difference was found in response between subjects given fluoxetine (74 percent) and those given placebo (58 percent). This disparity was attributed to the larger proportion of nonresponding subjects who dropped out of the placebo group. When response as measured by the CGI-I was categorized by the time required to attain two consecutive weeks of much or very much improvement, fluoxetine again was superior to placebo.

Emslie and associates (32) further analyzed weekly CDRS scores as a continuous variable and followed a last-observation-carried-forward methodology. With this approach, the exit CDRS scores of subjects who did not complete the eight-week protocol were carried forward to fill in for successive missing values. This analysis supported the CGI-I findings and also found that a significant treatment effect with fluoxetine first emerged after five weeks of treatment. Neither age nor sex affected the results. However, secondary measures of general psychiatric symptomatology as assessed by the Brief Psychiatric Rating Scale, global functioning as measured by the Child Global Assessment Scale, and self-reported improvement as measured by the CDI and the BDI did not show a significant difference between the drug and placebo; however, the analyses did show a significant decrease in symptoms from baseline to study exit. The discrepancy among assessment measures was not explained. Furthermore, although a statistically significant improvement was noted, complete remission as defined by a CDRS score of less than 28 was uncommon; the exit CDRS mean score was 38.4, and the baseline CDRS mean score was 58.5.

Simeon and coworkers (34) studied a mixed sample of 30 outpatient

and inpatient adolescents who had a baseline HDRS score greater than 20 and a diagnosis of major depressive disorder. However, the method of ascertaining the diagnosis was not specified. Fluoxetine was titrated to a fixed dose of 60 mg per day, and treatment continued for seven weeks. Response measures were changes on the HDRS, the CGI, the Raskin Depression Scale, the Covi Anxiety Scale, and the 58-item Hopkins Symptom Checklist. Although a significant improvement was noted by three weeks of treatment, response to fluoxetine was not superior to response to placebo. Overall, approximately two-thirds of patients responded with either treatment as measured by improvement on the HDRS of greater than 50 percent.

Only one treatment study of a new second-generation non-SSRI antidepressant for treating depressed youths has been published. Mandoki and colleagues (33) compared venlafaxine to placebo among 40 children and adolescent outpatients. After a one-week placebo washout, venlafaxine was titrated to a fixed dose of either 37.5 mg a day for children 12 years old and younger or 75 mg a day for adolescents 13 years old and older. The method of diagnostic ascertainment was not specified. Response was measured after six weeks by changes in subjects' scores on the CDI, the Children's Behavioral Checklist (CBCL), the HDRS, and the CDRS. Weekly cognitive-behavioral-oriented therapy was given concurrently with pharmacotherapy.

Thirty-three subjects completed the study. Over time, a significant improvement was noted on the HDRS, the CDRS, and the CBCL, but no significant medication effect was noted, nor were any improvement effects observed as measured by the CDI. However, the study was limited by the relatively low dose of venlafaxine and the brief treatment period. Of note is the lack of drug effect as measured by the CDI.

A multisite double-blind study of adolescent major depressive disorder that compared paroxetine to imipramine and placebo was recently completed (35). Early reports of this study suggested that paroxetine was superior to imipramine and placebo; however, considerable inconsistencies were found in the results. The inconsistencies reflected the fact that efficacy of paroxetine depended on which definition of response and which rating scale was used.

The differential recovery rates as measured by different scales and by different definitions of response were recently analyzed in an open treatment study of sertraline for adolescents with major depressive disorder (36). The report noted that categorical recovery rates can range from 26 percent to 65 percent at six weeks of treatment and from 55 percent to 85 percent at ten weeks of treatment. Furthermore, clinician-rated recovery as measured by the CGI-I consistently gave the highest and quickest recovery rates, while self-rated improvement as measured by the BDI was the most potent measure in the later weeks of treatment.

*What has been gleaned from this phase of pharmacotherapeutic studies of major depressive disorder in children and adolescents suggests that predominantly serotonergic agents may be beneficial for depressive states and that treatment should be maintained for at least eight to ten weeks.*

The investigation of the efficacy of second-generation antidepressants for depressed youths is just beginning. As noted, few double-blind studies have been reported; however, studies of fluoxetine, nefazodone, sertraline, and venlafaxine are currently under way or planned. What has been gleaned from this phase of pharmacotherapeutic studies of child and adolescent major depressive disorder suggests that predominantly serotonergic agents may be beneficial for depressive states in youths and that treatment should be maintained for at least eight to ten weeks. However, the dataset is quite preliminary, and the studies require replication.

In the course of these studies, it also became more apparent that the lack of convergence across several depression rating scales is a potential liability in furthering our understanding of antidepressant treatment in this age group. The findings may be further confused by the continued use in treatment studies of scales such as the CGI scales and the CDRS that are not standardized as both valid and sensitive to pharmacotherapy effects. The different methods of defining response, although standardized, also have not been consistently used. Investigators are not consistent in reporting response rates across continuous and categorical measures at the time of exit from the study, with the last observation carried forward, or among those who completed the study. Therefore, it has not always been possible to compare qualitative and quantitative response rates across studies.

### *Ancillary data on pharmacotherapy*

Although this review focuses on double-blind, placebo-controlled trials of antidepressants for children and adolescents, numerous open-label studies of antidepressants in this age group have clarified some methodological and treatment strategies. An evaluation of length of treatment suggested that pharmacotherapy should last at least ten weeks (23,36).

Furthermore, the choice of rating scales to evaluate drug response can produce a 50 percent variation in categorical response rates (36). Augmentation with lithium (37,38) or a monoamine oxidase inhibitor (39) may have some benefit for subjects who do not respond to tricyclic antidepressants. Monitoring of plasma levels may define a therapeutic range in prepubertal and adolescent treatment with imipramine (15,40) or nortriptyline (23,41). In addition, newer antidepressants, such as nefazodone, appear well tolerated and potentially helpful for juvenile mood disorders (42).

## Discussion and conclusions

Several attempts have been made to explain the weak response patterns to antidepressants among youths with major depressive disorder. Methodological critiques have suggested that dosing may be inadequate, but inadequate dosing was not substantiated in later studies of tricyclics that monitored plasma levels. Nonetheless, inadequate dosing is a viable factor in the current round of studies with second-generation agents, because there does not appear to be a correlation between response and plasma levels of medication. The changing hormonal status of children and adolescents compared with adults was postulated to account for the poor response to tricyclics, but no convincing evidence that sex hormones can consistently augment antidepressant response has been found.

The differential maturation of the noradrenergic versus serotonergic neurotransmitter systems has been proposed as an explanation of both the lack of response with the more noradrenergic agents, such as desipramine, and the initial positive response with fluoxetine (43). At this time, the hypothesis can be tested only indirectly by assessing the response patterns to the newer antidepressants that selectively affect one or both neurotransmitter systems.

Finally, it has been suggested that the pool of depressed youths studied represents a more heterogeneous sample of depressive subtypes than comparable adult cohorts. Early-onset depressive disorders frequently evolve into a bipolar pattern (44-46). Given this fact, Geller and colleagues (47) tested the hypothesis that poor response to antidepressants among preadolescents with major depressive disorder could be secondary to their high bipolar potential. However, lithium was not superior to placebo in this study, even though subjects were stratified according to family history of bipolarity.

The pattern of results reviewed here could therefore suggest that affective disorders among children and adolescents represent a distinct biological entity that has a differing response pattern to pharmacotherapy than adult-onset affective disorder. It could then be postulated that adults with depression who are nonresponsive to pharmacotherapy are in that group of adults with childhood-onset affective disorder (48).

Antidepressants are widely used to treat major depressive disorder among children and adolescents. Because of the significant morbidity of the disorder, this treatment seems appropriate despite the relative absence of evidence from controlled studies indicating antidepressant efficacy in youths. Psychotherapy or the newer classes of antidepressants may be shown to be efficacious, but until these studies are completed the treatment of child and adolescent major depressive disorder remains a difficult undertaking for the clinician and for patients and their families. ♦

### *References*


1. March JS, Biederman J, Wolkow R, et al: Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA 280:1752–1756, 1998
2. Riddle MA, Scahill L, King RA, et al: Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. Journal of the American Academy of Child and Adolescent Psychiatry 31:1062–1069, 1992
3. Elia J, Ambrosini PJ, Rapoport JL: Treatment of attention deficit-hyperactivity disorder. New England Journal of Medicine 340:780–788, 1999
4. Brent DA, Perper JA, Moritz G, et al: Suicide in affectively ill adolescents: a case-control study. Journal of Affective Disorders 31:193–202, 1994
5. Kovacs M, Goldston D: Cognitive and social cognitive development of depressed children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 30:388–392, 1991
6. Harrington R: The natural history and treatment of child and adolescent affective disorders. Journal of Child Psychology and Psychiatry 33:1287–1302, 1992
7. Kovacs M, Feinberg TL, Crouse-Novak M, et al: Depressive disorders in childhood: II. a longitudinal study of the risk for a subsequent major depression. Archives of General Psychiatry 41:643–649, 1984
8. Harrington R, Fudge H, Rutter M, et al: Adult outcomes of childhood and adolescent depression: I. psychiatric status. Archives of General Psychiatry 47:465–473, 1990
9. Kovacs M: Presentation and course of major depressive disorder during childhood and later years of the life span. Journal of the American Academy of Child and Adolescent Psychiatry 35:705–715, 1996
10. Brent DA, Holder D, Kolko D, et al: A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. Archives of General Psychiatry 54:877–885, 1997
11. Fleming JE, Offord DR, Boyle MH: Prevalence of childhood and adolescent depression in the community. Ontario Child Health Study. British Journal of Psychiatry 155:647–654, 1989
12. Lewinsohn PM, Hops H, Roberts RE, et al: Adolescent psychopathology: I. prevalence and incidence of depression and other DSM-III-R disorders in high school students. Journal of Abnormal Psychology 102:133–144, 1993
13. Lewinsohn PM, Rohde P, Klein DN, et al: Natural course of adolescent major depressive disorder: I. continuity into young adulthood. Journal of the American Academy of Child and Adolescent Psychiatry 38:56–63, 1999
14. Ambrosini PJ: Pharmacotherapy of child and adolescent major depression, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven, 1987
15. Puig-Antich J, Perel JM, Lupatkin W, et al: Imipramine in prepubertal major depressive disorders. Archives of General Psychiatry 44:81–89, 1987
16. Hazell P, O'Connell D, Heathcote D, et al: Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. British Medical Journal 310:897–901, 1995
17. Thurber S, Ensign J, Punnett AF, et al: A meta-analysis of antidepressant outcome studies that involved children and adolescents. Journal of Clinical Psychology 51:340–345, 1995
18. Kye CH, Waterman GS, Ryan ND, et al: A randomized, controlled trial of amitriptyline in the acute treatment of adolescent major depression. Journal of the American Academy of Child and Adolescent Psychi-

atry 35:1139–1144, 1996

19. Birmaher B, Waterman GS, Ryan ND, et al: Randomized, controlled trial of amitriptyline versus placebo for adolescents with "treatment-resistant" major depression. Journal of the American Academy of Child and Adolescent Psychiatry 37:527–535, 1998

20. Geller B, Cooper TB, Graham DL, et al: Double-blind placebo-controlled study of nortriptyline in depressed adolescents using a "fixed plasma level" design. Psychopharmacology Bulletin 26:85–90, 1990

21. Geller B, Cooper TB, Graham DL, et al: Pharmacokinetically designed double-blind placebo-controlled study of nortriptyline in 6- to 12-year-olds with major depressive disorder. Journal of the American Academy of Child and Adolescent Psychiatry 31:34–44, 1992

22. Kutcher S, Boulos C, Ward B, et al: Response to desipramine treatment in adolescent depression: a fixed-dose, placebo-controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry 33:686–694, 1994

23. Ambrosini PJ, Bianchi MD, Metz C, et al: Evaluating clinical response of open nortriptyline pharmacotherapy in adolescent major depression. Journal of Child and Adolescent Psychopharmacology 4:233–244, 1994

24. Walsh BT, Greenhill LL, Giardina EV, et al: Effects of desipramine on autonomic input to the heart. Journal of the American Academy of Child and Adolescent Psychiatry 28:1186–1192, 1999

25. Lambert MJ, Kingston MD, Edwards BC: Zung, Beck, and Hamilton Rating Scales as measures of treatment outcome: a meta-analytic comparison. Journal of Consulting and Clinical Psychology 54:54–59, 1986

26. Orvaschel H, Ambrosini PJ, Rabinovich H: Diagnostic issues in child assessment, in Handbook of Child and Adolescent Assessment. Edited by Ollendick TH, Hersen M, Hersen M. Needham Heights, Mass, Allyn & Bacon, 1993

27. Brent DA, Kolko DJ, Birmaher B, et al: A clinical trial for adolescent depression: predictors of additional treatment in the acute and follow-up phases of the trial. Journal of the American Academy of Child and Adolescent Psychiatry 38:263–270, 1999

28. Ambrosini PJ, Metz C, Bianchi MD, et al: Concurrent validity and psychometric properties of the Beck Depression Inventory in outpatient adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 30:51–57, 1991

29. McConville B, Ambrosini PJ, Somoza S, et al: Optimal cut-off points for depression rating scales in adolescent depression (abstr), in Scientific Proceedings of the American Academy of Child and Adolescent Psychiatry, Vol 11. Edited by Leventhal BL, Schwab-Stone ME. Washington, DC, American Academy of Child and Adolescent Psychiatry, 1995

30. Poznanski EO, Grossman JA, Buchsbaum Y, et al: Preliminary studies of the reliability and validity of the children's depression rating scale. Journal of the American Academy of Child Psychiatry 23:191–197, 1984

31. McLaughlin JL, Ambrosini PJ, Fallon T, et al: Validity parameters of the Children's Depression Inventory in pre-adolescent outpatients (abstr), in Scientific Proceedings of the American Academy of Child and Adolescent Psychiatry, Vol 13. Edited by Schwab-Stone ME. Washington, DC, American Academy of Child and Adolescent Psychiatry, 1997

32. Emslie GJ, Rush AJ, Weinberg WA, et al: A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Archives of General Psychiatry 54:1031–1037, 1997

33. Mandoki MW, Tapia MR, Tapia MA, et al: Venlafaxine in the treatment of children and adolescents with major depression. Psychopharmacology Bulletin 33:149–154, 1997

34. Simeon JG, Dinicola VF, Ferguson HB, et al: Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. Progress in Neuropsychopharmacology and Biologic Psychiatry 14:791–795, 1990

35. Wagner KD, Ryan ND: Multi-center trial of paroxetine and imipramine in the treatment of adolescent depression (abstr), in Scientific Proceedings of the American Academy of Child and Adolescent Psychiatry, Vol 14. Edited by Schwab-Stone ME. Washington, DC, American Academy of Child and Adolescent Psychiatry, 1998

36. Ambrosini PJ, Wagner KD, Biederman J, et al: Multi-center open label sertraline study in adolescent outpatients with major depression. Journal of the American Academy of Child and Adolescent Psychiatry 38:566–572, 1999

37. Ryan ND, Meyer V, Dachille S, et al: Lithium antidepressant augmentation in TCA-refractory depression in adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 27:371–376, 1988

38. Strober M, Freeman R, Rigali J, et al: The pharmacotherapy of depressive illness in adolescence: II. effects of lithium augmentation in nonresponders to imipramine. Journal of the American Academy of Child and Adolescent Psychiatry 31: 16–20, 1992

39. Ryan ND, Puig-Antich J, Rabinovich H, et al: MAOIs in adolescent major depression unresponsive to tricyclic antidepressants. Journal of the American Academy of Child and Adolescent Psychiatry 27:755–758, 1988

40. Strober M, Freeman R, Rigali J: The pharmacotherapy of depressive illness in adolescence: I. an open label trial of imipramine. Psychopharmacology Bulletin 26: 80–84, 1990

41. Geller B, Cooper TB, Chestnut EC, et al: Preliminary data on the relationship between nortriptyline plasma level and response in depressed children. American Journal of Psychiatry 143:1283–1286, 1986

42. Wilens TE, Spencer TJ, Biederman J, et al: Case study: nefazodone for juvenile mood disorders. Journal of the American Academy of Child and Adolescent Psychiatry 36:481–485, 1997

43. Ryan ND, Varma D: Child and adolescent mood disorders: experience with serotonin-based therapies. Biological Psychiatry 44:336–340, 1998

44. Geller B, Fox LW, Clark KA: Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. Journal of the American Academy of Child and Adolescent Psychiatry 33:461–468, 1994

45. Rao U, Ryan ND, Birmaher B, et al: Unipolar depression in adolescents: clinical outcome in adulthood. Journal of the American Academy of Child and Adolescent Psychiatry 34:566–578, 1995

46. Kovacs M, Pollock M: Bipolar disorder and comorbid conduct disorder in childhood and adolescence. Journal of the American Academy of Child and Adolescent Psychiatry 34:715–723, 1995

47. Geller B, Cooper TB, Zimerman B, et al: Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. Journal of Affective Disorders 51:165–175, 1998

48. Ambrosini PJ, Bianchi MD, Rabinovich H, et al: Antidepressant treatments in children and adolescents. I. Affective disorders. Journal of the American Academy of Child and Adolescent Psychiatry 32:1–6, 1993

## Change of Address

Authors of papers under peer review or being prepared for publication in *Psychiatric Services* are reminded to notify the editorial office of any changes in address. Please call the editorial office at 202-682-6070, or send updated information by fax to 202-682-6189 or by e-mail to psjournal@psych.org.