

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

MARTIN B. KELLER, M.D., NEAL D. RYAN, M.D., MICHAEL STROBER, Ph.D., RACHEL G. KLEIN, Ph.D., STAN P. KUTCHER, M.D., BORIS BIRMAHER, M.D., OWEN R. HAGINO, M.D., HAROLD KOPLEWICZ, M.D., GABRIELLE A. CARLSON, M.D., GREGORY N. CLARKE, Ph.D., GRAHAM J. EMSLIE, M.D., DAVID FEINBERG, M.D., BARBARA GELLER, M.D., VIVEK KUSUMAKAR, M.D., GEORGE PAPTAEODOROU, M.D., WILLIAM H. SACK, M.D., MICHAEL SWEENEY, Ph.D., KAREN DINEEN WAGNER, M.D., Ph.D., ELIZABETH B. WELLER, M.D., NANCY C. WINTERS, M.D., ROSEMARY OAKES, M.S., AND JAMES P. McCAFFERTY, B.S.

ABSTRACT

Objective: To compare paroxetine with placebo and imipramine with placebo for the treatment of adolescent depression. **Method:** After a 7- to 14-day screening period, 275 adolescents with major depression began 8 weeks of double-blind paroxetine (20–40 mg), imipramine (gradual upward titration to 200–300 mg), or placebo. The two primary outcome measures were endpoint response (Hamilton Rating Scale for Depression [HAM-D] score ≤ 8 or $\geq 50\%$ reduction in baseline HAM-D) and change from baseline HAM-D score. Other depression-related variables were (1) HAM-D depressed mood item; (2) depression item of the Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version (K-SADS-L); (3) Clinical Global Impression (CGI) improvement scores of 1 or 2; (4) nine-item depression subscale of K-SADS-L; and (5) mean CGI improvement scores. **Results:** Paroxetine demonstrated significantly greater improvement compared with placebo in HAM-D total score ≤ 8 , HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 or 2. The response to imipramine was not significantly different from placebo for any measure. Neither paroxetine nor imipramine differed significantly from placebo on parent- or self-rating measures. Withdrawal rates for adverse effects were 9.7% and 6.9% for paroxetine and placebo, respectively. Of 31.5% of subjects stopping imipramine therapy because of adverse effects, nearly one third did so because of adverse cardiovascular effects. **Conclusions:** Paroxetine is generally well tolerated and effective for major depression in adolescents. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(7):762–772. **Key Words:** paroxetine, imipramine, major depression, adolescent.

Accepted February 15, 2001.

From the Department of Psychiatry and Human Behavior, Brown University, Providence, RI (Dr. Keller); Department of Psychiatry, University of Pittsburgh School of Medicine (Drs. Ryan, Birmaher); UCLA Medical Center (Drs. Strober, Feinberg); New York University Child Study Center (Drs. Klein, Koplewicz); Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia (Dr. Kutcher); Department of Psychiatry, University of Pennsylvania, Philadelphia (Dr. Hagino); Department of Child and Adolescent Psychiatry, State University of New York at Stony Brook (Dr. Carlson); Center for Health Research, Portland, OR (Dr. Clarke); Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Dr. Emslie); Department of Psychiatry, Washington University School of Medicine, St. Louis (Dr. Geller); Department of Psychiatry, Grace-1WK Hospital, Halifax, Nova Scotia (Dr. Kusumakar); Department of Psychiatry, Sunnybrook Health Science Centre, University of Toronto (Dr. Papatheodorou); Department of Psychiatry, Oregon Health Sciences University, Portland (Drs. Sack, Winters); New York State Psychiatric Institute, New York (Dr. Sweeney); Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston (Dr. Wagner); Department of Psychiatry,

The treatment of depression in adolescents is an area of burgeoning interest. Unfortunately, few well-controlled, large-scale, randomized clinical trials have been conducted in this population. Data from the 1,769 adolescents and

Children's Hospital of Philadelphia (Dr. Weller); North America Medical Affairs, GlaxoSmithKline, Collegeville, PA (Ms. Oakes, Mr. McCafferty).

This study was supported by a grant from GlaxoSmithKline, Collegeville, PA. The authors acknowledge the contributions of the following individuals: Jill M. Abbott, Ellen Basian, Ph.D., Carolyn Boulos, M.D., Elyse Dubo, M.D., Mary A. Fristad, Ph.D., Joan Hebler, M.D., Kevin Kelly, Ph.D., Sharon Reiter, M.D., and Ronald A. Weller, M.D. Editorial assistance was provided by Sally K. Laden, M.S.

Reprint requests to Dr. Keller, Department of Psychiatry and Human Behavior, Brown University School of Medicine, 345 Blackstone Blvd., Providence, RI 02906.

0890-8567/01/4007-0762©2001 by the American Academy of Child and Adolescent Psychiatry.

young adult participants in the National Comorbidity Survey (Kessler and Walters, 1998) indicate a lifetime prevalence rate of 15.3% for major depression, comparable with the 17% lifetime prevalence of depression in adults (Kessler et al., 1994). As with adults, the course of major depression in adolescents is often characterized by protracted episodes, frequent recurrence, and impairment in social and academic domains (Rao et al., 1995). Suicide is the third leading cause of death in adolescents, and depressive disorders are strongly correlated with suicide attempts (Eisenberg, 1984; Kovacs et al., 1993). Depressed adolescents grow up to be depressed adults and, compared with healthy controls, have higher rates of suicide, psychiatric and medical hospitalizations, and impairment in work, family, and social lives (Weissman et al., 1999).

The efficacy of tricyclic antidepressants has been investigated in at least 11 double-blind, randomized studies (Dulcan et al., 1998; Ryan and Varma, 1998), none demonstrating superiority of active treatment over placebo. However, methodological deficiencies in these studies, including very small sample sizes and diagnostic heterogeneity, limit statistical inference and generalizability of the findings. At the same time, cardiovascular effects and lethality in overdose associated with the tricyclic agents have greatly limited their use in clinical practice.

Since the selective serotonin reuptake inhibitors (SSRIs) became commercially available, the safety, tolerability, and efficacy of these agents in treating major depression in adolescents have been noted in several open-label reports (Ambrosini et al., 1999; Apter et al., 1994; Masi et al., 1997; McConville et al., 1996; Rey-Sanchez and Gutierrez-Casares, 1997; Rodriguez-Ramos et al., 1996; Simeon et al., 1998). Placebo-controlled trials, which remain the standard against which efficacy is determined, number only two, both with fluoxetine (Emslie et al., 1997; Simeon et al., 1990). A small study by Simeon and associates (1990) was negative. In contrast, a large-scale trial by Emslie and colleagues (1997) showed a 23% drug-placebo difference in overall clinical improvement. The findings of a third study, which used a historical case-control design (Strober et al., 1999), suggested greater efficacy of fluoxetine compared with imipramine in a severely ill, inpatient population of adolescents with major depression. We now report principal findings from the first double-blind, placebo-controlled comparison of an SSRI, paroxetine, and a placebo-controlled comparison with a tricyclic antidepressant, imipramine, in the treatment of adolescents with major depression.

METHOD

Study Design

This was an 8-week, multicenter, double-blind, randomized, parallel-design comparison of paroxetine with placebo and imipramine with placebo in adolescents with major depression. The trial was conducted at 10 centers in the United States and 2 in Canada. Four hundred twenty-five subjects were screened for eligibility, and 275 subjects were randomly assigned to experimental treatment. The trial was conducted in accordance with good clinical practices and the Helsinki Declaration. All subjects and their parent(s) provided written informed consent before entry into the study; the identity of all subjects is completely blinded in this report. Funding for this study was provided by GlaxoSmithKline; each author had access to data and signed off on the manuscript before it was submitted for publication.

Patient Eligibility

Male and female subjects, aged 12 through 18 years, fulfilling the *DSM-IV* (American Psychiatric Association, 1994) criteria for a current episode of major depression of at least 8 weeks in duration were enrolled. Major depression was diagnosed by a systematic clinical interview which used the juvenile version of the Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version (K-SADS-L) rating scale. The K-SADS-L was developed by one of the authors (R.G.K.) through modification of the adult SADS assessment technique (Endicott and Spitzer, 1978) by providing uniform anchors so that symptoms were specifically rated for clinical relevance and by adding items to generate *DSM-IV* diagnoses. The K-SADS-L uses separate patient and parent reports to assess lifetime presence of affective and schizophrenic disorders, as well as the full range of childhood and adolescent psychopathological conditions. In addition to fulfilling *DSM-IV* criteria for major depression, subjects were required to have a total score of at least 12 on the 17-item Hamilton Rating Scale for Depression (HAM-D), a score of less than 60 on the Children's Global Assessment Scale, and a score of at least 80 on the Peabody Picture Vocabulary Test. All subjects were medically healthy.

Potential subjects in the study were screened initially by telephone, and candidates who were considered likely to meet diagnostic criteria were evaluated at the study site. Adolescents and parents were interviewed separately. For those cases in which there existed a significant discrepancy between information provided by the adolescent and information provided by the parent, the clinician met with both to discuss the information obtained and then rendered a rating. Eligible subjects and their parent(s) were required to reach agreement with the site investigator that the subject had a disorder requiring treatment. In cases in which the diagnosis was not certain, audiotapes of the screening interview were to be reviewed and the diagnosis was to be verified further by an independent expert from another participating site prior to certifying study eligibility.

Subjects with a current or lifetime *DSM-IV* diagnosis of bipolar disorder, schizoaffective disorder, eating disorder, alcohol or substance use disorder, obsessive-compulsive disorder, autism/pervasive developmental disorder, or organic brain disorder were excluded from consideration. A diagnosis of posttraumatic stress disorder within 12 months of recruitment was also exclusionary, as was current suicidal ideation with intent or specific plan, a history of suicide attempts by drug overdose, any medical condition in which the use of an antidepressant was contraindicated, current psychotropic drug use, an adequate trial of antidepressant medication within 6 months of study entry, or exposure to investigational drug use either within 30 days of

study entry or within five half-lives of the drug. Females who were pregnant or breastfeeding and those who were sexually active and not using reliable contraception were also excluded.

Blinding, Randomization, and Treatment

All subjects underwent a 7- to 14-day screening phase to determine persistence and severity of entry diagnostic and eligibility criteria and to obtain baseline global functioning scores, physical examination, and clinical laboratory studies. Placebo was not administered during the screening phase. By means of a computer-generated list, subjects who still met entry criteria were randomly assigned to an 8-week course of treatment with paroxetine, imipramine, or placebo in a 1:1:1 ratio. Tablets were overencapsulated in matching Supro B locking capsules to preserve medication blinding. Subjects assigned to paroxetine treatment received 20 mg/day in the morning for weeks 1 through 4. Optional dosage increases to 30 mg of paroxetine per day (divided dose) were allowed at week 5 and to 40 mg per day (divided dose) at weeks 6 through 8 if deemed necessary by the treating clinician. Imipramine treatment was initiated with a forced titration schedule in which subjects received daily doses of 50 mg during week 1, 100 mg during week 2, 150 mg during week 3, and 200 mg during week 4. Thereafter, optional dosage increases to 250 mg/day (during week 5) and to 300 mg/day (during weeks 6 through 8) were allowed if judged necessary by the research study clinician. Imipramine administration was divided between morning and evening for all daily doses of 100 mg or greater.

Subjects were instructed to take their medication twice daily, once in the morning and again in the evening. The number of active drug or matched placebo capsules administered per day was identical for each treatment group during forced titration. During weeks 1 and 2, subjects in the paroxetine or imipramine groups received one active drug capsule in the morning and one active drug or matched placebo capsule in the evening. Subjects in the placebo group received one capsule in the morning and one in the evening. During week 3, subjects received one active drug capsule in the morning and two active drug or matched placebo capsules in the evening. At week 4, subjects received one active drug capsule plus one matched placebo capsule in the morning and two active drug or matched placebo capsules in the evening. Beginning at week 5, subjects either remained at the week 4 dose level (i.e., four capsules per day) or were titrated upward to five or six capsules per day. Subjects who completed the study were offered the option of continuing blinded treatment at the same dose for 6 additional months. If subjects withdrew from the study prematurely for any reason, the dose of medication was gradually tapered over a 7- to 17-day period.

Supportive case management was provided to all subjects at each weekly clinic visit according to the method described by Fawcett et al. (1987). Such management was limited to psychosocial interaction that enabled observation of treatment effects. Interpersonal or cognitive-behavioral psychotherapeutic interventions were strictly prohibited.

Efficacy and Safety Evaluation

After randomization, subjects were seen at weekly intervals and evaluated with standardized instruments and global assessments for efficacy. The protocol described two primary outcome measures: (1) response, which was defined as a HAM-D score of ≤ 8 or a $\geq 50\%$ reduction in baseline HAM-D score at the end of treatment; and (2) change from baseline in HAM-D total score. Five other depression-related variables were declared a priori: (1) change in the depressed mood item of the HAM-D; (2) change in the depression item of the

K-SADS-L; (3) Clinical Global Impression (CGI) improvement scores of 1 (very much improved) or 2 (much improved); (4) change in the nine-item depression subscale of the K-SADS-L; and (5) mean CGI improvement scores.

Assessment of multiple domains of functioning, general health, and behavior consisted of (1) Autonomous Function Checklist, completed by the parent, which assessed the subject's autonomy in performing daily activities (Sigafos et al., 1988); (2) Self-Perception Profile, completed by the subject to measure self-esteem (Harter, 1988); and (3) Sickness Impact Scale, completed by the subject, to measure present health and quality of life (Bergner et al., 1981).

Adverse events, heart rate, blood pressure, and body weight were determined at each weekly visit. Rhythm strip electrocardiograms (ECGs) were obtained at each visit, and 12-lead ECGs were obtained during the screening phase and at weeks 4 and 8. Routine clinical laboratory studies were conducted during the screening phase and at week 8, or upon study withdrawal.

If changes in cardiovascular parameters occurred, then dosage reductions were required. Doses were reduced by 10 mg for paroxetine doses of 30 mg or 40 mg; subjects receiving 20 mg of paroxetine were withdrawn from the study. Similarly, imipramine doses of 250 mg or 300 mg per day were reduced by 50 mg, and subjects receiving ≤ 200 mg of imipramine were withdrawn from the study. Cardiovascular parameters necessitating dosage reduction or study withdrawal were defined prospectively as heart rate ≥ 110 beats per minute (bpm) at two consecutive visits or heart rate ≥ 130 bpm at a single visit; systolic blood pressure > 140 mm Hg or diastolic blood pressure > 85 mm Hg; PR interval ≥ 0.21 seconds; QRS interval ≥ 0.12 seconds and $\geq 150\%$ of baseline; or QT_c interval ≥ 0.48 seconds.

Blood samples were obtained from all patients at weeks 4 and 8 for determination of plasma concentrations of imipramine, desmethylimipramine (the major, pharmacologically active metabolite of imipramine), and paroxetine. Subjects were withdrawn from the study if the combined imipramine and desmethylimipramine concentration exceeded 500 ng/mL.

Statistical Methods

A sample size of 90 patients per arm was required to provide approximately 80% power to detect an effect size of 0.4 between an active regimen and placebo with an α level of 5% (two-tailed). The change from baseline in the HAM-D total score was used.

The efficacy analyses were performed on the population of patients who were randomized and had at least one postbaseline efficacy evaluation. Two datasets from this population were examined: (1) a last observation carried forward dataset in which the last observation on treatment was carried forward to estimate missing data for patients who withdrew prior to completing 8 weeks of treatment, and (2) a completer dataset that examined results in patients who received study medication for the full 8 weeks. Missing data were not estimated for the completer dataset.

Continuous variables, such as changes from baseline to endpoint in the HAM-D total score, CGI improvement scale, and K-SADS-L, were analyzed by a two-factor analysis of variance using the general linear model procedure of the Statistical Analysis System (SAS). The model included terms for treatment and investigator. Categorical variables, such as percentage of subjects responding to treatment, were analyzed with logistic analysis implemented in the categorical modeling procedure (CATMOD) of the SAS; the model included effects for investigator and treatment. Pairwise comparisons between each active treatment and placebo were two-tailed and performed at an α level of .05. Data are reported as least square means (\pm SD or SE).

RESULTS

Treatment groups were similar with regard to demographic characteristics and psychiatric profile (Table 1). Most subjects had a first-degree relative with major depression and were experiencing their first episode of major depression. The mean duration of the current depressive episode was more than 1 year, with a mean baseline HAM-D total score between 18 and 19. Features of melancholic or endogenous depression were exhibited by 35% to 40% of patients, and 20% had features of atypical depression. Despite exclusion criteria that limited many comorbid conditions, psychiatric comorbidity was common. Comorbid anxiety disorders, such as separation anxiety and social anxiety disorder, and externalizing disorders were present at the time of screening in 19% to 28% of subjects.

Premature Discontinuation

A total of 190 subjects (69% of 275) completed the 8-week study. Premature withdrawal rates were 24% for placebo, 28% for paroxetine ($p = .60$ versus placebo), and

40% for imipramine ($p = .02$ versus placebo). Premature study discontinuation due to adverse effects occurred at a rate of 6.9% in the placebo group. Study withdrawal due to adverse effects was the most common reason for discontinuation in the paroxetine (9.7%; $p = .50$ versus placebo) and imipramine (31.5%; $p < .01$ versus placebo) groups, respectively. Cardiac adverse effects consisting of tachycardia (8 patients), postural hypotension (2), prolonged QT intervals (2), arrhythmia (1), atrioventricular block (1), abnormal ECG (1), extrasystole (1), and hypertension (1) led to withdrawal among 14% of subjects in the imipramine group (13 subjects). Protocol violation, including lack of compliance, was the most common reason for withdrawal in the placebo group (8.0%).

Efficacy Results

Of the depression-related variables, paroxetine separated statistically from placebo at endpoint among four of the parameters: response (i.e., primary outcome measure), HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 (very much

TABLE 1
Demographic Characteristics and Mean Baseline Depression Scores for 275 Randomized Subjects

Parameter	Paroxetine (<i>n</i> = 93)	Imipramine (<i>n</i> = 95)	Placebo (<i>n</i> = 87)
Gender, M/F	35/58	39/56	30/57
Age, mean ± SD (yr)	14.8 ± 1.6	14.9 ± 1.6	15.1 ± 1.6
Race, no. (%)			
White	77 (82.8)	83 (87.4)	70 (80.5)
African American	5 (5.4)	3 (3.2)	6 (6.9)
Asian American	1 (1.1)	2 (2.1)	2 (2.3)
Other	10 (10.8)	7 (7.4)	9 (10.3)
CGAS, mean ± SD	42.7 ± 7.5	42.5 ± 7.4	42.8 ± 8.3
Duration of current depressive episode, mean ± SD (months)	14 ± 18	14 ± 18	13 ± 17
No. of prior depressive episodes (%)			
0	81	79	77
1	12	14	14
≥2	7	6	8
First-degree relative with major depression (%)	86	90	95
Age at onset of first episode, mean ± SD (yr)	13.1 ± 2.8	13.2 ± 2.7	13.5 ± 2.3
Mean baseline HAM-D total score	18.98 ± 0.43	18.11 ± 0.43	18.97 ± 0.44
Features of melancholic or endogenous depression	36	35	40
Features of atypical depression (%)	25	16	9
Current comorbid psychiatric diagnosis (%)			
Any diagnosis	41	50	45
Anxiety disorder ^a	19	26	28
Externalizing disorder ^b	25	26	20

Note: CGAS = Children's Global Assessment Scale; HAM-D = Hamilton Rating Scale for Depression.

^a Includes separation anxiety, panic ± agoraphobia, agoraphobia, social anxiety disorder, generalized anxiety disorder.

^b Includes conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder.

improved) or 2 (much improved) and trended toward statistical significance on two measures (K-SADS-L nine-item depression subscore and mean CGI score) (Table 2). The response to imipramine was not significantly different from that for placebo across any of the seven depression-related variables.

A total of 63.3% of paroxetine subjects (57/90; $p = .02$ versus placebo), 50% of imipramine subjects (47/94; $p = .57$ versus placebo), and 46% of placebo subjects (40/87) achieved a HAM-D total score of ≤ 8 at endpoint (Fig. 1). The time course of response in mean HAM-D total score is shown in Figure 2. Among patients who completed 8 weeks of treatment, 76.1% of paroxetine subjects (51/67; $p = .02$ versus placebo), 64.3% of imipramine subjects (36/56; $p = .44$ versus placebo), and 57.6% of placebo subjects (38/66) achieved a mean HAM-D total score of ≤ 8 . In the paroxetine group, 65.6% of patients were considered very much or much improved on the CGI ($p = .02$ versus placebo); rates for the imipramine and placebo groups were 52.1% ($p = .64$ versus placebo) and 48.3%, respectively. Improvement in baseline depressed mood as

measured by the HAM-D and the K-SADS-L depressed mood items was significantly greater than placebo in the paroxetine group, but not significantly greater than placebo in the imipramine group. Improvements in the K-SADS-L depression subscore ($p = .07$) and mean CGI score ($p = .09$) trended toward statistical significance in the paroxetine group, but not in the imipramine group ($p = .98$ and $p = .90$, respectively) (Table 2).

Although neither paroxetine nor imipramine separated statistically from placebo across the nonsymptom measures of functioning, health, and behavior, improvements over baseline were achieved for each active treatment group. Placebo-treated subjects also improved along the behavioral measures, but to a lesser extent than patients in the active treatment groups.

Dosage Titration

Nearly half of subjects in the paroxetine group remained at the initial starting dose of 20 mg/day (48%). Mean dose at study endpoint for paroxetine was 28.0 mg (SD ± 8.54 mg) and for imipramine was 205.8 mg (SD

TABLE 2
Mean Scores of Depression-Related Variables in Adolescents With Major Depression^a
Who Were Treated With Paroxetine, Imipramine, or Placebo

Variable	Paroxetine				Imipramine				Placebo		
	Mean	(SE)	<i>n</i>	<i>p</i> ^b	Mean	(SE)	<i>n</i>	<i>p</i> ^b	Mean	(SE)	<i>n</i>
HAM-D ≤ 8											
Week 8 endpoint	63.3%	(—)	90	.02	50.0%	(—)	94	.57	46.0%	(—)	87
HAM-D ≤ 8 or 50% reduction in baseline HAM-D											
Week 8 endpoint	66.7%	(—)	90	.11	58.5%	(—)	94	.61	55.2%	(—)	87
HAM-D depressed mood item											
Baseline	2.99	(0.08)	90		2.79	(0.08)	94		2.86	(0.08)	87
Week 8 endpoint	0.99	(0.14)	9	.001	1.17	(0.14)	94	.14	1.53	(0.14)	87
K-SADS-L depressed mood item											
Baseline	4.57	(0.09)	83		4.29	(0.09)	87		4.63	(0.09)	85
Week 8 endpoint	2.37	(0.18)	83	.05	2.52	(0.18)	87	.87	2.90	(0.18)	85
CGI score of 1 or 2 ^c											
Week 8 endpoint	65.6%	(—)	90	.02	52.1%	(—)	94	.64	48.3%	(—)	87
K-SADS-L 9-item depression subscore											
Baseline	28.25	(0.52)	83		27.54	(0.51)	88		28.84	(0.52)	85
Week 8 endpoint	16.59	(0.84)	83	.07	17.99	(0.83)	88	.98	19.27	(0.83)	85
Mean CGI score											
Week 8 endpoint	2.37	(0.16)	90	.09	2.70	(0.15)	94	.90	2.73	(0.16)	87
HAM-D total score											
Baseline	18.98	(0.43)	90		18.11	(0.43)	94		18.97	(0.44)	87
Week 8 endpoint	8.24	(0.81)	90	.13	9.2	(0.81)	94	.87	9.88	(0.83)	87

Note: HAM-D = Hamilton Rating Scale for Depression; K-SADS-L = Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version; CGI = Clinical Global Impression.

^a The last evaluation during treatment for subjects who did not complete the entire study (i.e., the last observation carried forward) is reported.

^b The *p* values compare treatment difference in active versus placebo groups.

^c CGI score of 1 = very much improved; CGI score of 2 = much improved.

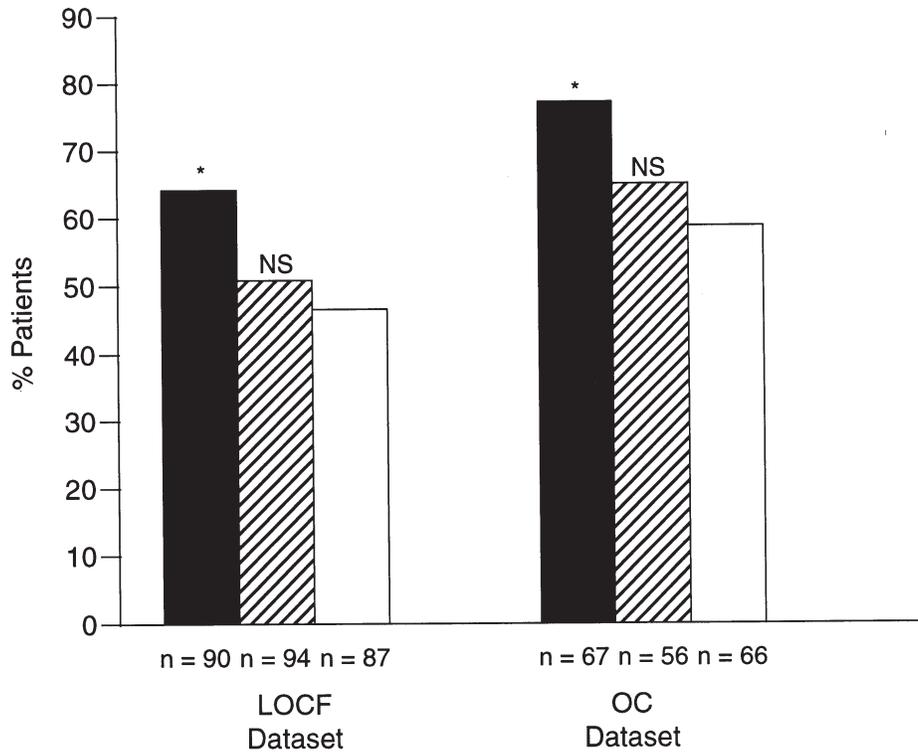


Fig. 1 Percentage of subjects treated with paroxetine (■), imipramine (▨), and placebo (□) who achieved a HAM-D total score ≤ 8 in the LOCF and completer (OC) subgroups at week 8. * $p = .02$; NS = $p \geq .44$. HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward; OC = observed cases.

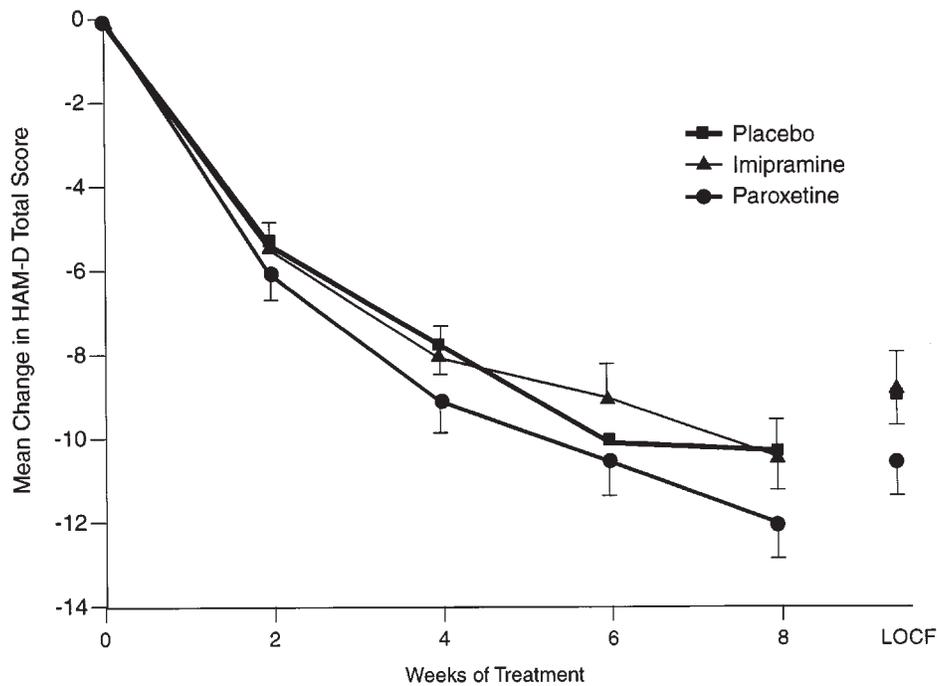


Fig. 2 Least square mean change HAM-D total score (\pm SEM) during an 8-week course of paroxetine ($n = 90$), imipramine ($n = 94$), and placebo ($n = 87$) administration in adolescents with major depression. HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward.

± 63.94 mg). The most common "doses" of placebo (administered as divided doses) were four capsules per day (31.0%) and six capsules per day (41.4%).

Adverse Effects

Paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious. The most common adverse effects reported during paroxetine therapy were headache, nausea, dizziness, dry mouth, and somnolence (Table 3). These occurred at rates that were similar to rates in the placebo group with the exception of somnolence, which occurred at rates of 17.2% for paroxetine and 3.4% for placebo. Dizziness, dry mouth, head-

ache, nausea, and tachycardia were most commonly reported during imipramine treatment. Tremor occurred in 10.8% of paroxetine-, 14.7% of imipramine-, and 2.3% of placebo-treated subjects.

Adverse effects in all treatment groups occurred most often during the first week of therapy. Dosage reductions were most often required for somnolence, insomnia, and restlessness among paroxetine-treated subjects. Dry mouth, constipation, and tremor were the most common adverse effects leading to imipramine dose reductions. Premature withdrawal from the study because of adverse effects occurred at rates of 9.7% for paroxetine, 31.5% for imipramine, and 6.9% for placebo. Clinically significant

TABLE 3
Adverse Effects Occurring in $\geq 5\%$ of Subjects in the Paroxetine, Imipramine, and Placebo Groups

Adverse Effect	Paroxetine (n = 93)	Imipramine (n = 95)	Placebo (n = 87)
Cardiovascular system			
Tachycardia	2 (2.2)	18 (18.9)	1 (1.1)
Postural hypotension	1 (1.1)	13 (13.7)	1 (1.1)
Vasodilation	0 (0)	6 (6.3)	2 (2.3)
Chest pain	2 (2.2)	5 (5.3)	2 (2.3)
Digestive system			
Dry mouth	19 (20.4)	43 (45.3)	12 (13.8)
Nausea	22 (23.7)	23 (24.2)	17 (19.5)
Constipation	5 (5.4)	9 (9.5)	4 (4.6)
Decreased appetite	7 (7.5)	2 (2.1)	4 (4.6)
Diarrhea	7 (7.5)	3 (3.2)	7 (8.0)
Dyspepsia	6 (6.5)	9 (9.5)	4 (4.6)
Tooth disorder	5 (5.4)	2 (2.1)	2 (2.3)
Vomiting	3 (3.2)	8 (8.4)	6 (6.9)
Abdominal pain	10 (10.8)	7 (7.4)	10 (11.5)
Nervous system			
Dizziness	22 (23.7)	45 (47.4)	16 (18.4)
Emotional lability	6 (6.5)	3 (3.2)	1 (1.1)
Hostility	7 (7.5)	3 (3.2)	0 (0)
Insomnia	14 (15.1)	13 (13.7)	4 (4.6)
Nervousness	8 (8.6)	6 (6.3)	5 (5.7)
Somnolence	16 (17.2)	13 (13.7)	3 (3.4)
Tremor	10 (10.8)	14 (14.7)	2 (2.3)
Headache	32 (34.4)	38 (40.0)	34 (39.1)
Respiratory system			
Cough increased	5 (5.4)	3 (3.2)	6 (6.9)
Pharyngitis	5 (5.4)	12 (12.6)	8 (9.2)
Respiratory disorder	10 (10.8)	7 (7.4)	11 (12.6)
Rhinitis	7 (7.5)	3 (3.2)	5 (5.7)
Sinusitis	6 (6.5)	2 (2.1)	7 (8.0)
Other			
Sweating	1 (1.1)	6 (6.3)	1 (1.1)
Abnormal vision	1 (1.1)	7 (7.4)	2 (2.3)
Asthenia	10 (10.8)	7 (7.4)	10 (11.5)
Back pain	4 (4.3)	2 (2.1)	10 (11.5)
Infection	10 (10.8)	5 (5.3)	9 (10.3)
Trauma	2 (2.2)	3 (3.2)	6 (6.9)

Note: Values represent no. (%).

increases or decreases in body weight were not observed among any of the three treatment arms of this study.

Serious adverse effects occurred in 11 patients in the paroxetine group, 5 in the imipramine group, and 2 in the placebo group. An event was defined as serious if it resulted in hospitalization, was associated with suicidal gestures, or was described by the treating physician as serious. The serious adverse effects in the paroxetine group consisted of headache during discontinuation taper (1 patient) and various psychiatric events (10 patients): worsening depression (2); emotional lability (e.g., suicidal ideation/gestures [5]); conduct problems or hostility (e.g., aggressiveness, behavioral disturbance in school [2]); and euphoria/expansive mood (1). Seven patients were hospitalized: 2 with worsening depression, 2 with emotional lability, 2 with conduct problems, and 1 with euphoria. Of the 11 patients, only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment.

The 5 serious adverse effects in the imipramine group consisted of maculopapular rash (1 patient), dyspnea/chest pain (1), hostility (1), emotional lability (1), and visual hallucinations/abnormal dreams (1). Two of the adverse effects (i.e., hallucinations, rash) were considered related to imipramine. All 5 patients were withdrawn from the study, and the patients with hostility or emotional lability were hospitalized. In the placebo group, emotional lability (1 patient) and worsening depression (1) were considered serious. The placebo-treated patient with emotional lability, which was considered to be related to placebo, was withdrawn from the study.

Of subjects in the imipramine group who stopped therapy because of adverse effects, nearly one third (13.7%) did so because of cardiovascular effects, including tachycardia, postural hypotension, and prolonged QT interval. Mean standing heart rate increased by 17 bpm over baseline among subjects treated with imipramine. Neither paroxetine nor placebo was associated with changes in heart rate.

DISCUSSION

This is the first study to compare efficacy of an SSRI and a tricyclic antidepressant with placebo in the treatment of major depression in adolescents. Paroxetine was significantly more effective than placebo with regard to achievement of both HAM-D total score ≤ 8 , CGI score of 1 (very much improved) or 2 (much improved), and improvements in the depressed mood items of the HAM-D and

the K-SADS-L. Paroxetine did not separate statistically from placebo for K-SADS-L depression subscore, mean CGI score, or HAM-D total score.

The demonstration of efficacy for paroxetine in this study is in accordance with findings of open-label studies of SSRIs (Ambrosini et al., 1999; Apter et al., 1994; Masi et al., 1997; McConville et al., 1996; Rey-Sanchez and Gutierrez-Casares, 1997; Rodriguez-Ramos et al., 1996; Simeon et al., 1998) and results from placebo-controlled (Emslie et al., 1997) and historical case-control (Strober et al., 1999) studies. These findings of efficacy for paroxetine and other SSRIs are notable in that randomized, double-blind, placebo-controlled trials (Geller et al., 1990; Hughes et al., 1990; Kashani et al., 1984; Klein et al., 1998; Kramer and Feiguine, 1981; Kutcher et al., 1994; Kye et al., 1996; Petti and Law, 1982; Preskorn et al., 1987) and one meta-analysis (Hazell et al., 1995) have not shown efficacy for the tricyclic antidepressants in the treatment of adolescent depression. Because efficacy has not been demonstrated for the tricyclic antidepressants and because these agents are associated with an unacceptably high risk of cardiotoxicity, especially in children, further controlled studies are not likely to be conducted. As such, future research involving bupropion or noradrenergic antidepressants not yet clinically available will be required to address more fully the question of preferential efficacy of the SSRIs in this age group.

Our study used a flexible-dose design in which doses could be adjusted on the basis of clinical response and tolerability. Roughly half of subjects were maintained at the paroxetine starting dose of 20 mg. The mean daily dose of paroxetine in this study, 28 mg, is comparable with that reported in flexible-dose trials in adults (Claghorn, 1992; Cohn and Wilcox, 1992; Dunbar et al., 1991; Fabre, 1992; Feighner and Boyer, 1992; Shrivastava et al., 1992; Smith and Glaudin, 1992).

The adverse-effect profile of paroxetine in this adolescent population was concordant with that reported in studies of adult patients with depression (Claghorn, 1992; Cohn and Wilcox, 1992; Dunbar et al., 1991; Fabre, 1992; Feighner and Boyer, 1992; Shrivastava et al., 1992; Smith and Glaudin, 1992). Serious adverse effects were reported during treatment with paroxetine (11 patients), imipramine (5), and placebo (2). Because these serious adverse effects were judged by the investigator to be related to treatment in only 4 patients (paroxetine, 1; imipramine, 2; placebo, 1), causality cannot be determined conclusively. Adverse cardiovascular effects were not

observed in subjects treated with paroxetine. In contrast, tachycardia, postural hypotension, and prolongation of QT intervals during imipramine therapy resulted in treatment discontinuation in one third of the 31.5% of subjects who stopped treatment prematurely with the tricyclic antidepressant.

Limitations

A high placebo response rate was observed in this study, which is not unusual for clinical trials of major depression in either pediatric or adult populations. In studies of pediatric patients with major depression, placebo response rates range from 20% to 80% (Birmaher et al., 1998; Emslie et al., 1997; Geller et al., 1992; Jensen et al., 1992; Kowatch et al., 1999). Placebo response also is high in adults with major depression as demonstrated by mean placebo response rates of approximately 30% to 40% in short-term studies (Brown, 1994; Schatzberg and Kraemer, 2000; Trivedi and Rush, 1994).

Several factors possibly contributed to the observed placebo response rate. A probable contributing factor was the weekly supportive case management sessions, which may have contributed to clinical improvement for patients in the placebo and active-treatment groups. In addition, the lack of a placebo run-in before randomization may have contributed to a higher placebo response. Inclusion of patients with externalizing disorders (e.g., conduct disorder, oppositional defiant disorder) also could be argued to have increased the placebo response rate. A post hoc analysis was conducted to assess this issue. However, the separate analysis of our database revealed that response rates to paroxetine, imipramine, and placebo among patients with attention-deficit/hyperactivity disorder (ADHD) were significantly lower than in patients without ADHD, regardless of treatment group assignment, including placebo (Birmaher et al., 2000).

The mean HAM-D total score from our sample at baseline in all three groups was 18 (± 0.43), possibly accounting for the high placebo response. In fact, there appears to be an inverse relationship between placebo response in adults and clinical severity of depression. Adults with less severe depression exhibit greater placebo response rates than more seriously ill patients. Mild to moderate depression (i.e., HAM-D total score < 19 in one study [Stewart et al., 1983], < 13 in another [Paykel et al., 1988]) was associated with no drug-placebo difference in tricyclic antidepressant treatment studies of adult outpatients. Moreover, in contrast with our study, the mean

baseline HAM-D total scores in short-term adult SSRI studies range from 23 to 28 (Cohn and Wilcox, 1985; Dunbar et al., 1991; Feighner and Overø, 1999; Reimherr et al., 1990; Stark and Hardison, 1985). It is important to emphasize, however, that comparisons in HAM-D scores between adults and adolescents may not be valid because of possible age-related variability in HAM-D.

Another methodological limitation must be acknowledged: the study was not designed to directly compare paroxetine with imipramine. The objective of the study was to determine the efficacy of two antidepressants with different mechanisms of action. To conduct a traditional three-arm comparative trial, this study would require testing at p values of .0167 rather than .05. To power a study at this level, it would have been necessary to enroll a greater number of patients, thus exposing more adolescents to the potential risks of clinical research.

Clinical Implications

Major depression in adolescents is an increasingly recognized clinical problem that is remarkably understudied. The majority of treatment studies involve the tricyclic antidepressants. Because these agents are associated with poor efficacy and cardiovascular adverse effects, their use is not recommended. In contrast, there are few large, well-controlled studies of SSRIs in adolescents. Our findings are therefore relevant to clinicians who are faced with treatment decisions for depressed adolescents and a relative paucity of data guiding therapeutic choice. Despite some methodological limitations, resulting in a high placebo response rate (outlined above), our study demonstrates that treatment with paroxetine results in clinically relevant improvement in depression scores. The SSRIs are the medications of choice for the treatment of major depression in adolescents because they are the only agents that have been shown to be efficacious in this population; they have a safer side-effect profile than other antidepressants, particularly in overdose; and they can be administered once daily. Clinicians should be aware that 8 weeks of treatment may not be sufficient to achieve a full clinical response, that some patients may benefit from higher doses, and that some as-yet unidentified groups of patients (e.g., more severely depressed; non-ADHD) may exhibit more robust responses to SSRI therapy.

Conclusion

The findings of this study provide evidence of the efficacy and safety of the SSRI, paroxetine, in the treat-

ment of adolescent depression. Additional studies are called for to define the optimal length of therapy and dose of SSRIs in this population.

REFERENCES

- Ambrosini PJ, Wagner KD, Biederman J et al. (1999), Multicenter open-label sertraline study in adolescent outpatients with major depression. *J Am Acad Child Adolesc Psychiatry* 38:566–572
- American Psychiatric Association (1994), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*. Washington, DC: American Psychiatric Association
- Apter A, Ratzoni G, King RA et al. (1994), Fluvoxamine open-label treatment of adolescent inpatients with obsessive-compulsive disorder or depression. *J Am Acad Child Adolesc Psychiatry* 33:342–348
- Bergner M, Bobbitt RA, Carter WB, Gilson BS (1981), The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 19:787–805
- Birmaher B, McCafferty JM, Bellew KM, Beebe KL (2000), Comorbid ADHD and other disruptive behavior disorders as predictors of response in adolescents treated for major depression. Abstract presented at American Psychiatric Association Annual Meeting, Chicago, May
- Birmaher B, Waterman GS, Ryan ND et al. (1998), Randomized, controlled trial of amitriptyline versus placebo for adolescents with “treatment-resistant” major depression. *J Am Acad Child Adolesc Psychiatry* 37:527–535
- Brown WA (1994), Placebo as a treatment for depression. *Neuropsychopharmacology* 10:265–269
- Claghorn JL (1992), The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. *J Clin Psychiatry* 53(suppl):33–35
- Cohn JB, Wilcox C (1985), A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. *J Clin Psychiatry* 46(suppl):26–31
- Cohn JB, Wilcox CS (1992), Paroxetine in major depression: a double-blind trial with imipramine and placebo. *J Clin Psychiatry* 53(suppl):52–56
- Dulcan MK, Bregman J, Weller EB, Weller R (1998), Treatment of childhood and adolescent disorders. In: *Textbook of Psychopharmacology*, 2nd ed, Schatzberg AF, Nemeroff CB, eds. Washington, DC: American Psychiatric Press, pp 803–850
- Dunbar GC, Cohn JB, Fabre LF et al. (1991), A comparison of paroxetine, imipramine, and placebo in depressed outpatients. *Br J Psychiatry* 159:394–398
- Eisenberg L (1984), The epidemiology of suicide in adolescents. *Pediatr Ann* 13:47–54
- Emslie GJ, Rush AJ, Weinberg WA et al. (1997), A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54:1031–1037
- Endicott J, Spitzer RL (1978), A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 35:837–844
- Fabre LF (1992), A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. *J Clin Psychiatry* 53:40–43
- Fawcett J, Epstein P, Fiester SJ, Elkin I, Autry JH (1987), Clinical management: imipramine/placebo administration manual. *Psychopharmacol Bull* 23:309–324
- Feighner JP, Boyer WF (1992), Paroxetine in the treatment of depression: a comparison with imipramine and placebo. *J Clin Psychiatry* 53(suppl):44–47
- Feighner JP, Overø K (1999), Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. *J Clin Psychiatry* 60:824–830
- Geller B, Cooper TB, Graham DL, Fetner HH, Marsteller FA, Wells JM (1992), Pharmacokinetically designed double-blind placebo-controlled study of nortriptyline in 6- to 12-year-olds with major depressive disorder. *J Am Acad Child Adolesc Psychiatry* 31:34–44
- Geller B, Cooper TB, Graham DL, Marsteller FA, Bryant DM (1990), Double-blind placebo-controlled study of nortriptyline in depressed adolescents using a “fixed plasma level” design. *Psychopharmacol Bull* 26:85–90
- Harter S (1988), *Manual for the Self Perception Profile for Adolescents*. Denver: University of Denver
- Hazell P, O’Connell D, Heathcote D, Robertson J, Henry D (1995), Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *BMJ* 310:897–901
- Hughes CW, Preskorn SH, Weller E, Weller R, Hassanein R, Tucker S (1990), The effect of concomitant disorders in childhood depression on predicting treatment response. *Psychopharmacol Bull* 26:235–238
- Jensen PS, Ryan ND, Prien R (1992), Psychopharmacology of child and adolescent major depression: present status and future directions. *J Child Adolesc Psychopharmacol* 2:31–45
- Kashani JH, Shekim WO, Reid JC (1984), Amitriptyline in children with major depressive disorder: a double-blind crossover pilot study. *J Am Acad Child Psychiatry* 23:348–351
- Kessler RC, McGonagle KA, Zhao S et al. (1994), Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 51:8–19
- Kessler RC, Walters EE (1998), Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depress Anxiety* 7:3–14
- Klein RG, Mannuzza S, Koplewicz HS et al. (1998), Adolescent depression: controlled desipramine treatment and atypical features. *Depress Anxiety* 7:15–31
- Kovacs M, Goldston D, Gatsonis C (1993), Suicidal behaviors and childhood-onset depressive disorders: a longitudinal investigation. *J Am Acad Child Adolesc Psychiatry* 32:8–20
- Kowatch RA, Carmody TJ, Emslie GJ, Rintelmann JW, Hughes CW, Rush AJ (1999), Prediction of response to fluoxetine and placebo in children and adolescents with major depression: a hypothesis generating study. *J Affect Disord* 54:269–276
- Kramer AD, Feiguine RJ (1981), Clinical effects of amitriptyline in adolescent depression: a pilot study. *J Am Acad Child Psychiatry* 20:636–644
- Kutcher S, Boulos C, Ward B et al. (1994), Response to desipramine treatment in adolescent depression: a fixed-dose, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 33:686–694
- Kye CH, Waterman GS, Ryan ND et al. (1996), A randomized, controlled trial of amitriptyline in the acute treatment of a major depression. *J Am Acad Child Adolesc Psychiatry* 35:1139–1144
- Masi G, Marcheschi M, Pfanner P (1997), Paroxetine in depressed adolescents with intellectual disability: an open label study. *J Intellect Disabil Res* 41:268–272
- McConville BJ, Minnery KL, Sorter MT, West SA, Friedman LM, Christian K (1996), An open study of the effects of sertraline on adolescent major depression. *J Child Adolesc Psychopharmacol* 6:41–51
- Paykel ES, Hollyman JA, Freeling P, Sedgwick P (1988), Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. *J Affect Disord* 14:83–95
- Petti TA, Law WD III (1982), Imipramine treatment of depressed children: a double-blind pilot study. *J Clin Psychopharmacol* 2:107–110
- Preskorn SH, Weller EB, Hughes CW, Weller RA, Bolte K (1987), Depression in prepubertal children: dexamethasone nonsuppression predicts differential response to imipramine vs placebo. *Psychopharmacol Bull* 23:128–133
- Rao U, Ryan ND, Birmaher B et al. (1995), Unipolar depression in adolescents: clinical outcome in adulthood. *J Am Acad Child Adolesc Psychiatry* 34:566–578
- Reimherr FW, Chouinard G, Cohn CK et al. (1990), Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry* 51(suppl B):18–27
- Rey-Sanchez F, Gutierrez-Casares JR (1997), Paroxetine in children with major depressive disorder: an open trial. *J Am Acad Child Adolesc Psychiatry* 36:1443–1447
- Rodriguez-Ramos P, de Dios-Vega JL, San Sebastian-Cabases J, Sordo-Sordo L, Mardomingo-Sanz MJ (1996), Effects of paroxetine in depressed adolescents. *Eur J Clin Res* 8:49–61
- Ryan ND, Varma D (1998), Child and adolescent mood disorders: experience with serotonin-based therapies. *Biol Psychiatry* 44:336–340
- Schatzberg AF, Kraemer HC (2000), Use of placebo control groups in evaluating efficacy of treatment of unipolar major depression. *Biol Psychiatry* 47:736–744
- Shrivastava RK, Shrivastava SH, Overweg N, Blumhardt CL (1992), A double-blind comparison of paroxetine, imipramine, and placebo in major depression. *J Clin Psychiatry* 53(suppl):48–51

- Sigafoos AD, Feinstein CB, Damond M, Reiss D (1988), The measurement of behavioral autonomy in adolescence: the autonomous functioning checklist. *Adolesc Psychiatry* 15:432-462
- Simeon JG, Dinicola VF, Ferguson HB, Copping W (1990), Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog Neuropsychopharmacol Biol Psychiatry* 4:791-795
- Simeon JG, Nixon MK, Milin RP, Spent W, Smith D (1998), Sertraline in adolescent depression and dysthymia: a six-month open trial. Presented at the 151st Annual Meeting of the American Psychiatric Association; May 30-June 4; Toronto
- Smith WT, Glaudin V (1992), A placebo-controlled trial of paroxetine in the treatment of major depression. *J Clin Psychiatry* 53:36-39
- Stark P, Hardison CD (1985), A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. *J Clin Psychiatry* 46:53-58
- Stewart JW, Quitkin FM, Liebowitz MR, McGrath PJ, Harrison WM, Klein DF (1983), Efficacy of desipramine in depressed outpatients: response according to research diagnosis criteria diagnoses and severity of illness. *Arch Gen Psychiatry* 40:202-207
- Strober M, DeAntonio M, Schmidt-Lackner S et al. (1999), The pharmacotherapy of depressive illness in adolescents: an open-label comparison of fluoxetine with imipramine-treated historical controls. *J Clin Psychiatry* 60:164-169
- Trivedi MH, Rush H (1994), Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? *Neuropsychopharmacology* 11:33-43
- Weissman MM, Wolk S, Goldstein RB et al. (1999), Depressed adolescents grown up. *JAMA* 281:1707-1713