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IN THE TREATMENT OF ADOLESCENT MAJOR DEPRESSION:

A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT (428)

Context: Depression, a highly prevalent disorder among adolescents, has continuity into adulthood and causes significant impairment and risk of suicide. Antidepressant treatment of adolescent depression is vastly understudied. Tricyclic antidepressants are the most well-studied agents to date, but are associated with significant cardiotoxicity and lethality in overdose.

Objective: To compare the efficacy and safety of paroxetine with placebo and imipramine with placebo in the treatment of adolescent depression.

Design: 8-week, multicenter, randomized, double-blind trial.

Setting and Subjects: 275 adolescent subjects (aged 12 to 18 years) meeting DSM-IV criteria for major depression were randomized to treatment at 10 centers in the United States and 2 in Canada.

Intervention: After a 7- to 14-day screening period, subjects received a double-blind 8-week course of paroxetine, imipramine, or matching placebo. Paroxetine was administered in doses of 20 mg to 40 mg/day. Imipramine was gradually titrated upward, based on tolerance and response, to a minimum of 200 mg/day and a maximum of 300 mg/day.

Main Outcome Measures: 7 depression-related variables were assessed: 1) Response at end point (a HAM-D score ≤8 or a ≥50% reduction in baseline HAM-D score); 2) depressed mood item of HAM-D; 3) depression item of Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime Version (K-

SADS-L); 4) Clinical Global Impression (CGI) improvement scores of 1 (very much improved) or 2 (much improved); 5) 9-item depression subscale of K-SADS-L; 6) mean CGI improvement scores; and 7) change from baseline HAM-D total score. Measures of functioning, general health, and behavior were also assessed.

Results: Efficacy was demonstrated for paroxetine, with significantly greater improvement compared with placebo across measures of HAM-D total score ≤8, HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 or 2. In contrast, the therapeutic response to imipramine was not significantly different than the response to placebo for any of the measures of antidepressant efficacy. Although improvement over baseline occurred in all groups, neither paroxetine nor imipramine differed from placebo on parent- or self-rating measures. Paroxetine was well tolerated, with adverse effects that were similar in spectrum and severity as observed during treatment of adults. Imipramine was less well tolerated, with 31.5% of subjects withdrawing from the study because of adverse effects versus withdrawal rates of 9.7% and 6.9% for paroxetine and placebo, respectively.[1] Of the subjects stopping imipramine therapy, nearly one third did so because of adverse cardiovascular effects, including tachycardia, postural hypotension, and electrocardiographic (ECG) abnormalities.

VOTE CHANGE From Method 1

Conclusions: Paroxetine is a safe and effective treatment for major depression in adolescents. Further studies are warranted to determine the optimal dose range and duration of therapy.

[1] Jim McCafferty: Were these differences significant? If so, what are the P values? Thank you.

INTRODUCTION

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 1769 adolescents and young adult participants in the National Comorbidity Survey[1] indicate a lifetime prevalence rate of 15.3% for major depression, comparable to the 17% lifetime prevalence of depression in adults.[2] 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.[3] Suicide is the third leading cause of death in adolescents, and depressive disorders are strongly correlated with suicide attempts.[4,5] 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.[6]

The efficacy of tricyclic antidepressants has been investigated in at least 11 double-blind, randomized studies,[7,8] 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 their commercial availability, the safety, tolerability, and efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating major depression in adolescents have been noted in several open-label reports.[9-15] Placebo-controlled trials, which remain the standard against which efficacy is determined, number only 2, both with fluoxetine.[16,17] A small study by

Simeon and associates[17] was negative. In contrast, a large-scale trial by Emslie and colleagues[16] showed a 23% drug-placebo difference in overall clinical improvement. The findings of a third study, employing a historical case control design,[18] demonstrated 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.

METHODS

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 randomized to active treatment (Figure 1). 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. Funding for this study was provided by SmithKline Beecham Pharmaceuticals; 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 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* (DSM-IV)[19] 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 using 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 1 of the authors (R.G.K.) through modification of the adult SADS assessment technique[20] by providing uniform anchors so that symptoms were specifically rated for clinical relevance and by adding items in order 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 on the 17-item Hamilton Depression Rating (HAM-D) scale of at least 12, a Child Global Assessment Scale (C-GAS) score less than 60, and a Peabody Picture Vocabulary Test score of at least 80. 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 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 development 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 either investigational drug use within 30 days of study entry or within 5 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. Using a computer-generated list, subjects who still met entry criteria were randomized 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 per day in the morning for weeks 1 through 4. Optional dosage increases to 30 mg paroxetine per day were allowed at week 5 and to 40 mg per day 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 (in divided doses) during week 2, 150 mg during week 3,

and 200 mg during week 4. Thereafter, optional dosage increases to 250 mg per day for week 5 and to 300 mg per day for weeks 6 through 8 were allowed if judged necessary by the research study clinician.

Supportive case management was provided to all subjects at each weekly clinic visit according to the method described by Fawcett.[21] Such management was limited to clinical support and observation of treatment effects and strictly prohibited interpersonal or cognitive/behavioral psychotherapeutic interventions.

Efficacy and Safety Evaluation

Following randomization, subjects were seen at weekly intervals and evaluated with standardized instruments and global assessments for efficacy. Seven depression-related variables were declared *a priori*: 1) *response* at end point; 2) change in the depressed mood item of the HAM-D; 3) change in the depression item of the K-SADS-L; 4) CGI improvement scores of 1 (very much improved) or 2 (much improved); 5) change in the 9-item depression subscale of the K-SADS-L; 6) mean CGI improvement scores; and 8) change from baseline in HAM-D total score. Subjects were considered to be *responders* if, at the end of treatment, they had achieved a HAM-D score of ≤8 or a ≥50% reduction in baseline HAM-D score.

Assessment of multiple domains of functioning, general health, and behavior consisted of 1) Autonomous Function Checklist, completed by the parent, that assessed the subject's autonomy in performing daily activities;[22] 2) Self-Perception Profile, completed by the subject to measure self-esteem;[23] and 3) Sickness Impact Scale, completed by the subject, to measure present health and quality of life.[24]

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.

Changes in cardiovascular parameters required dosage reduction. Doses were reduced by 10 mg for paroxetine doses of 30 mg or 40 mg; subjects at 20 mg paroxetine were withdrawn from the study. Similarly, imipramine doses of 250 mg or 300 mg per day were reduced by 50 mg, and subjects at ≤200 mg 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 2 consecutive visits, or heart rate ≥130 bpm at a single visit; systolic blood pressure >140 mm Hg/diastolic blood pressure >85 mm Hg; PR interval ≥0.21 seconds; QRS interval ≥0.12 seconds and ≥150% of baseline, or QTC interval ≥0.48 seconds.

Blood samples were obtained 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. Mean plasma imipramine

concentrations were XX ng/mL and XX ng/mL at weeks 4 and 8, respectively. Further details about dosing and plasma concentrations will be reported in a separate publication.[2]

Statistical Methods

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

The efficacy analyses were performed on the population of patients who were randomized and had at least 1 post-baseline efficacy evaluation. Two datasets from this population were examined: 1) a last observation carried forward (LOCF) 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 end point in the total HAM-D score, Clinical Global Impression (CGI) improvement scale, and K-SADS-L, were analyzed by a 2-factor analysis of variance (ANOVA) using the general linear model procedure of the SAS. The model included terms for treatment and investigator. Categorical variables, such as percentage of subjects responding to treatment, were analyzed using logistic analysis implemented in the categorical modeling procedure (CATMOD) of the SAS system with model including effects for investigator and treatment. Pairwise comparisons

[2] Jim McCafferty: please provide this data. Thank you.

between each active treatment and placebo were two-tailed and performed at an alpha level of 0.05. Data are reported as least square means (+/- 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 over 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 limiting many comorbidities, 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 (Figure 1). 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), AV block (1), anbnormal 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 7 depression-related variables, paroxetine separated statistically from placebo at end point among 4 of the parameters: response, HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 (very much improved) or 2 (much improved) and trended toward statistical significance on 2 measures: K-SADS-L 9-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 7 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 ≤8 at end point (Figure 2). The time course of response in mean HAM-D total score is shown in Figure 3. 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 ≤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 non-symptom 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 (Table 3).

Dosage Titration

Nearly half of subjects in the paroxetine group remained at the initial starting dose of 20 mg per day (48%) (Table 4). Mean dose at study end point for paroxetine was 28.0 mg (SD ± 8.54 mg) and for imipramine was 205.8 mg (SD ± 63.94 mg). The most common "doses" of placebo (administered as divided doses) were 4 capsules per day (31.0%) and 6 capsules per day (41.4%).

Adverse Effects THIS IS A MISCODING "HOMBLING"

Paroxetine was well tolerated in this adolescent population, and most adverse effects were mild to moderate in severity. The most common adverse effects reported during paroxetine therapy were headache, nausea, dizziness, dry mouth, and somnolence (Table 5). These occurred at rates that were similar to 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, headache, 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 (Figure 1). Clinically significant increases or decreases in body weight were not observed among any of the 3 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, such as overdose, or was described by the treating physician as serious. The serious adverse effects in the paroxetine group consisted of headache during down-titration (1 patient), and various psychiatric events (10 patients): worsening depression (2); emotional lability (eg, suicidal ideation/gestures, overdoses, 5); conduct problems or hostility (eg, aggressiveness, behavioral disturbance in school, 2); and mania (1). Of these, worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment. Seven patients were hospitalized, and 6 were withdrawn from the study. Hospitalization was ordered for both patients with worsening depression, 2 patients with suicidal ideation, both patients with conduct problems, and the single patient reported to be euphoric. Five of the 11 paroxetine-treated patients with serious events completed 8 weeks of 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). Three of the adverse effects (ie, hallucinations, chest pain/dyspnea, and rash) were considered related or possibly 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 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.

COMMENT

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 and a 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. Trends toward statistical significance were observed on paroxetine compared with placebo for K-SADS-L depression subscore, mean CGI score, and HAM-D total score.

A large 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). Placebo response is also 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, 2000; Trivedi and Rush, 1994).

There are several possible factors that contributed to the placebo response rate observed in this study. For example, the weekly supportive case management sessions could have resulted in clinical improvement for patients in the placebo group. Additionally, the lack of a placebo run-in before randomization may have contributed to the observed placebo response. It is also possible that the observed between-group differences may be due to the relatively low HAM-D threshold at entry of ≥12. Findings in the literature on the treatment of depression in adults suggest an inverse relationship between placebo response and clinical severity of depression on the HAM-D.[25] The inclusion of patients with externalizing disorders (eg, conduct disorder, oppositional defiant disorder, others) also could be argued to have increased the placebo response rate. However, a 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, 199X).[3]

[3] Jim McCafferty: This statement derived from the ADHD abstract. When was this presented? Who were the authors? What were the P values?

Several methodological limitations of this study also must be acknowledged. First, the study was not designed to directly compare paroxetine with imipramine. The objective of the study was to determine the efficacy of 2 antidepressants with different mechanisms of action. In order to conduct a traditional 3-arm comparative trial, this study would require testing at *P* values of 0.0167 rather than 0.05. To power a study at this level, it would have been necessary to enroll approximately 50% to 60% more patients[4], thus exposing a greater number of adolescents to the risks of clinical research. A second potential limitation was the entry criteria of a minimum HAM-D total score of 12. The HAM-D rating scale was designed for adults rather than adolescents; in order for the HAM-D scores of the pediatric patients in this study to reflect the severity of their disorder, the minimum entry criteria was decreased to 12. Nonetheless, the mean HAM-D total scores at baseline in all 3 groups was 18 (± 0.43), which demonstrates the severity of depression in this population.

The demonstration of efficacy for paroxetine in this study is in accordance with findings of open-label studies of SSRIs,[9-15] and results from placebo-controlled[16] and historical case-control[18] studies. These findings of efficacy for paroxetine and other SSRIs are notable in that randomized, double-blind, placebo-controlled trials[26-34] and 1 meta-analysis[35] 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

[4] Jim McCafferty: Kindly provide the exact numbers of patients needed to test at P=.0167. Thank you.

to more fully address the question of preferential efficacy of the SSRIs in this age group.

Our study employed a flexible-dose design in which doses could be adjusted based on 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 to that reported in flexible-dose trials in adults.[36-42]

The adverse-effect profile of paroxetine in this adolescent population was concordant with that reported in studies of adult patients with depression.[36-42] 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.

In conclusion, the findings of this study provide evidence of the efficacy and safety of the selective serotonin reuptake inhibitor, paroxetine, in the treatment of adolescent depression. Additional studies are called for to define the optimal length of therapy and dose of selective serotonin reuptake inhibitors in this population.

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Table 1. Demographic characteristics and mean baseline depression scores for 275 randomized subjects

Parameter	Paroxetine N=93	Imipramine N=95	Placebo N=87
Gender, M/F	35/58	39/56	30/57
Age, mean ± SD, y	14.8 ± 1.6	14.9 ± 1.6	15.1 ± 1.6
Race			
White	77 (82.8%)	83 (87.4%)	70 (80.5%)
Black	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%)
Child Global Assessment Scale (mean ± SD)	42.7 ± 7.5	42.5 ± 7.4	42.8 ± 8.3
Duration of current depressive episode in months (mean ± SD)	14 ± 18	14 ± 18	13 ± 17
Number of prior depressive episodes			
0	81%	79%	77%
1	12%	14%	14%
≥2	7%	6%	8%

Table 1 (continued). Demographic characteristics and mean baseline depression scores for 275 randomized subjects

Parameter	Paroxetine N=93	Imipramine N=95	Placebo N=87
First-degree relative with major depression	86%	90%	95%
Age at onset of first episode in years (mean ± SD)	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/ endogenous depression	36%	35%	40%
Features of atypical depression	25%	16%	9%
Current comorbid psychiatric diagnosis			
Any diagnosis	41%	50%	45%
Anxiety disorder*	19%	26%	28%
Externalizing disorder†	25%	26%	20%

HAM-D indicates Hamilton Rating Scale for Depression.

* Includes separation anxiety, panic ± agoraphobia, agoraphobia, social anxiety disorder, generalized anxiety disorder.

† Includes conduct disorder, oppositional defiant disorder, and attention deficit/hyperactivity.

Table 2. Mean scores of depression-related variables in adolescents with major depression* who were treated with paroxetine, imipramine, or placebo†

	Paroxetine				Imipramine				Placebo		
Variable	Mean	(SE)	N	P‡	Mean	(SE)	N	P‡	Mean	(SE)	N
HAM-D ≤8											
Week 8 end point	63.3%	(-)	90	.02	50.0%	(-)	94	.57	46.0%	(-)	87
HAM-D ≤8 or 50% reduction in baseline HAM-D											
Week 8 end point	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 end point	0.99	(0.14)	90	.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 end point	2.37	(0.18)	83	.05	2.52	(0.18)	87	.87	2.90	(0.18)	85
CGI Score of 1 or 2†											
Week 8 end point	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 end point	16.59	(0.84)	83	.07	17.99	(0.83)	88	.98	19.27	(0.83)	85
Mean CGI score											
Week 8 end point	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 end point	8.24	(0.81)	90	.13	9.2	(0.81)	94	.87	9.88	(0.83)	87

HAM-D indicates Hamilton Rating Scale for Depression; K-SADS-L, Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime Version; CGI, Clinical Global Impression.

* The last evaluation during treatment for subjects who did not complete the entire study (ie, the last observation carried forward) is reported.

† P value compares treatment difference in active versus placebo groups.

‡ CGI score of 1 = very much improved; CGI score of 2 = much improved.

Table 3. Measures of functioning, general health, and behavior measures in adolescents with major depression* who were treated with paroxetine, imipramine, or placebo

	Paroxetine				Imipramine				Placebo		
Variable	Mean	(SE)	N	P†	Mean	(SE)	N	P†	Mean	(SE)	N
Autonomous Function Checklist											
Baseline	91.41	(3.80)	60	.58	96.02	(3.97)	57	.72	94.18	(3.74)	62
Week 8 end point	106.11	(2.80)	60	.15	107.59	(2.92)	57	.55	103.48	(2.75)	62
Self Perception Profile											
Baseline	63.48	(2.58)	61	.42	60.87	(2.67)	60	.96	60.69	(2.52)	63
Week 8 end point	76.73	(2.33)	61	.54	73.94	(2.41)	60	.59	72.05	(2.27)	63
Sickness Impact Profile											
Baseline	30.90	(1.46)	63	.51	30.38	(1.52)	60	.36	32.17	(1.42)	65
Week 8 end point	19.54	(1.55)	63	.46	17.46	(1.62)	60	.14	22.32	(1.51)	65

* The last evaluation during treatment for subjects who did not complete the entire study (ie, the last observation carried forward) is reported.

† *P* value compares treatment difference in active versus placebo groups.

Table 4. Medication doses at study end point (N=275)

Treatment group	Daily dose at end point (mg)	Number of subjects (%)
Paroxetine	20 mg	45 (48%)
N=93	30 mg	22 (23.7%)
	40 mg	26 (28.0%)
	Mean dose in mg ± SD	28.0 ± 8.54 mg
Imipramine	50 mg	3 (3%)
N=95	100 mg	11 (11.5%)
	150 mg	5 (5.3%)
	200 mg	45 (47.4%)
	250 mg	15 (15.8%)
	300 mg	16 (16.8%)
	Mean dose in mg ± SD	205.8 ± 63.94 mg
Placebo	2 capsules	5 (5.7%)
N=87	3 capsules	5 (5.7%)
	4 capsules	27 (31.0%)
	5 capsules	14 (16.1%)
	6 capsules	36 (41.4%)

Table 5. Adverse effects occurring in ≥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%)
Vasodilatation	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%)

Table 5 (continued). Adverse effects occurring in ≥5% of subjects in the paroxetine, imipramine, and placebo groups

Adverse effect	Paroxetine N=93	Imipramine N=95	Placebo N=87
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%)

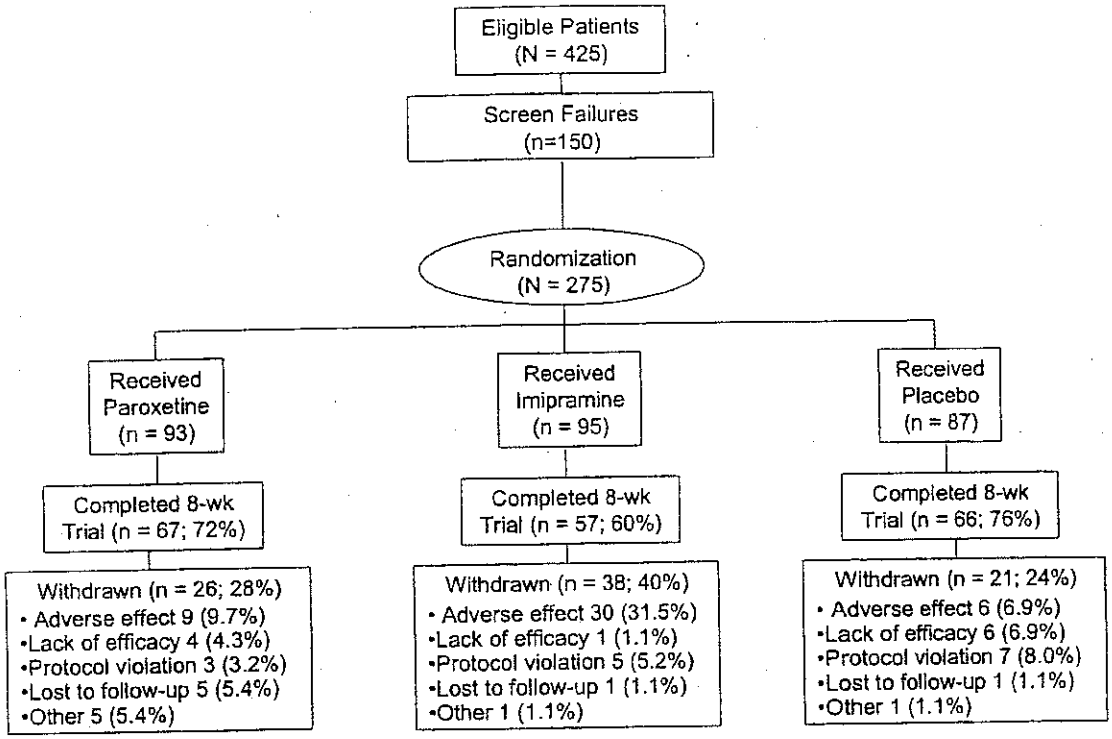

Figure 1. Of 425 adolescents who were screened, 275 fulfilled criteria for major depression and were randomized to receive 8 weeks of treatment with paroxetine (93 subjects), imipramine (95 subjects), or placebo (87 subjects). A total of 69% of subjects (N=190) completed the trial. Withdrawal rates were 28% for paroxetine, 40% for imipramine, and 24% for placebo.[5]

[5] Figure 1 could be deleted; this was required by JAMA, but not by Am J Psychiatry.

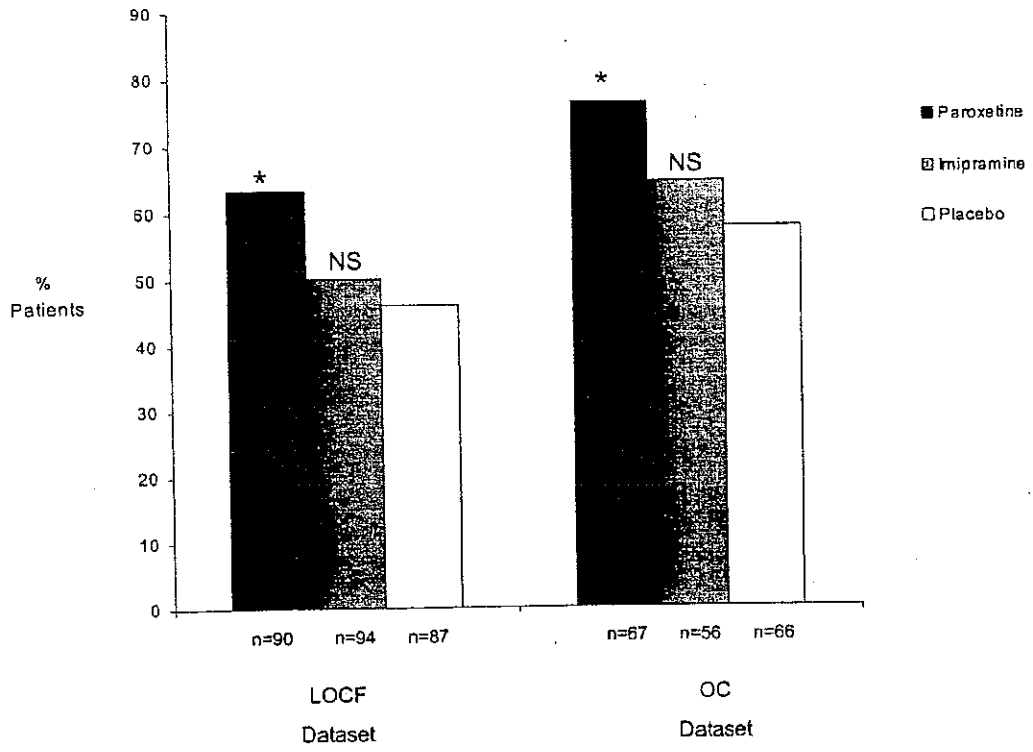

Figure 2. Percentage of paroxetine, imipramine, and placebo-treated subjects achieving a HAM-D total score ≤8 in the last-observation carried forward (LOCF) and completer subgroups at week 8. * P=.02; NS = P≥.44. HAM-D indicates Hamilton Rating Scale for Depression, OC, observed cases.

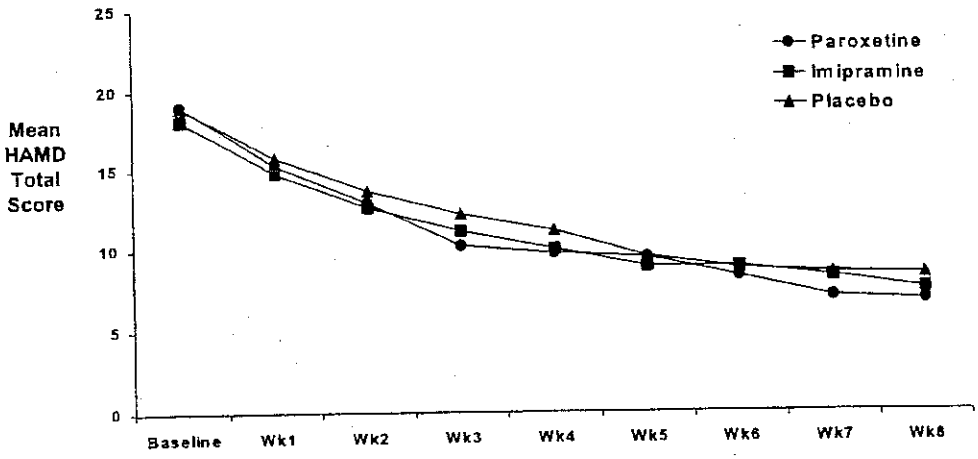

Figure 3. Mean HAM-D total scores during an 8-week course of paroxetine (N=90), imipramine (N=94), and placebo (N=87) administration in adolescents with major depression.