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July 26, 1999

Martin B. Keller, MD
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Dear Dr Keller:

We are pleased to enclose all of the necessary materials for you to submit your manuscript, "Efficacy of Paroxetine but not Imipramine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial," to the *Journal of the American Medical Association*.

Please find enclosed the following items:

- Five copies of the manuscript (submit four to the journal; keep one for yourself)
- Four sets of laser-copy illustrations as required by *JAMA*
- A diskette containing the illustrations
- A draft of a cover letter to Dr Richard Glass, the editor of *JAMA* (please retype on your letterhead and revise as you like)
- A diskette containing your manuscript in Microsoft Word 97 format for your use in the event that revisions are needed
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On behalf of Sally Laden, it has been a pleasure working with you on this project. Please keep us apprised of the status of the paper. If revisions are required, we will be happy to assist you. If the paper is rejected, we will gladly work with you to submit it to another journal.

Thank you for your cooperation, and please do not hesitate to contact us with questions.

Kindest Regards,

Erika Dankovits
Copyediting Assistant

cc: J Romankiewicz, M Philips, S Laden, J McCafferty, B Brand, .1301

encl.

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EFFICACY OF PAROXETINE BUT NOT IMIPRAMINE IN THE TREATMENT OF ADOLESCENT MAJOR DEPRESSION: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT (434)

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. Until now there have been no double-blind, placebo-controlled comparisons of a selective serotonin reuptake inhibitor with placebo-controlled comparisons of a tricyclic antidepressant.

Objective: To compare the efficacy and safety of paroxetine 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: 8 depression-related variables were assessed: 1) Remission at end point (Hamilton Rating Scale for Depression [HAM-D] score ≤8

at end point); 2) Response at end point (a HAM-D score ≤8 or a ≥50% reduction in baseline HAM-D score); 3) depressed mood item of HAM-D; 4) depression item of Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime Version (K-SADS-L); 5) Clinical Global Impression (CGI) improvement scores of 1 (very much improved) or 2 (much improved); 6) 9-item depression subscale of K-SADS-L; 7) mean CGI improvement scores; and 8) change from baseline HAM-D total score. Measures of functioning, general health, and behavior were also assessed.

No distinction between 1° & 2° ~~variables~~ measures.

Results: Efficacy was demonstrated for paroxetine, with significantly greater improvement across measures of remission, 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. Neither paroxetine nor imipramine differed from placebo on parent- or self-rating measures, with improvement in all treatment groups. 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. Of the subjects stopping imipramine therapy, nearly one third did so because of adverse cardiovascular effects, including tachycardia, postural hypotension, and electrocardiographic (ECG) abnormalities.

change to "generally well tolerated."

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

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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 effectiveness 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 effectiveness 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. Another 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, placebo-controlled comparison of paroxetine and imipramine therapy 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.

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)

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 an Intelligence Quotient (IQ) score of at least 80, as determined by 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 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 mental 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. 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 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. Eight depression-related variables were declared *a priori*: 1) *remission* at end point; 2) *response* at end point; 3) change in the depressed mood item of the HAM-D; 4) change in the depression item of the K-SADS-L; 5) CGI improvement scores of 1 (very much improved) or 2 (much improved); 6) change in the 9-item depression subscale of the K-SADS-L; 7) mean CGI improvement scores; and 8) change from baseline in HAM-D total score. *Remission* was defined as a HAM-D score of ≤8 at end point. 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

WB 202281

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.

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 an intent-to-treat (ITT) population that included all randomized patients with at least 1 post-baseline efficacy evaluation. Using the ITT population, 2 datasets 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 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 positive family history for 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 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

see p 765 for rewording

Of the 8 depression-related variables, paroxetine separated statistically from placebo at end point among 4 of the parameters: remission, 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 8 depression-related variables.

WB 202284

This is explained by achieving ≤8

Remission, defined as a HAM-D total score of ≤8 at study end point, was achieved in 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) at end point (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 remission. 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).

o Remiss identical

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

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. Change from baseline to end point on paroxetine was numerically superior to placebo on all 8 of the prospectively defined measures of efficacy. Paroxetine was significantly more effective than placebo with regard to achievement of both full remission 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 {response (HAM-D score ≤8 or ≥50% reduction in baseline HAM-D total score)}, K-SADS-L depression subscore, mean CGI score, and HAM-D total score.

The large placebo response in this study may be attributed to the weekly supportive case management sessions. It is possible that the treatment difference observed may have been constrained by the relatively low HAM-D threshold at entry of ≥12. Findings in the literature on the treatment of depression in adults have reported an inverse relationship between placebo response and clinical severity of depression on the HAM-D.[25]

This demonstration of efficacy for paroxetine 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 noradrenergic antidepressants not yet clinically available will be required 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.

Added comments re 11 serious adverse effects c parox, with qualifiers that they were not related to parox

← LIMITATIONS + CLINICAL IMPLICATIONS INJECTED HOPE.

In conclusion, the findings of this study provide evidence of the effectiveness 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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WB 202294

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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%

WB 202296

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

Parameter	Paroxetine N=93	Imipramine N=95	Placebo N=87
Family history of 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%

changed back.

WB 202297

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†

Variable	Paroxetine Mean	(SE)	N	P†	Imipramine Mean	(SE)	N	P†	Placebo Mean	(SE)	N
Remission† Week 8 end point	63.3%	(-)	90	.02	50.0%	(-)	94	.57	46.0%	(-)	87
Response† 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)	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 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

changed to — HAM-D ≤ 8

changed to / ≤ 8, 35%

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.

‡ Remission = HAM-D total score ≤8 at end point; Response = HAM-D total score ≤8 or a 50% reduction in baseline HAMD score; 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 3+4 excluded

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%)

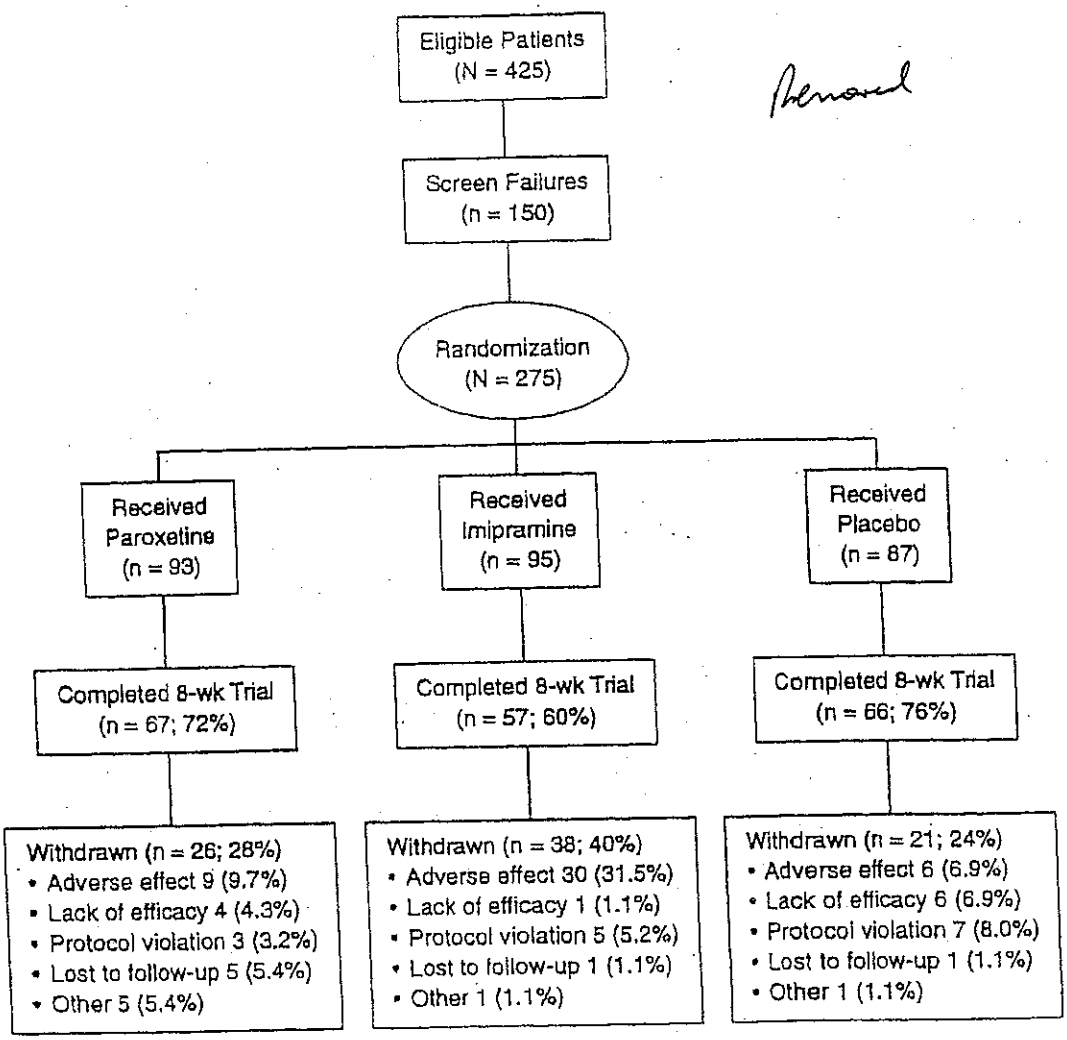

Figure 1. Of 425 adolescents who were screened, 275 fulfilled criteria for major depression and were randomized to receive 8 weeks of treatment with paroxetine (93 subjects), imipramine (95 subjects), or placebo (87 subjects). A total of 69% of subjects (N=190) completed the trial. Withdrawal rates were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

WB 202306

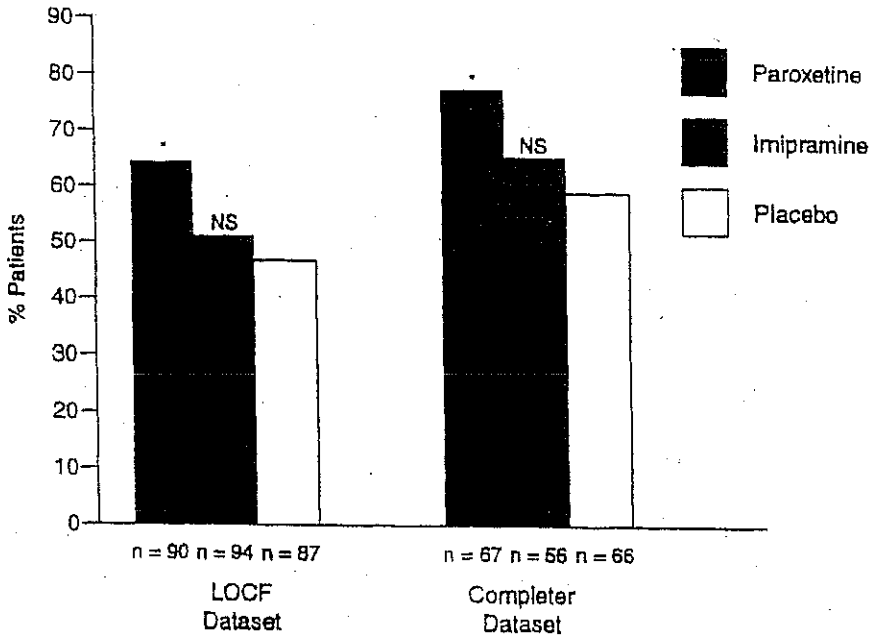

Figure 2. Percentage of paroxetine, imipramine, and placebo-treated subjects achieving remission in the last-observation carried forward (LOCF) and completer subgroups at week 8 (ie, HAM-D total score ≤8). * $P=.02$; NS = $P\geq.44$. HAM-D indicates Hamilton Rating Scale for Depression, OC, observed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

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