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December 18, 1998

Jim McCafferty
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SmithKline Beecham Pharmaceuticals
UP 4410
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Collegeville, PA 19426

RE: PAROXETINE ADOLESCENT DEPRESSION STUDY

Dear Jim:

I am pleased to enclose Draft I of the manuscript entitled "Paroxetine and Imipramine Treatment of Adolescent Depression: A Randomized, Controlled Trial." A copy is being sent to Marty Keller also. Note that the body of the manuscript is triple-spaced per the request of Dr Keller.

As you read the manuscript, please keep the following points in mind. The Discussion section (Comment section) is not complete. Rather it is presented in Draft I as a partially completed outline. I am looking for direction from you and Dr Keller before completing the Discussion, which will be completed for Draft II.

Queries that arose during writing are presented as footnotes in the text and tables.

Thanks for your attention to this, Jim. I will call you after the first of the year to discuss your comments on the manuscript. In the meantime, please do not hesitate to contact me by phone at (203) 272-3081, FAX at (203) 272-6917, or email at sallyl@stimedinfo.com.

Sincerely,

Sally Laden

Sally K. Laden, MS
Associate Editorial Director

encl
cc: .1301

PAR004368167

PAROXETINE AND IMIPRAMINE TREATMENT OF ADOLESCENT DEPRESSION: A RANDOMIZED, CONTROLLED TRIAL

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ABSTRACT (404)

Context: Depression is a highly prevalent disorder among adolescents. Antidepressant treatment of adolescent depression is vastly understudied. Tricyclic antidepressants, with their attendant cardiotoxicity and lethality in overdose, are the best studied agents to date. Until now there have been no double-blind, placebo-controlled comparisons of a selective serotonin reuptake inhibitor with a tricyclic antidepressant.

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

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

Setting and Patients: 275 adolescent patients (ages 12 to 18 years) meeting DSM-III-R criteria for major depression were randomized to treatment at 10 centers in the United States and 2 in Canada.

Intervention: After a 7- to 10-day screening period, patients 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 therapy was gradually titrated upwards, based on tolerance and response, to a maximum of 300 mg/day.

Main Outcome Measures: 1) Percentage remission at endpoint (HAMD score ≤ 8 at endpoint); 2) percentage response at endpoint (a HAMD score ≤ 8 or a ≥ 50% reduction in baseline HAMD score); 3) depressed mood item of HAMD; 4) depression item of K-SADS-L; 5) 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 HAMD total score. Measures of behavior (Autonomous Function Checklist; Self Perception Profile; Sickness Impact Scale) were also assessed.

Results: The therapeutic response to imipramine was not significantly different than placebo for any of the measures of antidepressant efficacy.

In contrast, efficacy was demonstrated for paroxetine, with significantly greater improvement across measures of remission, HAMD depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 or 2. Neither paroxetine nor imipramine differed from placebo across the behavioral measures, however, improvements over baseline were achieved for each treatment group. Paroxetine was very 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 patients withdrawing from the study due to adverse effects. Of the patients stopping imipramine therapy, nearly one-third did so because of adverse cardiovascular effects, including tachycardia, postural hypotension, and ECG abnormalities.

Conclusions: Paroxetine is safe and effective treatment of depression in the adolescent patient. Further studies are warranted to determine the optimal dose and duration of therapy.

INTRODUCTION

The treatment of depression in adolescents is an area of burgeoning research interest. Adolescents in general and depressed adolescents in particular traditionally have not been the focus of clinical drug studies. This is unfortunate, as major depression in the adolescent population is as prevalent as in adults. Data from the 1,769 adolescents and young adults who participated in the National Comorbidity Survey indicate a lifetime prevalence rate of 15.3% for major depression (Kessler et al, 1998), which is comparable to the 17% lifetime prevalence of depression in adults (Kessler et al, 1994).

Adolescents share with adults many of the hallmark features of major depression (Kovacs and Devlin, 1998; Post et al, 1998). Adolescents typically exhibit dysphoria, feelings of worthlessness, loss of interest in activities, impoverished self-esteem, poor concentration, anergia, and suicidal tendencies. The depressed adolescent may also be irritable and have failed relationships (Committee on Adolescent Health Care, 1997; Post et al, 1998). Adolescents are adept at hiding symptoms from peers and family, which

can perpetuate social isolation and missed diagnoses. Undiagnosed and untreated depression can lead to dwindling academic performance, failure to graduate, poor peer relationships, family conflict, and suicide (Committee on Adolescent Health Care, 1997).

Preliminary evidence from the published literature supports anecdotal clinical experience that antidepressants are effective treatments for the adolescent patient with depression. Although the tricyclic antidepressants are the most well-studied antidepressants in adolescents, none of the few controlled clinical studies demonstrates significant differences from placebo (Dulcan et al, 1998). Moreover, concerns about cardiovascular effects and lethality in overdose associated with the use of tricyclic antidepressants in young patients has limited their widespread clinical use. Intentional overdose of cardiotoxic tricyclic antidepressants is a particularly salient concern among younger patients for whom suicidality is a factor that must be assessed.

The few open-label studies of adolescent and childhood depression suggest efficacy of the selective serotonin reuptake inhibitors (Masi et al, 1997;

McConville et al, 1996; Rey-Sanchez and Guttierrez-Casares, 1997; Rodriguez-Ramos et al, 1996; Simeon et al, 1996). However, the published database is small and findings are variable (Dulcan et al, 1998). The findings from a double-blind study of fluoxetine and placebo in children and adolescents with depression support the role of the SSRIs for treatment in this population (Emslie et al, 1997). The need for rigorously designed clinical studies of antidepressant therapy for adolescent depression led to the first double-blind, placebo-controlled comparison of a selective serotonin reuptake inhibitor, paroxetine, with the tricyclic antidepressant, imipramine.

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 two in Canada. XXX patients[1] were screened for eligibility, and 275 patients were randomized to active treatment. The trial was conducted in accordance with good Clinical Practices and the Helsinki

Declaration. All patients and their parent(s) provided written informed consent before entry into the study.

Patient Eligibility

Male and female patients ages 12 through 18 years of age fulfilling the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, revised* (DSM-III-R) criteria for a current episode of major depression of at least 8 weeks in duration were enrolled (American Psychiatric Association, 1987). Major depression was diagnosed using the Schedule for Affective Disorders and Schizophrenia for Adolescents - Lifetime Version (K-SADS-L) rating scale, which has been modified from the adult SADS assessment technique (Endicott and Spitzer, 1978). The K-SADS-L is a semi-structured clinical interview that uses separate patient and parent reports to assess lifetime presence of affective and schizophrenic disorders, attention deficit/hyperactivity disorder, antisocial personality disorder, and social anxiety disorder. Eligible patients 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

---

[1] Reviewers: How many patients were screened?

at least 80 as determined by the Peabody Picture Vocabulary Test. All patients were medically healthy.

Eligible patients and their parent(s) agreed that the patient had a disorder requiring treatment. In cases where the diagnosis was not certain, videotapes of the screening interview were reviewed and the diagnosis was verified by an independent expert prior to determining study eligibility.

Patients with a current or lifetime DSM-III-R diagnosis of bipolar disorder, schizo-affective disorder, eating disorder, alcohol or substance use disorder, obsessive-compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder were not eligible for study enrollment. A diagnosis of post-traumatic stress disorder within the prior 12 months was also considered an exclusionary criterion. Also excluded were patients with current suicidal ideation or a history of suicide attempts by drug overdose, cardiovascular disease, current psychotropic drug use, an adequate trial of antidepressant medication within 6 months of study entry, or investigational drug use within 30 days of study entry or within 5 half-lives of the investigational drug. Patients with organic brain disease, epilepsy, mental

retardation, who were pregnant or breastfeeding, and females who were sexually active and not using reliable contraception were also excluded.

Blinding, Randomization, and Treatment

All patients underwent a 7- to 10-day screening phase to determine study eligibility and to obtain baseline global functioning scores, physical examination, and clinical laboratory studies. Using a computer-generated list, eligible patients 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. Patients 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 investigator. Imipramine treatment was initiated with a forced titration schedule in which patients received daily doses of 50 mg during week 1, 100 mg (in divided doses) during week 2, 150 mg during week 3, 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 by the investigator to be needed.

Supportive psychotherapy for depression was provided to all patients at each weekly clinic visit according to the method of Fawcett (Fawcett et al, 1987). Psychotherapy was limited to clinical support and observation of medication effects and did not include interpersonal or cognitive/behavioral psychotherapeutic interventions.

Efficacy and Safety Evaluation

After randomization to treatment, patients were seen in the clinic at weekly intervals and were evaluated with standardized instruments and global assessments for efficacy. Eight primary efficacy parameters were assessed. Primary efficacy parameters were defined as 1) percentage *remission* at endpoint; 2) percentage of *response* at endpoint; 3) the depressed mood item of the HAMD; 4) the depression item of the K-SADS-L; 5) CGI improvement scores of 1 (very much improved) or 2 (much improved); 6) 9-item depression subscale of the K-SADS-L; 7) mean Clinical Global Impressions (CGI) improvement scores; and 8) change from baseline in HAMD total score. Criteria were defined in order to determine a robust clinical response. Patients were considered to be *responders* if, at the end of treatment, they

had achieved a HAMD score ≤ 8 or a ≥ 50% reduction in baseline HAMD score.

Remission was defined as a HAMD score ≤ 8 at endpoint.

The secondary efficacy parameters consisted of 1) Autonomous Function Checklist completed by the parent that assessed autonomy in performing daily activities (Sigafoos et al, 1988); 2) Self Perception Profile completed by the patient to determine self-esteem (Harter, 1988); and 3) Sickness Impact Scale completed by the patient to measure present health and quality of life (Bergner et al, 1981).

Adverse effects were determined at each weekly visit by asking patients non-leading questions. Vital signs and body weight were measured at each visit. Rhythm strip EKGs were obtained at each visit, and 12-lead EKGs 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; patients 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 patients at ≤ 200 mg imipramine were withdrawn from the study. Cardiovascular parameters necessitating dosage reduction or study withdrawal 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 mmHg/diastolic blood pressure < 85 mmHg, 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, desipramine (the major, pharmacologically active, metabolite of imipramine), and paroxetine. Patients were withdrawn from the study if the combined imipramine and desipramine concentration exceeded 500 ng/mL. The paroxetine plasma concentration cut-off point for study withdrawal was XXXX.[2]

[2] Reviewers: Is this statement necessary? If so, the cut-off point was not included in the Clinical Report.

Statistical Methods

Changes from baseline to endpoint in the total HAMD score, CGI improvement scale, and K-SADS-L were analyzed by using a 2-factor analysis of variance (ANOVA) implemented in the SAS procedure General Linear Models (GLM). The model included terms for treatment group, investigator, and investigator-by-treatment interaction. Categorical variables, such as the percentage of patients responding to treatment, were analyzed using logistic analysis implemented in the categorical modeling procedure (CATMOD) of the SAS system. Pair-wise comparisons between treatments were made at the 0.05 level of significance using the CONTRAST statement.[3]

All statistical tests comparing active treatments to placebo were two-tailed and performed at an alpha level of 0.05. Using a power of 0.80, to detect a difference between active treatments and placebo, 275 patients was determined as the target recruitment. Efficacy analyses were carried out on the sample of randomized patients with at least one post-baseline efficacy evaluation (N=275, referred to herein as the "efficacy population"). For patients who did not complete the entire study, endpoint was defined as the last

[3] Reviewers: P values are available for active treatments vs placebo; are P values available for paroxetine vs imipramine? Should this data be included?

evaluation during treatment and was used as an estimate of the missing data (ie, last observation carried forward); this was the primary population reported. Data are reported as mean values (± standard deviation or standard error) and 95% confidence intervals are reported where appropriate.

RESULTS

Of XXX patients who were screened, 275 were enrolled in the study and randomized for treatment (Figure 1).[4] Treatment groups were well-matched with regard to demographic characteristics and psychiatric profile (Table 1). A typical patient was female, 15 years of age, and Caucasian. Most patients had a positive family history for depression and had experienced only one prior episode of major depression. The mean duration of the current depressive episode was over one year. Mean baseline HAMD total scores were between 18 and 19. Approximately 30% of patients exhibited features of melancholic or endogenous depression, and 20% had features of atypical depression. Psychiatric comorbidity was common; anxiety disorders, such as separation anxiety and social anxiety disorder, occurred in approximately 20%

[4] Reviewers: How many patients were screened?

to 30% of patients. Externalizing disorders, including conduct disorder, and attention deficit disorder, were also common in this population.

Premature Discontinuation

A total of 190 patients (69% of 275) completed the 8-week study (Figure 1). Premature withdrawal rates were 28% for paroxetine, 40% for imipramine, and 24% for placebo. Study withdrawal due to adverse effects was the most common reason for discontinuation in the paroxetine (9.7%) and imipramine (31.5%) groups, respectively. Cardiac adverse effects led to withdrawal among 14% of patients in the imipramine group (13 patients). Protocol violation, including lack of compliance, was the most common reason for withdrawal in the placebo group (8.0%).[5]

Efficacy Results

Of the 8 primary efficacy variables, paroxetine separated statistically from placebo along 4 of the parameters: remission, HAMD depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 (very much improved) or 2

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[5] Reviewers: Did differences between active treatments and placebo attain statistical significance?

(much improved)(Table 3). The response to imipramine was not significantly different than placebo across any of the 8 primary efficacy variables.

Patients in all treatment groups exhibited progressively greater remission rates, defined as a HAMD total score ≤ 8 at study endpoint, during the first 4 weeks of the study. Remission was achieved in 63.3% of paroxetine patients (57/90; *P*=.019 versus placebo), 50% of imipramine patients (47/94; *P*=.574 versus placebo), and 46% of placebo patients (40/87) at endpoint (Figure 2). Although neither paroxetine nor imipramine separated statistically from placebo across the secondary efficacy variables, improvements over baseline were achieved for each active treatment group (Table 4).

Dosage Titration

Nearly half of patients in the paroxetine group remained at the initial starting dose of 20 mg per day (48%). Mean doses at study endpoint for paroxetine were 28.0 mg (s.d. ± 8.54 mg) and imipramine 205.8 mg (s.d. ± 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

Paroxetine was well-tolerated in this adolescent population. 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 patients.[6]

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 patients. Dry mouth, constipation, and tremor were the most common adverse effects leading to imipramine dose reductions. Premature withdrawal from the study due to adverse effects occurred at rates of 9.7% for paroxetine, 31.5% for imipramine, and 6.9% for placebo (Figure 1). Clinically significant

[6] SB reviewers: Did between-group differences attain statistical significance?

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

Of patients in the imipramine group who stopped therapy due to 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 beats per minute over baseline among patients treated with imipramine. Neither paroxetine nor placebo was associated with changes in heart rate.

COMMENT[7]

This is the first study to compare an SSRI with placebo in the treatment of adolescent depression. Paroxetine was numerically superior to placebo on all 8 of the prospectively defined measures of efficacy. Of these, paroxetine was significantly more effective than placebo in the depression item of the HAMD and the K-SADS-L, the percent patients with a CGI score of 1 or 2, and the percent patients achieving full remission.

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[7] Reviewers: The discussion section (Comment) is not complete; rather it is presented in Draft I in outline form.

Discussion of high placebo response. Were the 45-minute supportive psychotherapy sessions a factor in the placebo response rate? Is the HAMD a meaningful measure of depression and response in adolescents? Are the other tools more meaningful? Would a longer treatment period be expected to show greater between-group differences?

This study employed a flexible-dose design in which doses could be adjusted based on clinical response and tolerability. Roughly half of patients were maintained at a 20-mg daily dose of paroxetine. The mean daily dose of paroxetine in this study was 28 mg, which is comparable to the findings of 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).

Adverse cardiovascular effects were not observed in patients 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 patients who prematurely stopped treatment with the tricyclic antidepressant.

In conclusion, the findings of this study provide the first validation of preliminary evidence of the effectiveness and safety of the selective serotonin reuptake inhibitor, paroxetine, in the treatment of adolescent depression. Additional studies are warranted 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 patients

Parameter	Paroxetine N=93	Imipramine N=95	Placebo N=87
Gender M/F	35/58	39/56	30/57
Mean age ± s.d. (y)	14.8 ± 1.6	14.9 ± 1.6	15.1 ± 1.6
Race			
Caucasian	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%)
Child Global Assessment Scale (mean ± s.d.)	42.7 ± 7.5	42.5 ± 7.4	42.8 ± 8.3
Duration of current depressive episode in months (mean ± s.d.)	14 ± 18	14 ± 18	13 ± 17
Number of prior depressive episodes			
1	81%	79%	77%
2	12%	14%	14%
≥3	7%	6%	8%

Family history of major depression	86%	90%	95%
Age at onset of first episode in years (mean ± s.d.)	13.1 ± 2.8	13.2 ± 2.7	13.5 ± 2.3
Mean baseline HAMD 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%
Comorbid psychiatric diagnosis			
Any diagnosis	41%	50%	45%
Anxiety disorder[a]	19%	26%	28%
Externalizing disorder[b]	25%	26%	20%

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

[b] Includes conduct disorder, oppositional defiant disorder, and attention deficit/hyperactivity.

Table 2. Medication Doses at Study Endpoint (N=275)

Treatment Group	Daily Dose at Endpoint (mg)	Number of Patients (%)
Paroxetine	20 mg	45 (48%)
N=93	30 mg	22 (23.7%)
	40 mg	26 (28.0%)
	Mean dose in mg ± s.d.	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 ± s.d.	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 3. Summary of primary efficacy variables in adolescents with major depression* who were treated with paroxetine, imipramine, or placebo†

Variable	Paroxetine Mean	(s.e.)	N	Imipramine Mean	(s.e.)	N	Placebo Mean	(s.e.)	N	Paroxetine vs. Placebo P	95% CI	Imipramine vs. Placebo P	95% CI
Remission††													
Week 8 endpoint	63.3%	(-)	90	50.0%	(-)	94	46.0%	(-)	87	.019	2.8 to 34.2	.574	-10.6 to 8.6
Response††													
Week 8 endpoint	66.7%	(-)	90	58.5%	(-)	94	55.2%	(-)	87	.11	-2.8 to 25.7	.61	-11.1 to 17.7
HAMD 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)	90	1.17	0.14)	94	1.53	(0.14)	87	.001	--**	.13	--**
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	2.52	0.18)	87	2.90	(0.18)	85	.049	--**	.86	--**
CGI Score of 1 or 2													
Week 8 endpoint	65.6%	(-)	90	52.1%	(-)	94	48.3%	(-)	87	.02	2.9 to 31.7	.64	-10.6 to 24.3
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	17.99	0.83)	88	19.27	(0.83)	85	.065	-4.40 to 0.22	.98	-2.28 to 2.32
Mean CGI score													
Week 8 endpoint	2.37	(0.16)	90	2.70	0.15)	94	2.73	(0.16)	87	.094	-0.80 to 0.08	.89	-0.46 to 0.40
HAMD 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	9.2	(0.81)	94	9.88	(0.83)	87	.133	-3.92 to 0.62	.87	-2.09 to 2.45

* The last evaluation during treatment for patients who did not complete the entire study (ie, the last observation carried forward) is reported.
† Data presented as mean (+/-) s.e.
†† Remission = HAMD total score ≤ 8 at endpoint; Response = HAMD total score ≤ 8 or a 50% reduction in baseline HAMD score; CGI score of 1 = very much improved; CGI score of 2 = much improved
** SB Reviewers: are CI data available?

Table 4. Summary of second efficacy variables in adolescents with major depression* who were treated with paroxetine, imipramine, or placebo†

Variable	Paroxetine Mean	(s.e.)	N	Imipramine Mean	(s.e.)	N	Placebo Mean	(s.e.)	N	Paroxetine vs. Placebo P	95% CI	Imipramine vs. Placebo P	95% CI
Autonomous Function Checklist													
Baseline	91.41	(3.80)	60	96.02	(3.97)	57	94.18	(3.74)	62	.584	--	.719	--
Week 8 endpoint	106.11	(2.80)	60	107.59	(2.92)	57	103.48	(2.75)	62	.148	--	.546	--
Self Perception Profile													
Baseline	63.48	(2.58)	61	60.87	(2.67)	60	60.69	(2.52)	63	.418	--	.960	--
Week 8 endpoint	76.73	(2.33)	61	73.94	(2.41)	60	72.05	(2.27)	63	.542	--	.586	--
Sickness Impact Profile													
Baseline	30.90	(1.46)	63	30.38	(1.52)	60	32.17	(1.42)	65	.511	--	.363	--
Week 8 endpoint	19.54	(1.55)	63	17.46	(1.62)	60	22.32	(1.51)	65	.463	--	.143	--

* The last evaluation during treatment for patients who did not complete the entire study (ie, the last observation carried forward) is reported.
† Data presented as mean (+/-) s.e.

Table 5. Adverse effects occurring in ≥ 5% of patients 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%)	7 (7.4%)	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%)

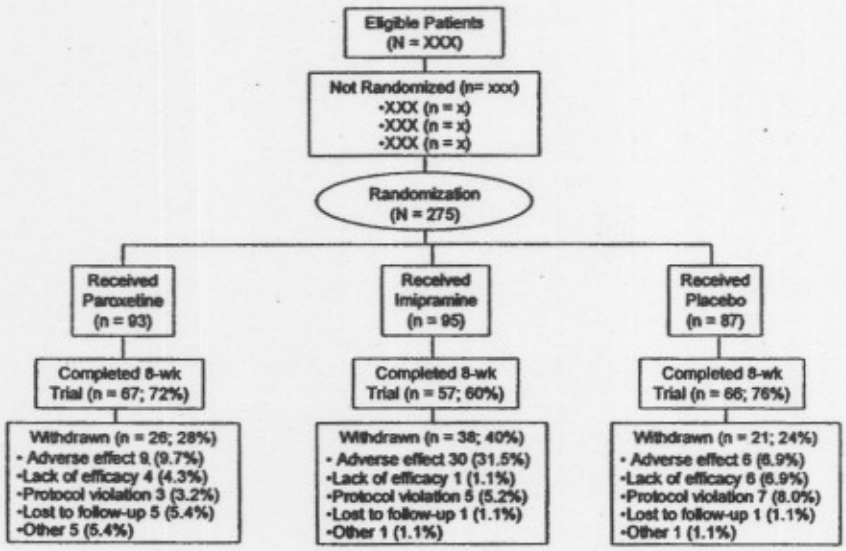

Figure 1.[8] Of XXX adolescents who were screened, 275 fulfilled criteria for major depression and were randomized to receive 8 weeks of treatment with paroxetine (93 patients), imipramine (95 patients), or placebo (87 patients). A total of 69% of patients (N=190) completed the trial. Withdrawal rates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

[8] SB reviewers: *JAMA* requires this figure. Please provide the overall number of patients who were screened prior to randomization and itemize reasons for exclusion. Thank you.

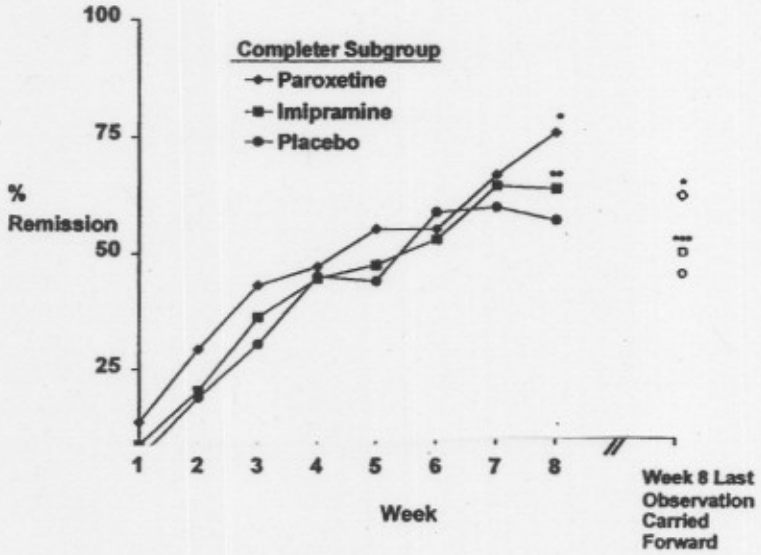

Figure 2. Percentage of paroxetine, imipramine, and placebo-treated patients achieving remission in the completer and last-observation carried forward subgroups (ie, HAMD total score ≤ 8). * *P*=.019; ** *P*=.440; *** *P*=.574.