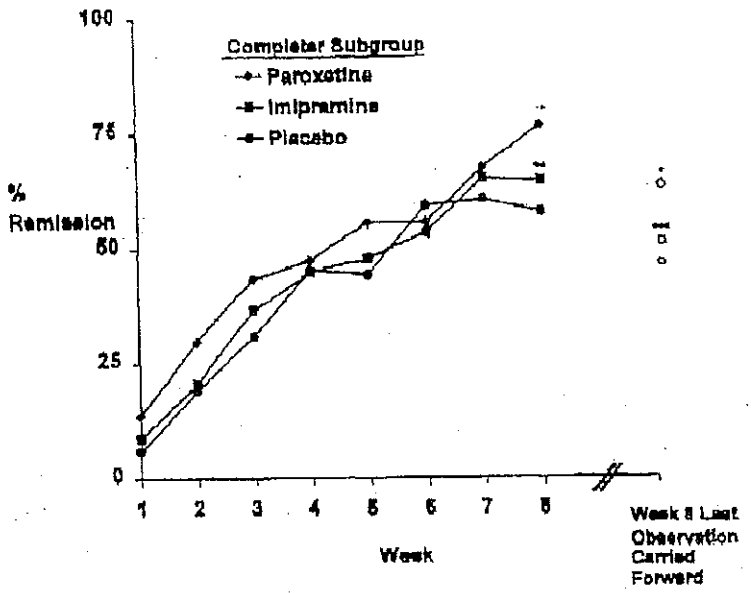

Figure 2. Percentage of paroxetine, imipramine, and placebo-treated subjects achieving remission in the completer and last-observation carried forward subgroups (ie, HAMD total score ≤ 8). * P=.019; ** P=.440; *** P=.574.

WB 202530

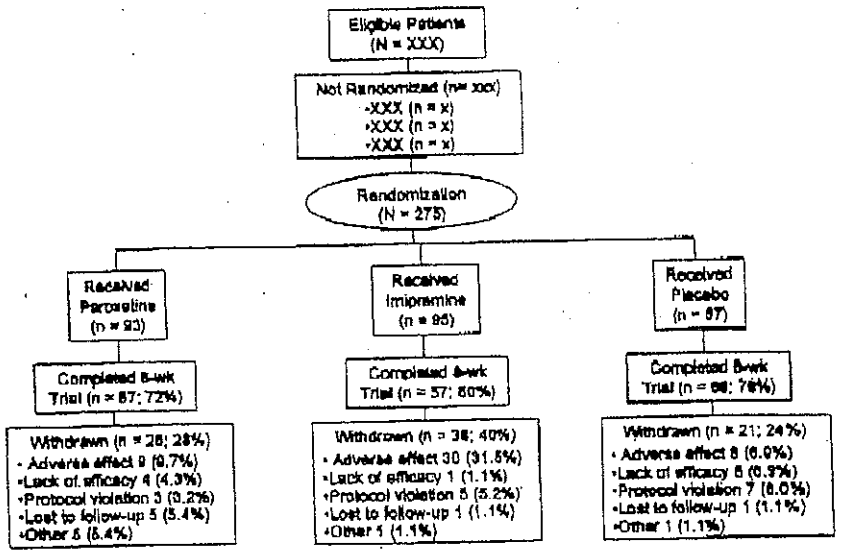

Figure 1.[1] Of XXX adolescents who were screened, 275 fulfilled criteria for major depression and were randomized to receive 8 weeks of treatment with paroxetine (93 subjects), imipramine (95 subjects), or placebo (87 subjects). A total of 69% of subjects (N=190) completed the trial. Withdrawal rates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

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

WB 202529

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%)

WB 202528

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%)	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%)

? why was this more primary

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 subjects who did not complete the entire study (ie, the last observation carried forward) is reported.
† Data presented as mean (+/-) s.e.

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

Treatment Group	Daily Dose at Endpoint (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 ± 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%)

WB 202525

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.

WB 202524

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
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%

WB 202523

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WB 20519

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WB 202518

of QT intervals during imipramine therapy resulted in treatment discontinuation in one-third of the 31.5% of subjects who prematurely stopped treatment with the tricyclic antidepressant.

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.

~~This question will not be answered with trials involving tricyclic~~ involving →
~~antidepressants.~~ ~~Rather, studies in adolescents of~~ noradrenergic
Available will be required to address
antidepressants not yet clinically ~~available may provide more information on~~
the question of ~~differential~~ preferential efficacy of
~~their use~~ 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 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 subjects treated with paroxetine. In contrast, tachycardia, postural hypotension, and prolongation

WB 202516

This demonstration of efficacy for paroxetine ~~further supports the~~ findings is in accordance with
of open-label studies of ~~paroxetine, fluvoxamine, fluoxetine, and sertraline~~ serotonin reuptake inhibitor antidepressants
(Apter et al, 1994; Boulos et al, 1992; Masi et al, 1997; McConville et al, 1996; Rey-Sanchez et al, 1997; Rodriguez-Ramos et al, 1996; Simeon et al, 1998), a retrospective review of fluoxetine (Jain et al, 1992), and ~~four~~ results from ~~randomized~~, placebo-controlled ~~studies of fluoxetine~~ (Emslie et al, 1997) and historical case-control ~~Simeon et al, 1990~~; (Strober et al, 1999)~~2~~ studies. These findings of efficacy for paroxetine and other SSRIs are notable in that randomized, double-blind, placebo-controlled trials (Geller et al, 1990, 1989; Hughes et al, 1990; Kashani et al, 1984; Klein et al, 1992; Kramer and Feiguine, 1981; Kutcher et al, 1994; Kye et al, 1996; Patti and Law, 1982; Preskorn et al, 1987; Puig-Antich et al, 1987) and one meta-analysis (Razali et al, 1995) have not shown efficacy for the tricyclic antidepressants in the treatment of adolescent depression. Because the tricyclic antidepressants are no longer under patent protection and they are associated with an unacceptably high risk of cardiotoxicity, especially in children, further controlled studies of these agents are not likely to be conducted. As such, future research ~~Are serotonergic antidepressants (ie, the SSRIs) more effective than agents with primarily noradrenergic effects?~~

WB 202515

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

Of subjects 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 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 that of an SSRI with a tricyclic antidepressant in the treatment of adolescent depression. major depressive disorder. Paroxetine was numerically superior to placebo on all 8 of the prospectively defined measures of efficacy, and ~~of these, paroxetine was~~ statistically significantly more effective than placebo with regard to the depression item of the HAMD and the K-SADS-L, the percent of subjects achieving a CGI score of 1 (very much improved) or 2 (much improved), and the percent of subjects achieving full remission.

WB 202514

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 subjects.[7]

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 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

Statistically significant?

See page 16

[7] GG reviewers: Did between-group differences attain statistical significance?

WB 202513

Subjects 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 subjects (57/90; P=.019 versus placebo), 50% of imipramine subjects (47/94; P=.574 versus placebo), and 46% of placebo subjects (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. Improvements in the K-SADS-L depression subscore (P=.065) and mean CGI score (P=.094) trended toward statistical significance in the paroxetine group, but not in the imipramine group (P=.98 and P=.89, respectively) (Table 4).

Does this imply that we saw no comparable trend for placebo?

Dosage Titration

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

WB 202512

Premature Discontinuation

A total of 190 subjects (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 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%).[6]

← what about placebo?

↑ We should note statistical differences, where appropriate; e.g., differences in withdrawal between groups.

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

→ and [illegible] statistical significance on the measures

What for

K-SADS-L depressed [illegible] and mean CGI [illegible]

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

standard deviation or standard error) and 95% confidence intervals are reported where appropriate.

RESULTS

Of XXX subjects who were screened, 275 were enrolled in the study and randomized for treatment (Figure 1).[5] Treatment groups were well-matched with regard to demographic characteristics and psychiatric profile (Table 1). A typical subject was female, 15 years of age, and Caucasian. Most subjects 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, with a mean baseline HAMD total score between 18 and 19. Approximately 30% of subjects 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, and externalizing disorders, occurred in approximately 20% to 30% of subjects.

WB 202510

included in the Clinical Report.
[5] Reviewers: How many subjects were screened?

(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 subjects 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.

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, a sample size of 275 subjects was determined a priori as the target recruitment.* Efficacy analyses were carried out on the sample of randomized subjects with at least one post-baseline efficacy evaluation (N=275, referred to herein as the "efficacy population"). For subjects who did not complete the entire study, endpoint was defined as the last evaluation during treatment and was used as an estimate of the missing data (ie, last observation carried forward)[1]; this was the primary population reported. Data are reported as mean values (±

WB 202509

[1] Reviewers: Is this statement necessary? If so, the cut-off point was not

* Jim - See Neals note - I assumed we used the adult data for effect sizes. Is this correct

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 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, 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. The paroxetine plasma concentration cut-off point for study withdrawal was XXXX.[4]

Did we have such a withdrawal for parox treated subjects?

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

WB 202508

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 the subject's autonomy in performing daily activities (Sigafoos et al, 1988); 2) Self Perception Profile, completed by the subject to determine self-esteem (Harter, 1988); and 3) Sickness Impact Scale, completed by the subject, to measure present health and quality of life (Bergner et al, 1981).

Adverse events, heart rate, blood pressure, and body weight were determined at each weekly visit. Rhythm strip 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; subjects at 20 mg paroxetine were withdrawn from the study. Similarly, imipramine doses of 250

WB 202507

per day for week 5 and to 300 mg per day for weeks 6 through 8 were allowed if judged necessary by the investigator.

Supportive case management was provided to all subjects at each weekly clinic visit according to the method described by Fawcett (Fawcett et al, 1987). 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 primary efficacy parameters were assessed: 1) *remission* at endpoint; 2) *response* at endpoint; 3) change in the depressed mood item of the HAMD; 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 Clinical Global Impressions (CGI) improvement scores; and 8) change from baseline in HAMD total score.

Subjects were considered to be *responders* if, at the end of treatment, they

WB 202506

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 10-day screening phase to determine persistence of entry diagnostic and severity 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 investigator. 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

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interviewed separately. For those cases where there existed a significant discrepancy between information provided by the adolescent and the parent, the clinician met with both ~~the adolescent and the parent~~ to discuss the information and reach a consensus. Eligible subjects and their parent(s) agreed that ~~the patient~~ had a disorder requiring treatment. In cases where the diagnosis was not certain, audiotapes of the screening interview were reviewed and the diagnosis was verified further by an independent expert from another participating site prior to certifying study eligibility.

Subjects 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 brain disorder were excluded from consideration. A diagnosis of post-traumatic stress disorder within 12 months of recruitment was also ~~considered~~ exclusionary, as was current suicidal ideation or a history of suicide attempts by drug overdose with intent or specific plan, 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~~.

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(DSM-III-R) (American Psychiatric Association, 1987) criteria for a current episode of major depression of at least 8 weeks in duration were enrolled. Major depression was diagnosed by structured interview using the juvenile version (Endicott and Spitzer, 1978) of 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. The K-SADS-L uses separate patient and parent reports to assess lifetime presence of affective and schizophrenic disorders, ~~attention deficit/hyperactivity disorder, and the~~ full range of childhood and adolescent psychopathological conditions. In addition to fulfilling 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-CAS) 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.

The K-SADS reference should be inserted here

as well as the

Potential participants in the study were screened initially by telephone, and candidates who were considered likely to meet diagnostic criteria were evaluated immediately at the study site. Adolescents and parents were

[1] Reviewers: How many subjects were screened?

double-blind, placebo-controlled comparison of a selective serotonin reuptake inhibitor, paroxetine, with a 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 subjects[3] were screened for eligibility, and 275 subjects were randomized to active treatment. The trial was conducted in accordance with good Clinical Practices and the Helsinki Declaration. All subjects and their parent(s) provided written informed consent before entry into the study.

Patient Eligibility

Male and female subjects, ages 12 through 18 years of age, fulfilling the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, revised*

[2] Dr Ryan: please provide complete citation for this paper; a search of MedLine did not identify it.

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time, cardiovascular effects and lethality in overdose associated with the tricyclic agents has greatly limited their use in clinical practice. Intentional overdose of cardiotoxic tricyclic antidepressants is a particularly salient concern for younger patients for whom ~~suicidality may be~~ a factor use of medication in suicidal attempts is a major clinical problem and is believed to limit prescription of these medications in this population.

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 (Apter et al, 1994; Boulos et al, 1992; Masi et al, 1997; McConville et al, 1996; Rey-Sanchez et al, 1997; Rodriguez-Ramos et al, 1996; Simeon et al, 1998). Although controlled trials remain the standard against which effectiveness is determined, only three have been reported (Emslie et al, 1997; Simeon et al, 1996; Strober et al, 1999[2]). One placebo-controlled study (Emslie et al, 1997) showed a drug-placebo difference in efficacy of 23%. [mention the specific outcome for this difference - from the Emslie article] Another study, employing a historical case control design (Strober et al, 1999) demonstrated greater efficacy of fluoxetine compared to imipramine in a severely ill, inpatient population of adolescents with major depression. We now report principal findings from the first

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[1] Dr Ryan: please confirm that this is the paper you asked to be included.

INTRODUCTION

The treatment of depression in adolescents is an area of burgeoning research interest. Unfortunately, few well-controlled, large-scale, randomized assignment clinical trials have been conducted in this population to date. Data from the 1,769 adolescents and young adult participants in the National Comorbidity Survey (Kessler et al, 1998) indicate a lifetime prevalence rate of 15.3% for major depression, comparable to the 17% lifetime prevalence of depression in adults (Kessler et al, 1994). As with adults, the course of major depression in adolescents is often characterized by protracted episodes, frequent recurrence, and impairment in social and academic domains (Rao et al, 1995).[1]

The efficacy of tricyclic antidepressants have been investigated in at least 11 double-blind, randomized studies (Dulcan et al, 1998; Ryan and Varma, 1998), none demonstrating superiority of active treatment over placebo. However, methodological deficiencies in these studies, including very small sample sizes and heterogeneity of diagnostic composition of subjects, limit statistical inference and generalizability of the findings. At the same

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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 placebo for any of the measures of antidepressant efficacy. 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 subjects withdrawing from the study due to adverse effects. Of the subjects stopping imipramine therapy, nearly one-third did so because of adverse cardiovascular effects, including tachycardia, postural hypotension, and ECG abnormalities.

I assume these were statistically significant. Can we report them?

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

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ABSTRACT (404)

Context: Depression is a highly prevalent disorder among adolescents, and suicide is the second leading cause of death in this age group. 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 Subjects: 275 adolescent subjects (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, 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 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: Efficacy was demonstrated for paroxetine, with significantly greater improvement across measures of remission, HAMD depressed mood item,

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

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