Report Synopsis

Title

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression - Acute Phase (29060/329)

Investigators and Centers

Investigators from 10 centers in the United States and 2 in Canada participated in the study. All were affiliated with either a university or a hospital psychiatry department and had extensive experience in treating adolescent patients.

Publications

Keller MB, Ryan ND, Birmaher B, Klein RG, Strober M, Wagner KD, Weller EB, Paroxetine and Imipramine in the Treatment of Adolescent Depression. Abstract NR206, Annual Meeting of the American Psychiatric Association (APA), Toronto Ontario, Canada, 2 June 1998.

Wagner KD, Birmaher B, Carlson G, Clarke G, Emslie G, Geller B, Keller M, Klein R, Kutcher, S, Papatheodorou G, Ryan N, Strober M, Weller E, Safety of Paroxetine and Imipramine in the Treatment of Adolescent Depression. Abstract 69, Annual Meeting of New Clinical Drug Evaluation Program (NCDEU), Boca Raton, Florida, USA, 11 June, 1998,

Study Dates

The first patient received study medication on 20 April 94, the final patient was enrolled on 15 March 1997. The final study visit for the acute phase occurred on 07 May 1997, the final study visit for the continuation phase occurred on 15 February 1998.

Objectives

The primary objective was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

The secondary objectives were as follows: to identify predictors of treatment outcomes across clinical subtypes of major depressive disorder; to provide information on the safety profile of paroxetine and imipramine when these agents were given for an extended period of time; to estimate the rate of relapse among imipramine, paroxetine and placebo responders who were maintained on treatment.

This report presents the results from the 8 week acute phase. Findings from the continuation phase, which include long term safety and the analysis of relapse, will be reported separately.

Study Design

This was a multi-center, double-blind, placebo controlled, parallel group trial of the efficacy and safety of treatment with paroxetine or imipramine compared with placebo in adolescents with major depressive disorder. The study plan included two phases, an acute phase in which patients were treated for 8 weeks and a continuation phase in which responders had the option to continue to receive blinded study medication for an additional 6 months. Eligible patients were randomized to treatment with paroxetine, imipramine or placebo for 8 weeks; clinic visits for efficacy and safety assessments were made weekly. At the completion of the 8 week study, patients who met specific criteria for a clinical response could be continued on the same medication in a double-blind manner for a 6 month continuation treatment phase; clinical visits were made monthly.

Study Population

Eligible patients were adolescents (12 years 0 months through 18 years 11 months inclusive), were currently in an episode of major depression (DSM-III-R criteria) for at least 8 weeks, and had a total score ≥ 12 on the 17-item Hamilton Depression Scale (HAM-D).

Treatment and Administration

Test product: Paroxetine was supplied as film coated, capsule shaped tablets, yellow containing 10 mg (batch no U95085) and pink containing 20 mg (batch no. U95086).

Reference therapies: Imipramine (50 mg) was bought commercially and supplied as green film coated round tablets (batch nos. U95121, U-93135, and U-93139). "Paroxetine placebos" (batch no. U95084) matched the paroxetine 20 mg tablets, and "imipramine placebos" (batch no. U95087) matched the imipramine tablets.

All tablets were over-encapsulated in bluish-green capsules to preserve blinding. Patients took their study medication twice daily, once in the morning and once at night. Total daily doses of imipramine were 50, 100, 150, 200, 250, and 300 mg for dosing levels 1 to 6, respectively. Daily doses of paroxetine were 20 mg for levels 1 to 4, 30 mg for level 5, and 40 mg for level 6. At the beginning of the study, all patients were started at level 1 and titrated up to level 4 at weekly intervals, regardless of response. Non-responders could be titrated up to level 5 or 6 during the next 4 weeks.

Evaluation Criteria

Efficacy Parameters: The efficacy assessments in the trial included the Hamilton Rating Scale for Depression (HAM-D), the 9-item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School-age Children - Lifetime Version (K-SADS-L), the Clinical Global Improvement (CGI), and the following functional and quality of life assessments: the Self Perception Profile (SPP), the Autonomous Functioning Checklist (AFC), and the Sickness Impact Profile (SIP).

The protocol defined the primary efficacy parameters as the change from baseline in the HAM-D total score, and the proportion of responders defined as patients with a 50% reduction in the total HAM-D or a score of 8 or less. Secondary parameters included the change in baseline in the K-SADS-L depression subscale, the mean CGI score, and the functional/quality of life instruments. An analytical plan developed prior to opening of the blind also described additional outcome measures including patients in "remission" (a score of 8 or less on the HAM-D total), and the mean change in the depressed mood items from the HAM-D and the K-SADS-L instruments.

Safety Parameters: Adverse experiences, vital signs and body weight; clinical laboratory evaluations, and electrocardiograms (EKGs).

Other Parameters: Plasma paroxetine and serum IMI and DMI concentrations were determined at the completion of 4 and 8 weeks of treatment.

Statistical Methods

All patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment were included in the ITT efficacy population. Statistical conclusions concerning the efficacy of paroxetine and imipramine were made using data obtained from the last observation carried forward (LOCF) and observed cases (OC) datasets. The last observation carried forward consisted of each patient's last on-therapy assessment during the acute phase. All hypotheses were two sided. The comparisons of interest were paroxetine vs. placebo and imipramine vs. placebo at week 8 LOCF. Hypotheses concerning these comparisons were tested at the alpha level of 0.05. No comparisons were made between paroxetine and imipramine. Interactions were considered significant at the 10% level of significance. Continuous efficacy variables were analyzed by analysis of variance using the general linear model (GLM) procedure of SAS with effects for treatment and investigator. Categorical data were analyzed by logistic analysis using the categorical modeling procedures (CATMOD) of SAS with effects for treatment and investigator. Covariate analyses were also carried out using the general linear model procedures. For the covariate analyses, each analysis used a model including effects for treatment, covariate, and treatment by covariate interaction.

Patient Disposition and Key Demographic Data

Two hundred and seventy five patients were enrolled in the acute phase and randomized to the three treatment regimens: 93 paroxetine, 95 imipramine, 87 placebo. The baseline demographic features and the clinical features of depression of the three treatment groups were comparable at entry. Over 70% of the paroxetine and the placebo patients completed the 8-week acute phase. In contrast, 60% of imipramine patients completed the acute phase. The most common reason for early withdrawal for the imipramine group was adverse events.

Demographic and Clinical Characteristics at Entry			
	Paroxetine N = 93	**Imipramine N = 95**	**Placebo N = 87**
Age (yrs.) mean (S.D.)	14.8 (1.6)	14.9 (1.7)	15.1 (1.6)
Weight (lbs) mean (S.D.)	146.3 (38.9)	139.4 (36.7)	145.3 (40.8)
Race			
Caucasian	83%	87%	81%
Black	5%	3%	7%
Other	12%	9%	13%
Female	62%	59%	66%
Duration of current depressive episode (mos.) mean (S.D.)	14.4 (17.5)	14.2 (17.9)	12.5 (16.6)
Age at first episode (yrs.) mean (S.D.)	13.2 (2.8)	13.2 (2.7)	13.5 (2.3)
% patients with > 1 prior episode	18%	19%	22%
Baseline Mean HAM-D at entry (S.D.)	19.0 (4.1)	18.3 (4.3)	19.2 (4.3)

Patient Disposition			
	Paroxetine	**Imipramine**	**Placebo**
Entered	93	95	87
Completed 8 weeks	72%	60%	76%
Reason for Withdrawal			
Adverse Event	10%	32%	7%
Lack of efficacy	4%	1%	7%
Other reason+	14%	7%	10%
Mean dose (mg) (S.D.)	28.0 (8.5)	206 (64.0)	0

+ Other includes patients withdrawn for protocol violations and lost to follow-up

Efficacy Results

The protocol described two primary efficacy endpoints: the change in the total HAM-D score, and the percentage of responders, defined as patients with at least 50% reduction in the baseline HAM-D score or a score of 8 or less. There were six secondary measures. These included the change from baseline in the 9-item K-SADS-L depression subscore, the change in the depression item scores of both the HAM-D and the K-SADS-L, the mean global improvement scores, percent of patients rated "very much" or "much improved," and the percent of patients in remission defined as patients with a final HAM-D score of 8 or less.

The analyses of these measures support that paroxetine is beneficial in treating adolescents with major depression, but the support is derived mainly from the secondary measures. In the protocol defined primary endpoints, the placebo response was large and the magnitude of the benefit of paroxetine response over

placebo was modest and did not achieve statistical significance. For the LOCF dataset, the mean change in the HAM-D scores for the paroxetine group was approximately 2 points greater than placebo (-10.7 units vs -8.9; p=0.113). In the responder analyses, 67% of paroxetine patients and 55% of placebo patients were classified as responders (p=0.112).

In the secondary measures, however, paroxetine treatment was numerically superior to placebo in all six endpoints and achieved statistical significance in four: the depression item of the HAM-D (p=0.003), the depression item from the K-SADS-L (p=0.049), the percent of patients rated "very much" or "much improved" (p=0.020), and the percent of patients in remission (p=0.019).

There was little evidence to support the benefit of imipramine at the doses tested in treating adolescents with depression.

Mean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission

	Week 8 ITT Population				
	Paroxetine	**Imipramine**	**Placebo**	**Paroxetine vs Placebo**	**Imipramine vs Placebo**
***Mean Change in HAM-D Total (SEM)**					
Wk 8 OC	-12.2 ± 0.88	-10.6 ± 0.97	-10.5 ± 0.88	p = 0.153	p = 0.945
Wk 8 LOCF	-10.7 ± 0.81	-8.9 ± 0.81	-9.1 ± 0.83	p = 0.133	p = 0.873
Mean Change HAM-D Depressed Mood (SEM)					
Wk 8 OC	-2.21 ± 0.17	-1.76 ± 0.18	-1.56 ± 0.17	p = 0.003	p = 0.358
Wk 8 LOCF	-2.0 ± 0.14	-1.62 ± 0.14	-1.33 ± 0.14	p = 0.001	p= 0.135
Mean Change in K-SADS-L 9-Item Depression Subscore (SEM)					
Wk 8 OC	-12.0 ± 0.93	-10.7 ± 1.02	-10.8 ± 0.93	p = 0.348	p = 0.883
Wk 8 LOCF	-11.7 ± 0.84	-9.6 ± 0.83	-9.6 ± 0.83	p = 0.065	p = 0.984
Mean Change in K-SADS-L Depression Item (SEM)					
Wk 8 OC	-2.35 ± 0.20	-2.05 ± 0.22	-1.93 ± 0.20	P = 0.113	P = 0.661
Wk 8 LOCF	-2.20 ± 0.18	-1.77 ± 0.18	-1.73 ± 0.19	P = 0.049	P = 0.868
Mean Clinical Global Improvement Score (SEM)					
Wk 8 OC	1.9 ± 0.15	2.2 ± 0.17	2.4 ± 0.16	p = 0.030	p = 0.371
Wk 8 LOCF	2.4 ± 0.16	2.7 ± 0.15	2.7 ± 0.16	p = 0.094	p = 0.896
***% Responders (50% ↓ HAM-D Total or a Score ≤ 8)**					
Wk 8 OC	81% (54/67)	73% (41/56)	65% (43/66)	p = 0.051	p = 0.363
Wk 8 LOCF	67% (60/90)	59% (55/94)	55% (48/87)	p = 0.112	p = 0.612
% Responders (CGI Rating of "Very Much Improved" or "Much Improved")					
Wk 8 OC	79% (53/67)	68% (38/56)	61% (40/66)	p = 0.020	p = 0.506
Wk 8 LOCF	66% (59/90)	52% (49/94)	48% (42/87)	p = 0.020	p = 0.642
% Remission (HAM-D Score ≤ 8)					
Wk 8 OC	76% (51/67)	64% (36/56)	58% (38/66)	p = 0.019	p = 0.440
Wk 8 LOCF	63% (57/90)	50% (47/94)	46% (40/87)	p = 0.019	p = 0.574

* Protocol defined primary measures of efficacy.

Safety Results

Adverse Experiences:

The nature and incidence of adverse events reported for the paroxetine group were similar to that reported for adult depressed patients receiving paroxetine in controlled trials of comparable duration[1] and as described in the Paxil U.S. prescribing information. Two exceptions to the profile seen in adults include tooth disorder and hostility. The latter term includes aggressiveness and conduct disorders. These exceptions may be related to the age of the study population. As in the adult, adverse events were more likely to occur during the initial weeks of treatment. Analysis by age suggests that events associated with the nervous

system (dizziness, sleep problems, and conduct disorders) were more likely to occur in the younger subset (<15 yrs.).

There were no deaths during the trial. Serious adverse events occurred in 18 patients, 11 in the paroxetine group, 5 in the imipramine group, and 2 in the placebo group. One of the paroxetine patients experienced migraine headache during down titration after completing 8 weeks of treatment. For the remaining patients the events were psychiatric in nature and included worsening depression, suicidal ideation/gestures, and conduct disturbances (hostility). In the imipramine group, one patient developed a maculopapular rash, one had dyspnea associated with chest pain, one reported auditory hallucinations, and two were reported to have serious conduct disturbances (hostility). In the placebo group, the two serious events were worsening depression.

Adverse Events Occurring in ≥ 5% of Any Group and at Least 2X Placebo			
	Paroxetine N = 93	**Imipramine N = 95**	**Placebo N = 87**
Cardiovascular			
Tachycardia	2 (2%)	18 (19%)	1 (1%)
Postural Hypotension	1 (1%)	13 (14%)	1 (1%)
Vasodilatation	0 (0)	6 (6%)	2 (2%)
Chest Pain	2 (2%)	5 (5%)	2 (2%)
Gastrointestinal			
Dry Mouth	19 (20%)	43 (45%)	12 (14%)
Dyspepsia	6 (7%)	9 (9%)	4 (5%)
Constipation	5 (5%)	9 (10%)	4 (5%)
Tooth Disorder	5 (5%)	2 (2%)	2 (2%)
Central Nervous System			
Somnolence	16 (17%)	13 (14%)	3 (3%)
Insomnia	14 (15%)	13 (14%)	4 (5%)
Hostility	7 (8%)	3 (3%)	0 (0)
Emotional Lability	6 (7%)	3 (3%)	1 (1%)
Dizziness	22 (24%)	45 (47%)	16 (18%)
Tremor	10 (11%)	14 (15%)	2 (2%)
Other			
Abnormal Vision	1 (1%)	7 (7%)	2 (2%)
Sweating	1 (1%)	6 (6%)	1 (1%)

Vital Signs:

Changes in vital signs (blood pressure and pulse rate) as well as body weights were small in the paroxetine and placebo treatment groups. In the imipramine treatment group, however, marked increases were seen in the mean pulse rate.

Laboratory Tests:

The number of patients identified with laboratory values of clinical concern was low in all treatment groups. None were considered to be of clinical significance.

Conclusions

This study supports that paroxetine is beneficial in treating adolescents with major depression although the support is derived mainly from secondary measures. The superiority of the paroxetine response over placebo appears less than seen in adults; this may be a result of the weekly supportive psychotherapy sessions allowed by the protocol producing a large "placebo" response. The safety profile of paroxetine in the adolescent appears similar to that reported in adults. The study provided little support for the benefit of imipramine in treating adolescent depression.