Report Synopsis

Title

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression–Continuation Phase (29060/329) [Addendum to Acute Phase Report]

Study Dates

The final date on which the last patient took study medication during the continuation phase was 03 September 1997.

Objectives

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

In this continuation phase, the objectives were as follows:

To provide information on the safety profile of paroxetine and imipramine when these agents are given to adolescents for an extended period of time.

To estimate the rate of relapse among paroxetine, imipramine, and placebo responders who were maintained on treatment.

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 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 six months. 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 six-month continuation treatment phase; clinic visits were made monthly.

The acute phase has been reported separately. This report on the continuation phase is an addendum to the Acute Phase Report.

Study Population

Patients eligible for the acute phase were adolescents (12 years 0 months through 18 years 11 months inclusive) who were currently in an episode of major depression (DSM-III-R criteria) for at least 8 weeks, and who had a total score ≥12 on the 17-item Hamilton Depression Scale (HAM-D). Patients eligible for the continuation phase were patients judged to be responders, defined as having a final (week 8) HAM-D score that was ≤8, or a decrease in HAM-D score at week 8 that was at least 50% of the baseline score.

Treatment and Administration

Patients took their study medication twice daily, once in the morning and once at night. Total daily doses of paroxetine were 20 mg for dose levels 1 to 4, 30 mg for level 5, and 40 mg for level 6. Total daily doses of imipramine were 50, 100, 150, 200, 250, and 300 mg for dose levels 1 to 6, respectively. At the beginning of the continuation phase, all patients started at the same level at which they completed the acute phase. Doses could be titrated up to dose level 6 at the discretion of the investigator. Titration up or down no more often than once per week was permitted

Evaluation Criteria

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

Efficacy Parameters: The efficacy assessment for estimation of rate of relapse in the trial was the Hamilton Rating Scale for Depression (HAM-D). The percent of patients withdrawing for lack of efficacy was evaluated once at the end of the continuation phase for each patient. Other assessments were 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).

Other Parameters: Blood samples for determination of serum imipramine and desipramine concentrations were taken at the completion of 20 and 32 weeks of treatment.

Patient Disposition and Key Demographic Data

Of the 190 patients who completed the acute phase of the study, 65 patients did not enter the continuation phase. Lack of efficacy was the predominant reason for patients not participating in the continuation phase.

Thirty-five percent of the patients (44/125) who entered the continuation phase completed six additional months of treatment as prescribed by the protocol. The proportions of patients completing the continuation phase were generally comparable in all three treatment groups. In the imipramine group, 20% of the patients withdrew due to adverse events, compared to 12% in the placebo group and 8% in the paroxetine group. The proportions of patients withdrawn for lack of efficacy or lost to follow-up were comparable across treatment groups.

Patient Disposition

	Treatment Group			
	Paroxetine n = 52	**Imipramine n = 40**	**Placebo n = 33**	**Total n = 125**
Withdrawn Before 6 Months	34 (65.4%)	27 (67.5%)	20 (60.6%)	81 (64.8%)
Adverse Events	4 (7.7%)	8 (20.0%)	4 (12.1%)	16 (12.8%)
Lack of Efficacy	7 (13.5%)	6 (15.0%)	6 (18.2%)	19 (15.2%)
Protocol Violation (including non-compliance)	12 (23.1%)	7 (17.5%)	4 (12.1%)	23 (18.4%)
Lost to Follow-up	3 (5.8%)	2 (5.0%)	3 (9.1%)	8 (6.4%)
Other	8 (15.4%)	4 (10.0%)	3 (9.1%)	15 (12.0%)
Completed 6 Months	18 (34.6%)	13 (32.5%)	13 (39.4%)	44 (35.2%)
Mean duration of exposure (days) ± SE	114.3 ± 9.32	110.2 ± 10.25	110.9 ± 13.30	

Safety Results

Extent of Exposure: The mean duration of exposure to study medication in the continuation phase was approximately four months in each of the three treatment groups. In the paroxetine group, 23/93 (24.7%) patients had long-term exposure (>168 days).

Adverse Events: There were no deaths during the trial. Serious adverse events during the continuation phase occurred in nine patients, six in the paroxetine group, two in the imipramine group, and one in the placebo group. One of the paroxetine patients experienced a peptic ulcer hemorrhage, which was considered unrelated to study medication by the investigator. For the remaining patients in the paroxetine group the serious events were psychiatric in nature and included intentional overdose (three patients) and manic reaction (one patient); one patient experienced agitation, fatigue, nausea, drowsiness, and tremor after missing some doses of taper medication. In the imipramine group, one patient developed tricyclic toxicity and another took an intentional overdose. In the placebo group, one patient had homicidal and suicidal ideation.

Four patients (7.7%) in the paroxetine group, eight patients (20.0%) in the imipramine group, and four patients (12.1%) in the placebo group were withdrawn due to an adverse event. Adverse events related to the nervous system and leading to withdrawal occurred in three patients in the paroxetine group (all for adverse events of emotional lability), three patients in the imipramine group (one for emotional lability, one for neurosis, and one for convulsion), and one patient in the placebo group (for emotional lability, hostility, and manic reaction). All other events leading to withdrawal occurred in no more than one patient in any group.

Five adverse events occurred in 5% or more of the patients in the paroxetine group and with a frequency at least twice that of placebo. Three of these events occurred in the Nervous System body system: emotional lability, tremor, and insomnia. In the imipramine group, there were 6 adverse events that occurred in 5% or more of the patients and at least twice that in the placebo group.

Adverse Events Occurring in ≥5% of Any Group and at Least 2X Placebo

Adverse Event	Paroxetine N = 52	Imipramine N = 40	Placebo N = 33
Abdominal Pain	6 (11.5%)	4 (10.0%)	1 (3.0%)
Weight Gain	4 (7.7%)	1 (2.5%)	0 (0.0%)
Emotional Lability	4 (7.7%)	1 (2.5%)	1 (3.0%)
Insomnia	4 (7.7%)	3 (7.5%)	1 (3.0%)
Tremor	3 (5.8%)	0 (0.0%)	0 (0.0%)
Tachycardia	1 (1.9%)	2 (5.0%)	0 (0.0%)
Dry Mouth	1 (1.9%)	3 (7.5%)	0 (0.0%)
Myalgia	1 (1.9%)	3 (7.5%)	0 (0.0%)
Dyspepsia	0 (0.0%)	2 (5.0%)	0 (0.0%)

Vital Signs: Changes in blood pressure and pulse rate were small in the paroxetine and placebo treatment groups. In the imipramine treatment group, however,

substantial increases were seen in the standing pulse rate (mean change of 15.2 bpm from acute baseline to endpoint), and seven patients had a standing pulse rate meeting potential clinical concern criteria (>120 bpm and increase ≥30 bpm from acute baseline). Weight gain of concern (increase ≥7% from acute baseline) was seen in 25% of patients in the paroxetine group, compared to 15% of patients in the imipramine group and 18% of patients in the placebo group.

Laboratory Tests: The number of patients identified with laboratory values meeting the potential clinical concern criteria was low in all treatment groups. None was considered to be clinically significant by the investigator except for one patient in the imipramine group with anemia (low hematocrit).

Other: Two patients in the imipramine group developed tricyclic toxicity during the continuation phase.

Adverse Events in the Continuation Phase Compared to the Acute Phase: The nature of adverse events reported for the paroxetine group in the continuation study was generally similar to that reported in the acute phase. Most of the more common adverse events in the acute phase were seen less frequently during the continuation phase. Weight gain occurred with greater frequency in the continuation phase than in the acute phase.

Efficacy Results

The continuation phase of this study was designed to estimate the rate of relapse in the three treatment groups. The proportion of patients relapsing at any time during the continuation phase, regardless of HAM-D at endpoint, was similar in the imipramine group (38.7%) to the paroxetine group (36.4%), but slightly less (23.1%) in the placebo group. The mean time to relapse in the imipramine group was 61.5 days, compared to approximately 79 days in each of the other treatment groups. The proportion of patients whose HAM-D at endpoint of the continuation phase was >8 and >50% of the acute baseline HAM-D was similar in all treatment groups.

There were no significant differences between paroxetine and placebo or between imipramine and placebo in withdrawals due to lack of efficacy. The continuation phase of this study was not designed to analyze efficacy, as patients were not re-randomized at the end of the acute phase. In addition, only responders were to enter the continuation phase. Nevertheless, trends suggested that patients who

had responded to therapy in the acute phase continued to respond over the six months of the continuation phase, regardless of treatment assignment.

Conclusions

The long-term safety profile of paroxetine in adolescents appears similar to that reported following short-term dosing. In general, the incidence (new onset) of those adverse events identified as occurring in the acute phase at an incidence of at least 5% and at least twice placebo was less in the continuation phase. Weight gain was the only vital sign of concern that occurred with greater frequency in the paroxetine group than in the other treatment groups, and with greater frequency in the continuation phase than in the acute phase. However, with such a small sample size, in the absence of pre- and post-dose body mass index data, the clinical relevance of such findings is difficult to establish in an actively growing and maturing population such as this.

The proportion of patients relapsing at any time during the continuation phase was similar in the paroxetine and imipramine groups and slightly lower in the placebo group. The proportions of patients relapsing at endpoint were similar in all treatment groups. There were no significant differences between paroxetine and placebo or between imipramine and placebo in withdrawals due to lack of efficacy. Trends suggested that patients who had responded to therapy in the acute phase continued to respond over the six months of the continuation phase.