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Adolescent depression: efficacy of paroxetine

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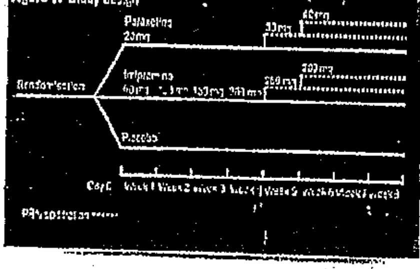
Introduction

- Depression in adolescents is a common problem; life-time prevalence rates of over 15% have been reported (1). 'Masking' of symptoms and atypical presentation such as hyperphagia, hypersomnia and externalisation can complicate the diagnosis. In addition, the use of rating scales to aid in detection and monitoring of treatment can be problematic as many have not been validated for this age group.
- Failure to diagnose and treat effectively can lead to the development of comorbid anxiety disorders, the impairment of cognitive and psychosocial functioning, and a high risk of suicide.
- Because of the chronic nature of depression, treatment needs to be well tolerated, with minimal disruptive effects on lifestyle. Antidepressants with concomitant efficacy against anxiety disorders provide the clinician with the option of monotherapy in patients presenting with these disorders.
- Few trials have been conducted to investigate antidepressant efficacy in this group of patients, and most have failed to show significant benefits over placebo (2). Small open-label studies have shown paroxetine to be effective in treating depression in adolescents (3). Reported here are the results of a study which compared the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression.

Methods

- This was a double-blind, multi-centre, parallel-group, placebo-controlled study conducted in 12 centres in North America. Patients were randomised to receive either paroxetine (n=93), imipramine (n=95) or placebo (n=87). Patients randomised to paroxetine treatment began on 20 mg/day. Patients randomised to imipramine began on 50 mg/day, titrated up to 200 mg/day by week 4 (Figure 1). If no response had been observed by 4 weeks of treatment, the respective doses were titrated upwards during the remaining 4 weeks, to a maximum of 40 mg/day paroxetine and 300 mg/day imipramine.

Figure 1. Study design



- The Clinical Management for Adolescent Depression Manual was used to define the level of psychosocial supportive therapy permitted between patients and investigators. Interpersonal, cognitive or behavioural psychotherapy was not permitted.
- Adolescents (aged between 12 years and 18 years 11 months) who were currently experiencing an episode of major depression (DSM-III-R criteria) of a minimum duration of 8 weeks, and diagnosed using the Schedule for Affective Disorders and Schizophrenia for School-age Children - Lifetime version (K-SADS L), were recruited to the study. In addition, patients had to have a total score of ≥12 on the 17-item Hamilton Depression Scale (HAM-D) and a severity score of <60 on the Child Global Assessment Scale.

Efficacy parameters

- Primary:
  - the proportion of responders with a ≥ 50% reduction in the total HAM-D score or a HAM-D score of ≤8 at week 8;
  - change from baseline in HAM-D total score at week 8.
- Secondary:
  - mean Clinical Global Impression (CGI) global improvement scores;
  - change from baseline on the 9-item depression subscale of the K-SADS-L at week 8.

Safety assessments

- Adverse events were monitored by non-leading questions. Clinical laboratory tests were performed at the screening visit and at the end of the study. Treatment discontinuations due to either adverse events or lack of drug efficacy were also recorded.

Statistical methods

- Statistical conclusions concerning the efficacy of paroxetine and imipramine were made using data obtained from the last assessment of the intention-to-treat population (observed cases). Changes from baseline to endpoint in HAM-D score, CGI Improvement Scale scores and changes from baseline in the 9-item depression subscale of the K-SADS-L were analysed using a 2-factor analysis of variance. The proportion of patients who responded to treatment were analysed using logistic analysis implemented in the SAS procedure Categorical Modeling. Pair-wise comparisons between the two active agents and placebo were made at the 0.05 level of significance using the Least Square Means procedure.

Results

- The three treatment groups were balanced with respect to demographic variables (Table 1).

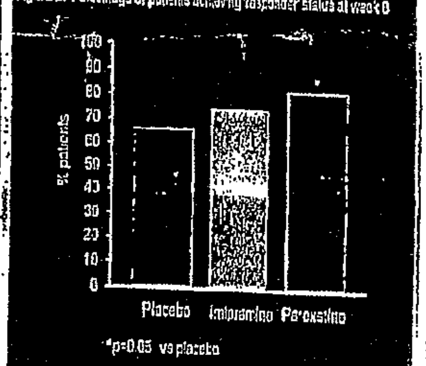
Table 1. Patient demographics and clinical characteristics at entry

	Paroxetine n=93	Imipramine n=95	Placebo n=87
Mean age, years (SD)	14.8 (1.6)	14.9 (1.7)	15.1 (1.6)
Female (%)	67	59	66
Duration of current depressive episode (months) mean (SD)	14.4 (17.5)	14.3 (17.9)	12.5 (14.8)
Age at first episode (years) mean (SD)	13.2 (2.4)	13.2 (2.7)	13.5 (2.0)
Patients with ≥1 prior episode (%)	15	20	22
Mean HAM-D score at entry (SD)	18.9 (3.9)	18.1 (3.9)	19.0 (3.7)

Primary efficacy parameters

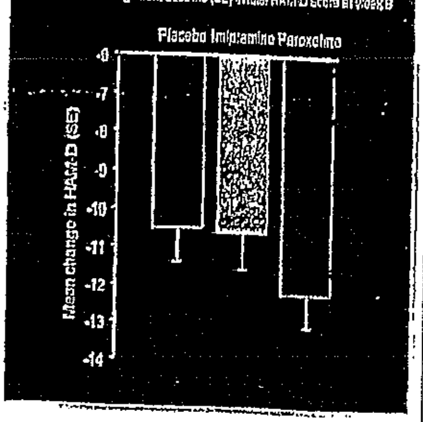
- By week 4, approximately half the patients in each treatment group were classed as responders (Figure 2). This proportion increased further during the study and by week 8 there was a statistically significantly greater number of responders in the paroxetine group compared with placebo (81% vs 65%). The imipramine group did not separate from placebo for this efficacy parameter (73% vs 65%).

Figure 2. Percentage of patients achieving 'responder' status at week 8



- After 8 weeks of treatment, patients receiving paroxetine experienced a greater decrease in total HAM-D score than the placebo group (Figure 3). This difference showed a trend towards statistical significance. The change in HAM-D score in the imipramine group was comparable with that of placebo.

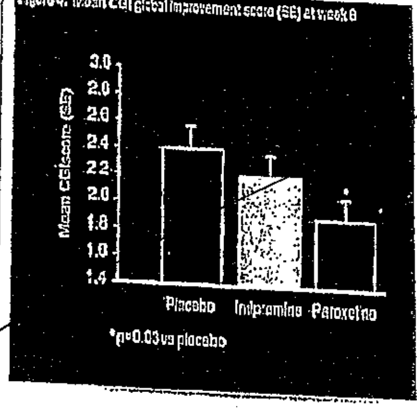
Figure 3. Mean change from baseline (SE) in total HAM-D score at week 8



Secondary efficacy parameters

- Progressive improvement in mean CGI scores (global improvement item), with continuing treatment, occurred in all groups. At week 8, a statistically significantly greater improvement was observed in paroxetine-treated patients, compared with those receiving placebo (Figure 4). There was no significant difference between the imipramine and placebo groups.

Figure 4. Mean CGI global improvement score (SE) at week 8



distorts data

- A progressive reduction in mean scores on the K-SADS-L depression 9-item scale was observed during the course of the study in all three treatment arms. The mean decrease from baseline at week 8 was greatest in the paroxetine group, but this did not reach statistical significance.

Safety

One hundred and ninety patients completed the 8-week study (Table 2). This included 72% of patients receiving paroxetine, 60% of those receiving imipramine and 76% of those receiving placebo. Thirty-two percent of the treatment discontinuations in the imipramine group were due to adverse events, compared with 10% and 7% in the paroxetine and placebo groups, respectively.

Table 2. Treatment discontinuations

	Paroxetine	Imipramine	Placebo
No. 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*	11	7	10
Mean dose (mg) (SD)	28.0 (8.5)	206 (64.0)	-

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

Ignores 'external' [illegible] data

Conclusions

- Paroxetine provides effective treatment for major depression in adolescents.
- Paroxetine is better tolerated than imipramine. Three times as many patients discontinued imipramine than paroxetine, secondary to adverse events.
- The large 'placebo' response occurring in adolescents may result from psychosocial supportive therapy provided by the investigators.
- There was little support for the use of imipramine in this vulnerable population, which is in agreement with smaller trials.

References

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2. Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. *Br Med J* 1995; 310: 897-901.
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