The Pharmacotherapy of Depressive Illness in Adolescents: An Open-Label Comparison of Fluoxetine With Imipramine-Treated Historical Controls

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Background: This open-label, 6-week clinical trial investigated the response to fluoxetine in medication-naive adolescents hospitalized for treatment of major depression.

Method: A total of 52 consecutively admitted patients (mean age = 15.7 years) fulfilling Research Diagnostic Criteria for unipolar, nonpsychotic major depression received fluoxetine monotherapy (mean dose = 33.2 mg/day) in conjunction with psychosocial therapies. Outcome was assessed weekly using the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions Scale (CGI). Response in this cohort was compared with that observed in 28 historical controls treated with imipramine (mean dose = 217 mg/day) who were consecutively admitted patients to this same facility and assessed in an identical, standardized, open-label protocol.

Results: HAM-D scores decreased by a mean of 13.2 in the fluoxetine group compared with 10.2 in the group receiving imipramine ($p < .002$). The mean percentage decreases in HAM-D scores in the 2 groups were 54.3% and 41.4%, respectively ($p < .003$). The percentages of patients classified as responders based on a final CGI score of 2 or less were 48.1% and 17.9%, respectively ($p = .009$). Medications were generally well tolerated with only 5 patients failing to complete the full 6 weeks of their original treatment.

Conclusion: In spite of the uncontrolled nature of these data, the findings add to recent evidence suggesting more favorable response to selective serotonin reuptake inhibitors than tricyclics in adolescents with depressive illness.

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In spite of a burgeoning literature attesting to strong continuities between juvenile and adult depression in episode duration, recurrence risks, familiality, and psychosocial morbidity,[1] a consensus has yet to develop on the role played by pharmacologic treatments in the management of young affectively ill patients. Whereas some open-label studies of tricyclic compounds[2,3] and one double-blind, placebo-controlled trial[4] suggest an unusual resistance of unipolar depressed adolescents to this class of medication, in other recent controlled clinical trials, the proportion of placebo responders is too substantial to detect evidence of an active drug effect.[5] Factors possibly accounting for these conflicting findings include lack of adequate statistical power to detect moderate size drug effects, oversampling of nonendogenous depressives with high mood reactivity, sample heterogeneity, and various other methodological constraints.[5–7]

Until recently, data on the efficacy of newer generation selective serotonin reuptake inhibitors (SSRIs) in the treatment of adolescent depression were, likewise, scant, comprising observations on small samples of tricyclic-resistant patients,[8,9] from retrospective chart reviews,[10] and from one negative double-blind clinical trial with a sizable placebo response rate.[11] An important exception is the recent report of Emslie and colleagues,[12] who documented a statistically greater rate of improvement on fluoxetine treatment compared with placebo in children and adolescents with major depression enrolled in a well-conducted parallel-group, double-blind, placebo-controlled trial. We now extend these observations by reporting the results of an open-label study of the effectiveness of fluoxetine in a large consecutive series of adolescents hospitalized for treatment of major depression. Specifically, we compare the response in this sample to that observed in historical controls treated with imipramine and examine safety and tolerability profiles in the 2 cohorts.

METHOD

Patients

All 80 patients included in this report were consecutive admissions to the adolescent inpatient service of the Uni-

versity of California at Los Angeles (UCLA) Neuropsychiatric Institute with a primary diagnosis of major depression as determined by 2 senior faculty. In each case, the patient fulfilled Research Diagnostic Criteria,[13] as well as criteria for major depression in the particular edition of the DSM in use at the time of the patient's index admission. Diagnoses were based on structured interviews using the Schedule for Affective Disorders and Schizophrenia (SADS),[14] review of all available medical records from prior psychiatric treatment, hospital observation, and information obtained from parents on the course of the patient's illness prior to admission. Only diagnoses made at the probable or definite level of certainty were considered. Patients received physical examinations upon admission that included standard laboratory tests and toxicology screens for amphetamines, cocaine, hallucinogenic compounds, and opiates. Of the 80 patients included in this report, diagnoses were made at the definite level of certainty in 71 (88.8%). Parental information was obtained systematically using the childhood version of the SADS[15] and the Psychosocial Schedule for School-Age Children.[16] Lifetime histories of psychiatric illness in parents and extended relatives of patients were also obtained from lifetime SADS and Family History Research Diagnostic Criteria interviews[17] of parents. All case file materials were coded so that familial diagnoses were made without knowledge of pedigree status, patient treatment group, or treatment response as described herein.

To avoid potential bias or confounding of the analyses, only patients who had been naive to pharmacotherapy prior to their UCLA admission were included in this study. Additional exclusions included prior history of hypomania or mania, current psychosis, evidence of neurologic or severe medical illness, substance abuse, antisocial disorder, or pervasive developmental disorders.

All patients were English speaking, of at least average IQ, resided with at least one rearing parent, and were preponderantly Caucasian (90.0%) and from middle- to upper-class socioeconomic backgrounds. Distribution by age was as follows: 13 years, 11.2%; 14 years, 17.5%; 15 years, 30.0%; 16 years, 21.3%; 17 years, 20.0%. Females comprised 71.3% (N = 57) of the sample. Of the 80 patients, 21 (26.3%) had antecedent nondepressive psychiatric disorders, including obsessive-compulsive disorder (N = 4, 5.0%), phobic disorder (N = 5, 6.3%), generalized anxiety (N = 6, 7.5%), and separation anxiety (N = 6, 7.5%). A total of 13 patients (16.3%) had preexisting chronic minor depression, and 11 (13.8%) had prior episodes of depression. Mean duration of the index episode at the time of the UCLA admission was 20.4 weeks (range, 6 to 55 weeks). A total of 49 patients (61.3%) met RDC for endogenous subtype at the probable or definite level of certainty, and 48 (60.0%) had either a first- or second-degree relative with a history of major depression.

Treatment Protocol

Patients were entered into a standardized open-label protocol only if they maintained a daily Hamilton Rating Scale for Depression (HAM-D)[18] score of 16 or greater and a Clinical Global Impressions Scale (CGI)[19] score of 3 (minimal improvement) or greater for not fewer than 5 days following admission. Patients fulfilling these criteria were then treated openly for 6 weeks. Fluoxetine, which became the standard first-line pharmacotherapy for our patients upon its commercial availability in early 1988, was routinely started at 10 mg/day, increasing to 20 mg/day by day 7. Depending on tolerability, the dose was increased to 30 mg/day if clinical improvement was rated as minimal after 21 days and to 40 mg/day if there was no evidence of improvement after 4 weeks of treatment. A total of 52 patients were entered into the fluoxetine protocol between 1988 and 1995. The final mean ± SD dose in the sample was 33.2 ± 7.6 mg/day.

Response in the fluoxetine-treated cohort was compared with outcome in 28 historical controls treated with imipramine monotherapy. These controls also comprised consecutive admissions to the same inpatient service (between 1984 and 1988) and received the same complement of psychosocial therapies administered to fluoxetine-treated patients. The imipramine target dose was 5 mg/kg/day, up to a maximum dose of 300 mg/day, with upward titration against clinical response and side effects over 14 days. The final mean dose was 217 ± 52 mg/day, with a steady-state imipramine plus desmethylimipramine plasma concentration of 243 ± 151 ng/mL. It is to be noted that the total sample of 80 patients constitute 2 sequentially ascertained cohorts, imipramine being the standard first-line pharmacotherapy employed on our service prior to the introduction of fluoxetine.

Assessment of Clinical Response and Statistical Analyses

Evaluations of outcome were performed weekly using the 17-item HAM-D and the CGI. Ratings were performed by highly trained clinical nurses with extensive experience in clinical trial assessments. Intraclass coefficients of reliability based on joint HAM-D assessments at baseline of 20 patients in the fluoxetine group and 15 patients in the imipramine group were 0.84 and 0.89, respectively. The same joint ratings were repeated at week 6, resulting in intraclass coefficients of 0.87 and 0.81, respectively. Kappa coefficients based on CGI classifications of response/nonresponse were 0.87 and 0.91, respectively.

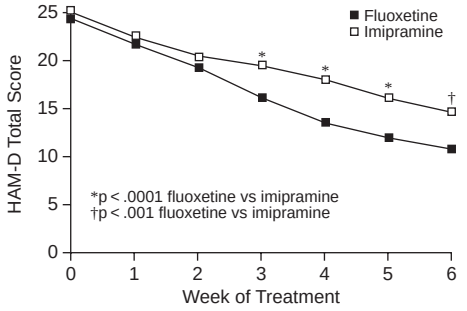
All analyses used intent-to-treat data with the last available observation carried forward. All patients had at least 7 days of treatment, and no patient initially exposed to treatment with either medication discontinued treatment before 7 days. The main efficacy parameters included the assessment of change in total 17-item HAM-D score from baseline to week 6, the percentage decrease in

Table 1. Primary Efficacy Variables in Adolescents With Major Depression Treated With Fluoxetine and Imipramine*

Variable	Treatment Group: Fluoxetine (N = 52)	Treatment Group: Imipramine (N = 28)	p Value
HAM-D (mean values)			
Baseline	24.3	25.0	NS
Change from baseline	–13.2	–10.2	< .002
% Change	–54.3	–41.4	< .003
% Responders	53.8	39.3	NS
CGI (mean values)			
Score at completion	2.5	3.4	< .001
% Responders	48.1	17.9	.009

*Abbreviation: NS = not significant.

Figure 1. Weekly Mean HAM-D Total Scores by Treatment Group



HAM-D score from baseline, and the CGI score at last assessment. Responders were defined categorically in 2 ways: (1) based on a 50% or greater decrease in HAM-D scores from baseline to final assessment and (2) based on a more stringent classification requiring a final CGI score of 1 (very much improved) or 2 (much improved). The effect of treatment group on outcome was analyzed by analysis of covariance (ANCOVA) using the baseline HAM-D score as the covariate. Significant F ratios were followed by independent means t tests; within-treatment-group changes from baseline were assessed using paired t tests. Comparability of the treatment groups on baseline characteristics was assessed using t tests for quantitative measures and either chi-square or Fisher exact test for qualitative measures. Two-sided alpha levels of $p < .05$ were used to determine statistical significance. The difference between treatment groups in time to onset of sustained improvement, defined a priori as a CGI score of ≤ 2 maintained continuously until completion of the study period, was also tested by Kaplan-Meier survival analysis,[20] with equality of the survivor distributions determined by the log-rank test.

RESULTS

Baseline Characteristics

In spite of the nonrandom ascertainment of these cohorts, the groups were comparable in age, sex, social class, baseline HAM-D score, duration of index episode at admission, and the proportions with prior episodes of major depression, antecedent nondepressive diagnoses, antecedent chronic minor depression, major depression in relatives, and RDC for probable or definite endogenous subtype.

Change Scores From Baseline

The primary efficacy findings are summarized in Table 1. Weekly mean HAM-D scores by treatment group are displayed graphically in Figure 1. A statistically significant ($p < .0005$) improvement in clinical state was observed in both the imipramine and fluoxetine treatment groups over 6 weeks. In patients receiving fluoxetine, the mean ± SD HAM-D change from baseline score was 13.2 ± 4.1 (95% confidence interval [CI], 12.1 to 14.1). For the historical controls treated with imipramine, the mean change from baseline was 10.2 ± 4.6 (95% CI, 8.4 to 12.0). The mean decrease in HAM-D score was significantly greater for patients in the fluoxetine treatment group ($p < .002$; 95% CI for fluoxetine vs. imipramine treatment difference, 1.0 to 5.0). Statistical significance of between-treatment group HAM-D scores emerged first at week 3 and continued thereafter. Week-by-week mean treatment differences in HAM-D scores ([baseline HAM-D score – weekly HAM-D score for fluoxetine] – [baseline HAM-D score – weekly HAM-D score for imipramine]), along with 95% confidence intervals for the treatment difference, are given in Table 2.

For patients treated with fluoxetine, the mean percentage decrease in HAM-D score from baseline to endpoint was 54.3% (± 15.7%), compared to 41.4% (± 18.4%) for patients treated with imipramine ($p < .003$; 95% CI for treatment difference, 5.1 to 20.7).

Responder Analysis

The percentages of patients in the fluoxetine and imipramine treatment groups achieving a 50% or greater decease in HAM-D score from baseline were 53.8% and 39.3%, respectively, a nonsignificant difference. However, a significantly greater ($p = .009$) number of patients in the fluoxetine (N = 25, 48.1%) than imipramine (N = 5, 17.9%) treatment group were classified as responders based on final CGI scores of very much or much improved (crude odds ratio = 4.3; 95% CI, 1.4 to 12.9). At the same time, few patients in either group met criteria for full remission using a final HAM-D cutoff score of ≤ 7 (7.7% vs. 7.1% in fluoxetine and imipramine treatment groups, respectively). Mean CGI scores at endpoint differed significantly between the groups, 2.5 ± 1.0 for patients receiving fluoxetine vs. 3.4 ± 1.0 for patients receiving imipramine ($p < .001$; 95% CI for treatment difference, 0.4 to 1.3).

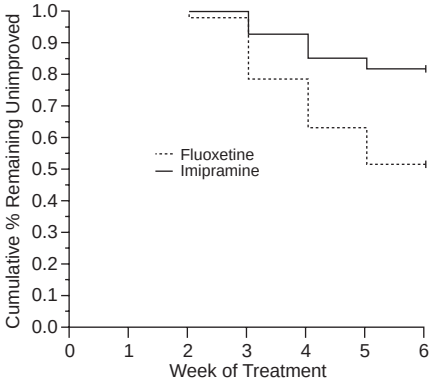
The cumulative proportions of patients in the 2 treatment groups remaining unimproved over the 6-week trial are shown in Figure 2. The mean survival (i.e., time in weeks unimproved) was 4.9 weeks (95% CI, 4.6 to 5.3) for fluoxetine-treated patients, compared to 5.6 weeks (95% CI, 5.3 to 5.9) for imipramine-treated patients. The 2 survival distributions differed significantly ($p < .01$).

Table 2. Mean ± SE[a] Weekly Treatment Effects in HAM-D Scores

Variable	Week 1	Week 2	Week 3[b]	Week 4[b]	Week 5[b]	Week 6[b]
Treatment effect[b,c]	0.0 ± 0.3	0.5 ± 0.5	2.6 ± 0.7	3.7 ± 0.8	3.2 ± 0.9	2.9 ± 1.0
95% CI[d]	–0.5 to 0.6	–0.5 to 1.5	1.3 to 4.0	2.2 to 5.2	1.4 to 4.9	0.9 to 4.9

[a]Standard error of the difference.
[b]$p < .0005$.
[c]Weekly change in HAM-D score from baseline for fluoxetine treatment group minus change from baseline for imipramine treatment group.
[d]95% confidence interval for the treatment effect.

Figure 2. Kaplan-Meier Probabilities of Time to Onset of Sustained Improvement



Treatment-Emergent Adverse Events

Two patients in the imipramine group and 3 in the fluoxetine group (total, 6.3%) discontinued their treatment prior to completion of the 6-week trial. Reasons for discontinuation of imipramine were rash and severe orthostatic hypotension; for fluoxetine, the reasons were headache (N = 2) and nausea. The numbers of patients with at least 1 treatment-emergent side effect were 21 (75%) in the imipramine group and 42 (80.8%) in the fluoxetine group. The most frequently occurring (incidence of 10% or greater) events in the imipramine group were hypotension, dry mouth, and somnolence. In the fluoxetine-treatment group, the most frequent adverse events were headache, nausea, and nervousness.

Post Hoc Secondary Analyses

Within each treatment group, and aggregating across all patients, we used logistic regression to examine the effects on CGI classification of response/nonresponse, of the following predictor variables: age, sex, duration of episode at intake, HAM-D score at baseline, endogenous subtype, family history of major depression, preexisting nondepressive disorder, and antecedent chronic minor depression. None achieved statistical significance.

DISCUSSION

We sought to determine if unipolar, nonpsychotic moderately to severely depressed adolescents who received fluoxetine in a 6-week open-label protocol had response profiles that differed from historical controls treated with imipramine. Improvement in HAM-D and CGI scores, in terms of absolute mean change from baseline as well as the proportions of patients classified as responders, was greater in the group receiving fluoxetine. Treatment-emergent adverse events were common in both groups, yet neither drug caused serious events and treatment discontinuation as a result of side effects was uncommon. Differences that were seen in side effect profiles corresponded with those well documented in the literature.

The findings have to be put in the context of several limitations. Considering that patients were receiving a variety of psychosocial interventions along with social supports inherent to the inpatient setting, it is likely that some of the improvement is attributable to nonpharmacologic effects. Likewise, since the study had neither a placebo control nor random allocation of patients to parallel treatment arms, the efficacy findings must be interpreted with great caution. Historical case control designs have disadvantages that constrain interpretation of findings derived from comparisons of specific treatments.[21] These include the lack of comparability in diagnostic selection criteria across cohorts; generally poorer quality of archival databases with regard to outcome measures and assessment of potentially important moderators of treatment response; higher levels of adjunctive care typically received by patients receiving the newer, more contemporaneous treatment; and generally more restrictive rules governing protocol violations used in the monitoring of patients receiving the newer treatment. The major potential effect of concern arising out of these confounds is of a biased selection of historical and "experimental" cases, thereby resulting in the spurious attribution of greater therapeutic benefits to the newer treatment.

Still, we believe that these confounds have been effectively minimized in the present study in several ways. First, patients entered into these protocols comprise consecutive admissions to a single inpatient facility whose treatment philosophy and interdisciplinary treatment program have changed little over the study period. Second,

there was no change over time in diagnostic inclusionary and exclusionary criteria used to ascertain the samples. Third, the assessment measures and outcome variables were identical both within and across cohorts. Finally, we demonstrated excellent and equivalent levels of reliability of outcome assessments within each of the cohorts.

Other considerations converge in arguing against the possibility that the differences observed are attributable solely to nonpharmacologic factors. First, we think it implausible that differences favoring fluoxetine are due to general expectancy effects within patients or evaluators. Our study of imipramine was undertaken at a time when there was no a priori reason for assuming a broad resistance of adolescent depressives to tricyclic pharmacotherapy. By the same token, upon initiating the open-label study of fluoxetine, we had no reason to suppose that our patients would respond preferentially to serotonergic compounds. Second, whereas prior studies with adults have noted an association between placebo responsiveness and brief duration of illness, lesser severity of illness, and nonendogenous subtype,[22–25] the cohorts in the present study were comparable on these baseline characteristics. For this reason, we deem it unlikely that patients receiving fluoxetine were more inclined to be spontaneous remitters or to have differentially heightened reactivity to their concurrent psychosocial interventions.

We also considered, post hoc, the possibility that patients in the historical control cohort had significantly more features predictive of imipramine refractoriness, in particular "atypical" symptoms of heightened mood reactivity with extreme fatigue and lethargy, rejection sensitivity, increased appetite or weight gain, or hypersomnia.[26] However, a blind review of all the records indicated that only 5 (17.9%) of 28 imipramine controls and 10 (19.2%) of 52 patients in the fluoxetine treatment group fulfilled criteria for atypical depression[26] at the probable or definite level of certainty.

Several lines of neuropharmacologic evidence may be germane to the present observations. Considerable preclinical research on the ontogenesis of neurotransmitter systems suggests that central noradrenergic mechanisms do not fully develop anatomically or functionally until early adulthood, whereas maturation of serotonergic systems is more rapid.[27–32] Analogously, clinical data on neuroendocrine indices of noradrenergic activity (e.g., nocturnal cortisol secretion) have not been found to discriminate depressed teens from age-matched normal controls,[33,34] whereas nocturnal growth hormone secretion, a putative measure of regulatory serotonergic activity, has.[34] Age-related changes in the brain's hormonal milieu may, likewise, have neuropharmacodynamic significance, insofar as increases in circulating estrogen level during adolescence have been related to enhancement of serotonergic receptor activity.[35] The implication to be drawn is that given differential rates of maturation of brain regulatory systems, the possibility exists that serotonergic and tricyclic antidepressants may vary analogously in their capacity to alter aberrant neuroreceptor and neurotransmitter function in juvenile depressives.

Even if the treatment differences discussed herein are reliable, a more sobering observation is that response profiles in these patients, as a group, do not compare as favorably to those obtained in efficacy studies of imipramine and fluoxetine in adults.[36,37] Remission rates within both cohorts were low, and drug response rates were, by and large, lower than those reported in controlled trials of imipramine and SSRIs in inpatient adult depressives. Possibly relevant in this regard, once again from a developmental perspective, is a recent report by McCracken and Poland[38] showing that prepubertal rats fail to exhibit the same enhancement of prolactin response to acute challenge with the serotonin agonist 1-(*m*-trifluoromethylphenyl) piperazine as seen in adult animals after chronic treatment with amitriptyline. Since augmentation of central serotonergic function may be a common and therapeutically vital effect of long-term pharmacotherapy with either tricyclic or SSRI agents,[39] developmental differences in the functional organization of neurotransmitter systems, and in the response of these systems to pharmacologic perturbation, may be relevant to clinically observable differences among juvenile and adult depressives in responsiveness to antidepressant drugs.

Drug names: amitriptyline (Elavil and others), fluoxetine (Prozac), imipramine (Tofranil and others).

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