Do Depressed Subjects Who Have Failed Both Fluoxetine and a Tricyclic Antidepressant Respond to the Combination?

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Background: Recent evidence suggests that the combination of fluoxetine and desipramine may provide a rapid and effective treatment for depression.

Method: The current study evaluated 13 subjects with DSM-III-R nonpsychotic major depression who had previously failed either desipramine or imipramine and who were currently unsuccessfully treated with fluoxetine. Desipramine or imipramine was added to fluoxetine and Hamilton Rating Scale for Depression (HAM-D) scores, Beck Depression Inventory (BDI) scores, and plasma tricyclic levels were monitored for 3 weeks.

Results: Of the 13 subjects, 7 (54%) had a greater than 40% decline in HAM-D scores and 4 of these (31%) had 50% or greater decline in HAM-D. At week 3, responders (767 ± 282 nmol/L) had a significantly higher mean tricyclic level as compared with nonresponders (515 ± 95 nmol/L, $F = 25.1$, $p < .0001$), and change in BDI scores was significantly correlated with tricyclic level ($r = –0.60$, $p < .05$).

Conclusion: These findings suggest that in some subjects the positive clinical effect of combining fluoxetine and a tricyclic antidepressant may be related to the plasma levels of the tricyclic compound.

(J Clin Psychiatry 1999;60:613–616)

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The authors thank Cathy MacDonald for her contribution to the collection and management of the data for this study.

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The addition of tricyclic antidepressants, in particular desipramine, to fluoxetine has been reported to accelerate treatment response in acutely depressed subjects[1] and to be an effective treatment for resistant depression.[2–4] It has been suggested that the additive effect may result from a pharmacodynamic[1] and/or a pharmacokinetic action.[5,6] However, these studies have examined subjects who, for the most part, were desipramine naive before desipramine was added to fluoxetine,[1] or fluoxetine naive before fluoxetine was added to desipramine.[3] The question remains as to whether there is a specific effect of the combination in subjects who have failed treatment with both medications. The current study examines depressed subjects who had failed to respond to desipramine or imipramine and failed to respond to fluoxetine, who subsequently received an open trial of the tricyclic and fluoxetine in combination.

METHOD

Subjects were consecutive outpatients, diagnosed with nonpsychotic major depression according to DSM-III-R, who attended a university-affiliated clinic and gave informed consent. All subjects fulfilled the following criteria: (1) diagnosis confirmed by the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L),[7] (2) 18 to 65 years of age, (3) previous failure to respond to an adequate trial of either desipramine or imipramine, (4) failure to respond to a current adequate trial of at least 20 mg of fluoxetine daily for at least 5 weeks at a stable dose, (5) Hamilton Rating Scale for Depression (HAM-D)[8] score of 16 or greater, and (6) no substance abuse within the last 3 months. Subjects were taking no other psychotropic medications with the exception of benzodiazepines for sleep. For the purposes of this study, an adequate trial of desipramine or imipramine was defined as treatment for at least 5 weeks that resulted in therapeutic blood levels at the end of the trial, or when levels were unavailable, a dose of at least 2.5 mg/kg/day. Body weight was calculated from data available for the period of treatment or from patients' retrospective estimates.

Table 1. Demographic, Clinical, and Treatment Variables for Each Subject

Patient	Sex	Diagnosis	Age (y)	Age at Onset (y)	Duration Current Episode (y)	No. Lifetime Episodes[a]	No. Treatments Failed in Current Episode[a]	% Change HAM-D	% Change BDI	Response Status[b]
1	M	Bipolar (type II)	56	45	10	Too many to count	> 10	11.8	–4.3	NR
2	F	Bipolar (type II)	43	35	8	1	> 10	–87.5	–79.9	R
3	F	Unipolar	38	23	2	Too many to count	2	–50.0	–47.6	R
4	M	Unipolar	37	16	1.5	6	5	–22.2	4.5	NR
5	F	Unipolar	30	24	6	1	> 10	–47.8	–48.8	R
6	M	Unipolar	31	10	20	1	9	–47.0	–50.0	R
7	M	Unipolar	57	50	7	1	> 10	–19.0	–34.1	NR
8	M	Unipolar	42	18	20	1	8	–37.5	–50.0	NR
9	F	Unipolar	29	15	14	1	> 10	26.3	–20.0	NR
10	F	Unipolar	31	31	0.5	1	1	–44.4	–39.3	R
11	F	Unipolar	30	24	1.5	1	5	–81.2	–81.6	R
12	F	Unipolar	52	44	2	Too many to count	4	–93.8	–65.0	R
13	F	Unipolar	25	16	2	1	6	–28.0	–4.6	NR

[a]For the purposes of statistical analysis, if there were more than 10 failed treatments or more than 10 previous episodes, the number of failures or previous episodes was fixed, a priori, at 10.
[b]R = response; NR = nonresponse. Response is defined as a > 40% decline in HAM-D score.

Subjects then commenced a 3-week open trial of desipramine or imipramine (i.e., the drug they had previously failed) at approximately 1 mg/kg/day, added to fluoxetine. The dose of fluoxetine remained unchanged during the treatment. No new psychoactive drugs were added during the 3-week open trial, except benzodiazepines for sleep. The HAM-D and the Beck Depression Inventory (BDI) were repeated weekly, and blood samples were collected 12 hours after the last dose at the end of week 1 and week 3 for determination of plasma desipramine and imipramine levels. Subjects were classified as responders if the HAM-D score declined by more than 40% and the clinician judged the subject to have responded to treatment. Using 2 separate multivariate analyses of variance (MANOVAs), responders were compared with nonresponders on the following groups of variables: demographics (mean age, age at onset, duration of current episodes) and treatment variables (mean desipramine or desipramine plus imipramine levels, desipramine or imipramine dose, fluoxetine dose). Pearson product moment correlation coefficients were used to test the bivariate relationship between severity scores and the above variables.

RESULTS

Thirteen subjects (8 women, 5 men) entered and completed the study. Of these, 10 had previously failed desipramine and therefore received desipramine, and 3 had previously failed imipramine and therefore received imipramine. Seven subjects (5 taking desipramine, 2 taking imipramine) responded to the addition of the tricyclic to fluoxetine, and 6 did not respond. Of the 7 responders, 4 had a 50% or greater reduction in HAM-D scores. Two subjects had bipolar disorder type II and were not taking mood stabilizers. Neither subject switched into mania, and 1 responded to the combination. The demographic, clinical, and treatment variables for each individual are reported in Table 1, and the means for responders and nonresponders are reported in Table 2. MANOVA, with response status as a 2-level factor and demographic vari-

Table 2. Demographic and Treatment Variables in Responders and Nonresponders to 3 Weeks of Combined Tricyclic and Fluoxetine

	Responders (N = 7)		Nonresponders (N = 6)	
Variable	Mean	SD	Mean	SD
Demographic variables[a]				
Age, y	36.4	8.5	41.03	13.4
Age at onset, y	27.3	10.7	26.7	16.2
Duration current episode, y	5.7	6.9	9.1	7.2
Number lifetime episodes	5.0	6.8	4.2	5.7
Number treatments failed in current episode	5.9	3.8	8.2	2.2
Clinical variables[b]				
HAM-D				
Baseline	18.9	4.0	19.33	3.3
Week 3	5.7	3.9	17.5	3.9
BDI				
Baseline	33.0	8.4	31.2	10.9
Week 3	14.0	7.1	25.5	10.2
Treatment variables[c]				
Mean dose of fluoxetine	50.0	21.0	36.7	19.7
Mean dose of desipramine or imipramine	67.9	12.2	70.8	24.6
Desipramine ± imipramine levels (nmol/L)				
Week 1	520	134	420	64
Week 3[d]	767	282	515	95

[a]MANOVA Wilks lambda = .8, df = 4:8, p = NS.
[b]Paired samples t test, for BDI, t = 5.1, df = 12, p < .0001; and for HAM-D, t = 4.4, df = 12, p < .001.
[c]MANOVA Wilks lambda = .29, df 4:8, p < .03.
[d]F test, F = 25.1, df = 1,11; p < .0001.

ables as the dependent measures, was not significant (Wilks lambda = .8, df = 4:8; p = NS). MANOVA, with desipramine or imipramine dose, fluoxetine dose, duration of fluoxetine treatment, and plasma desipramine and/or imipramine levels as dependent variables, was significant (Wilks lambda = .29, df = 4:8, p < .03). Subsequent univariate F test demonstrated a significant difference between responders and nonresponders in mean desipramine ± imipramine levels at week 3 (F = 25.1, df = 1,11; p < .0001).

Analyses were repeated using a more stringent definition of response. Subjects were classified as full responders if the HAM-D score declined 50% or more (N = 4), partial responders if the HAM-D score declined by 25% to 50% (N = 5), and nonresponders if the HAM-D changed by less than 25% (N = 4). Using univariate ANOVA to compare the means of the demographic and treatment variables, the only significant finding was with respect to desipramine ± imipramine levels at week 3 (F = 6.6, df = 2,10; p < .02). On post hoc testing, significant differences existed between mean blood levels in responders (857 ± 155 nmol/L) as compared with partial responders (495 ± 226 nmol/L; p < .05), and in responders as compared with nonresponders (518 ± 107 nmol/L; p < .05). Similar results were found when the percent change in drug levels was examined.

Severity at week 3 was significantly correlated with desipramine ± imipramine levels at week 3 (BDI, r = –0.60, p < .05; HAM-D, r = –0.58, p < .05). Furthermore, change in severity was significantly correlated with change in desipramine ± imipramine levels (percent change in BDI, r = –0.83, p < .0001; percent change in HAM-D, r = –0.71, p < .01).

DISCUSSION

This study demonstrated that 7 of 13 subjects who had previously failed to respond to adequate treatment with desipramine or imipramine and who had currently failed to respond to adequate treatment with fluoxetine responded when receiving both fluoxetine and the tricyclic in combination. Using more stringent criteria (≥ 50% reduction in HAM-D), 4 subjects (31%) could be said to be responders. This confirms previous reports that the combination may be an effective approach to treatment-resistant depression.[1–4] However, the current data also suggest that the response may be closely related to blood levels of the tricyclic antidepressant. This finding raises the possibility that the impact of the combination of fluoxetine and the tricyclic may be a result of the capacity of fluoxetine to increase plasma tricyclic levels. The blood levels of desipramine ± imipramine in these subjects are considerably higher than one would expect for the doses that subjects received in this study, a finding that is consistent with previous reports.[9–11] The elevation in plasma levels most likely resulted from the inhibition of tricyclic 2-hydroxylation and the reduction in first-pass and systemic metabolism of the tricyclic induced by fluoxetine.[5,6,12] The levels of tricyclic may have been higher during the current course of treatment as compared with the previous, unsuccessful course of treatment. Unfortunately, all plasma levels at the time of the previous failed response are not available. It is possible that subjects in the current study may simply have responded to desipramine or imipramine alone, if these medications had been given at sufficiently high dosages. It is also possible that the addition of a tricyclic increased the plasma levels of fluoxetine, resulting in response. However, to our knowledge, there are no data regarding the impact on fluoxetine levels of adding a tricyclic to fluoxetine. Furthermore, although one report suggests that a higher fluoxetine-norfluoxetine ratio may be associated with excellent response,[13] there are no data to support a dose response relationship between plasma fluoxetine levels and severity of psychiatric symptomatology.[14,15]

These results in an open study involving a small number of patients should be viewed as preliminary. The patients in this study were highly treatment resistant and were taking somewhat higher does of fluoxetine than would be expected in patients in their first episode. Therefore, these results might not be generalizable to all patients taking fluoxetine. We did not have access to all previous tricyclic levels, and we did not measure plasma fluoxetine levels. Questions regarding the specificity of the effect of the combination are better addressed with this important information, or by using a double-blind comparison of tricyclic alone versus the combination, controlling for plasma levels of the tricyclic. Nonetheless, the current case series suggests that the combination of fluoxetine and desipramine or imipramine may be a well-tolerated and effective treatment in highly treatment-resistant depressed patients, and this effect is somehow tied to the plasma levels of the tricyclic drug.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac).

REFERENCES

1. Nelson JC, Mazure CM, Bowers MB, et al. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303–307
2. Eisen A. Fluoxetine and desipramine: a strategy for augmenting antidepressant response. Pharmacopsychiatry 1989;22:272–273
3. Weilburg JB, Rosenbaum JF, Biederman J, et al. Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. J Clin Psychiatry 1989;50:447–449
4. Weilburg JB, Rosenbaum JF, Meltzer-Brody S, et al. Tricyclic augmentation of fluoxetine. Ann Clin Psychiatry 1997;3:209–213
5. Bergstrom RF, Peyton AL, Lemberger L. Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. Clin Pharmacol Ther 1992;51:239–248
6. Preskorn SH, Alderman J, Chung M, et al. Pharmacokinetics of desipramine coadministered with sertraline or fluoxetine. J Clin Psychopharmacol 1994;14:90–98
7. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective

Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35:837–844
8. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
9. Aranow RB, Hudson JI, Pope HG, et al. Elevated antidepressant plasma levels after addition of fluoxetine. Am J Psychiatry 1989;146:911–913
10. Michals M, Stanley DA, Crismon ML, et al. Elevated tricyclic antidepressant plasma concentrations associated with fluoxetine: two case reports [letter]. J Neuropsychiatry Clin Neurosci 1990;2:466–467
11. Vandel S, Bertschy G, Bonin B, et al. Tricyclic antidepressant plasma levels after fluoxetine addition. Neuropsychobiology 1992;25:202–207
12. von Ammon C. Drug-drug interactions of fluoxetine with tricyclics. Psychosomatics 1990;31:273–276
13. Tyrer SP, Marshall EF, Griffiths HW. The relationship between response to fluoxetine, plasma drug levels, imipramine binding to platelet membranes and whole-blood 5-HT. Prog Neuropsychopharmacol Biol Psychiatry 1990;14:797–805
14. Kelly MW, Perry PJ, Holstad SG, et al. Serum fluoxetine and norfluoxetine concentrations and antidepressant response. Ther Drug Monit 1989; 11:165–170
15. Koran LM, Cain JW, Dominguez RA, et al. Are fluoxetine plasma levels related to outcome in obsessive-compulsive disorder? Am J Psychiatry 1996;153:1450–1454