*Journal of Clinical Pharmacy and Therapeutics* (2003) **28**, 379–384

# Double-blind comparison of fluoxetine and nortriptyline in the treatment of moderate to severe major depression

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## SUMMARY

***Background:*** **Depression is an international public health problem. Impairment in social and occupational functioning, increased comorbidity with other psychiatric and medical conditions, and an increased risk of mortality are a few of its consequences. Some psychiatrists have the impression that selective serotonin re-uptake inhibitors may not work as well as tricyclic anti-depressants in severe depression and/or melancholia. On the contrary, there is a general belief that selective serotonin re-uptake inhibitors are superior to the tricyclic anti-depressants in having fewer side-effects, particularly cardiovascular effects. The objective of this double-blind study was to compare the efficacy and safety of fluoxetine and nortriptyline in patients with moderate to severe major depression.**

***Methods:*** **A total of 48 adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), forth edition for major depression, based on the structured clinical interview for DSM IV participated in the trial. Patients had a baseline Hamilton Rating Scale for Depression score of at least 20. In this double-blind, single-center trial, patients were randomly assigned to receive nortriptyline 150 mg/day (group 1) or fluoxetine 60 mg/day (group 2) for 6-weeks. The outcome of the two groups was assessed using Hamilton Depression Rating Scale, a side-effect checklist and a regular ECG assessment.**

***Results:*** **The results suggest that the efficacy of nortriptyline is superior to fluoxetine in this group of major depressed patients. No significant differences were observed between dropout rates in the two groups but anti-cholinergic side-effects were significantly more frequent with nortriptyline than with fluoxetine but there was no significant difference in cardiovascular effects in particular QTc prolongation.**

***Conclusion:*** **The results of the current study suggest that nortriptyline was more effective than fluoxetine in the treatment of moderate to severe depression. A larger study is warranted.**

*Keywords:* **cardiovascular effects; depression; fluoxetine; nortriptyline**

Received 17 April 2003, Accepted 12 August 2003

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## INTRODUCTION

Depression, thought to result from biochemical changes in the brain (1), is a common disease of adulthood. This affective disorder afflicts about 5% of the adult population in the United States. The mainstay for the treatment of depression is pharmacotherapy, usually in combination with some type of limited supportive psychotherapy (2, 3). Until the 1980s, the so-called Tricyclic Anti-depressants (TCAs) had been the first-line drugs; however, this situation has changed because of the availability of newer second-generation anti-depressants that have more favorable side-effect profile and low toxicity associated with an overdose (4).

The effectiveness of the newer anti-depressants in comparison with the more established agents is frequently questioned. Although selective serotonin re-uptake inhibitors (SSRIs) show a high

degree of pharmacologic selectivity, this does not seem to translate into improved clinical efficacy. The clinical effectiveness of the tricyclic agents may be attributed to their dual inhibitory effects on both noradrenergic and serotonergic systems (5, 6). There is a commonly held belief among psychiatrists that newer anti-depressants, notably the selective serotonin re-uptake inhibitors, are clinically somewhat less effective than the TCAs in the treatment of severe depression. The limited number of clinical trials of SSRIs conducted in this patient population has, however, generally failed to confirm this contention (7–9). Nevertheless, the possibility of real differences in efficacy between TCAs and newer anti-depressants cannot be excluded (10).

Recently, the FDA and members of the medical community have raised concerns about medications associated with QTc prolongation. In normal cardiac conduction, the QTc interval is approximately 420 ms. However, if repolarization is delayed, prolongation of the QT interval results. In general, a QTc longer than 450 ms is of potential concern. Prolongation longer than 500 ms indicates an elevated risk of progression to tachyarrhythmias (torsade de points), which may be associated with symptoms such as palpitation, dizziness, lightheadedness, and syncope; and progression to ventricular fibrillation which can potentially cause sudden death (11).

The effects of anti-depressant drugs on the cardiac conduction system have been of long standing concern after the observation that overdoses of TCAs frequently lead to cardiac-related death. At therapeutic doses, these agents have been shown to increase PR, QRS, and QT intervals and to have quinidine-like class $I_A$ anti-arrhythmic properties. All drugs with class I action, including the TCAs, block fast sodium channels, and such activity more recently has been associated with increased mortality in the context of underlying cardiovascular disease. Subsequently, systematic studies of the TCAs in patients with and without cardiac disease documented a number of cardiovascular effects, most notably increase in heart rate and orthostatic hypotension. As a class, the SSRIs are believed to have more benign cardiovascular safety profiles than do the TCAs because they do not block fast sodium channels or prolong PR or QRS intervals (11).

For moderate to severe depression, nortriptyline continues to be regarded as the most effective treatment, particularly for elderly patients. Because of its benign side-effect profile in both acute and long-term treatment, nortriptyline is the most widely prescribed TCA today (12, 13). To our knowledge, there is only one published controlled comparison of the efficacy and safety of fluoxetine and nortriptyline in major depression (14). The studies that indicate superiority of SSRIs and in particular fluoxetine over TCAs, have used older reference TCAs such as imipramine or amitriptyline although nortriptyline has a very different side-effect profile (8, 9, 15).

Against this background we carried out a randomized trial of nortriptyline and fluoxetine in a double-blind study to compare the efficacy and safety of fluoxetine and nortriptyline and in particular their cardiovascular effects in patients with moderate to severe major depression.

## METHODS

### *Trial organization*

This was a 6-week, parallel group, randomized trial undertaken in outpatient clinic of Roozbeh Psychiatric Hospital, Tehran, Iran during January 2002 to February 2003.

### *Participants*

A total of 48 adult outpatients aged 19–54 who met the Diagnostic and Statistical Manual of Mental Disorders, Forth edition (16) (DSM IV) for major depression based on the structured clinical interview for DSM IV participated in the trial. Patients have a baseline Hamilton Rating Scale for Depression (HAM-D 17-item) (17) score of at least 20. The HAM-D, the most widely used physician-administrated rating scale for depression, summates 17 individual item scores to provide a total score indicative of the severity of depression. Participation was precluded for patients with any other primary psychiatric disease, current or past history of bipolar disorder, for patients requiring treatment with psychoactive drugs like anxiolytic, Monoamine Oxidase Inhibitors (MAOIs) or tryptophan, patients with organic brain disorders including epilepsy, patients with predominantly suicidal

tendencies, and with any severe general disease. In addition, pregnant and lactating women and patients with alcohol or drug dependency were excluded. As depression is a serious and potentially life-threatening condition and the participants were outpatients, extensive safeguards were needed. Patients were excluded if they posed a significant risk of suicide at any time during participation. All participants provided written informed consent, and the protocol satisfied the Ministry of Health and Medical education of Iran's Ethics Committee requirements.

Patients were randomly assigned to receive tablet nortriptyline 150 mg/day (titrated-up over 4 weeks and were put in capsules to provide similar appearance with fluoxetine) (group 1) or fluoxetine 60 mg/day (titrated-up over 4 weeks) (group 2) for the 6-week study. Eleven patients dropped out of the trial leaving 37 subjects who met the DSM IV criteria for major depression to complete the trial. Patients were assessed by a third-year resident of psychiatry, using a standardized protocol for the HAM-D, at baseline and after 1, 2, 4, and 6 weeks after the medication started. The principal measure of the outcome was the 17-item HAM-D. The mean decrease in HAM-D score from baseline was used as the main outcome measure of response of depression to treatment.

### *Side-effects*

Side-effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on days 7, 14, 28, and 42 (Table 2). All the clinical assessments, the ECG recordings and the assessment of changes in blood pressure were made blind with respect to the medication received and were assessed on days 7, 14, 28, and 42. Systolic and diastolic hypertension was considered as ≥140/90.

### *Statistical analysis*

A two-way repeated measures ANOVA (time–treatment interaction) was used. The two groups as a between-subjects factor (group) and the five measurements during treatment as the within-subjects factor (time) were considered. This was done for Hamilton Depression Rating Scale scores. In addition, a one-way repeated measures ANOVA with a two-tailed *post hoc* Tukey mean comparison test were performed on the change in Hamilton Depression Rating Scale scores from baseline. To compare the reduction in the Hamilton Depression Rating Scale score at week 6 compared with baseline, an unpaired two-sided Student's *t*-test was used. Results are presented as mean ± SEM differences and were considered significant with $P \leq 0{\cdot}05$. To compare the baseline data and frequency of side-effects between the protocols, Fisher's exact test was performed. A traditional 'observed cases' (OC, the patients who completed the trial) analysis at 6 weeks was the primary efficacy analysis. In addition, intention to treat (ITT) analysis with last observation carried forward (LOCF) procedure was also performed. All results discussed are based on OC analysis unless otherwise stated.

## RESULTS

A total of 106 patients were screened for the study and 48 were randomized to trial medication (24 patients in each group). No significant differences were identified between patients randomly assigned to the two groups with regard to basic demographic data including age and gender (Table 1). Thirty-seven patients completed the trial. In the nortriptyline and fluoxetine group the number of dropouts were 4, and 7, respectively. Although the number of dropouts in the fluoxetine group was higher than the nortriptyline group, this was not significant ($P = 0{\cdot}49$) (Fig. 1).

### *Efficacy: nortriptyline vs. fluoxetine*

The mean ± SEM scores of two groups of patients are shown in Fig. 2. There were no significant differences between the two groups in week 0 (baseline) on the Hamilton Depression rating scale

**Table 1.** Baseline data.

| | Nortriptyline | Fluoxetine | *P* |
|---|---|---|---|
| Age (mean ± SD) | 35·44 ± 10·60 | 36·24 ± 8·11 | 0·76 |
| Gender | Male: 14, Female: 10 | Male: 15, Female: 9 | 1·00 |

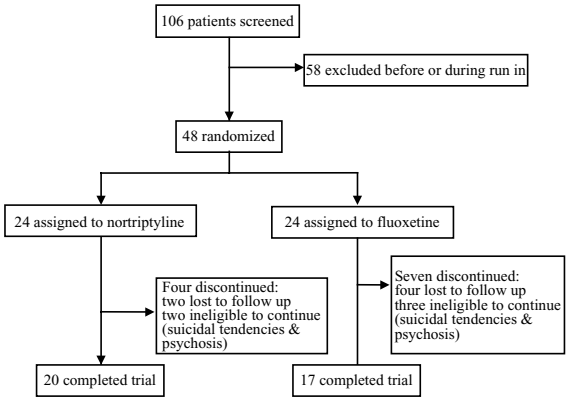


**Fig. 1.** Trial profile.

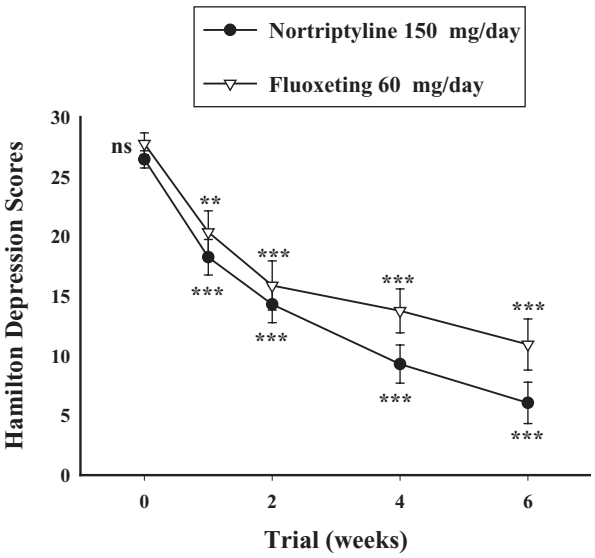


**Fig. 2.** Mean ± SEM scores of the two protocols on the Hamilton Depression scores. ns, non-significant; $^{**}P < 0{\cdot}01$ and $^{***}P < 0{\cdot}001$.

($t = 0{\cdot}79$, d.f. = 46, $P = 0{\cdot}43$). The difference between the two protocols was not quite significant as indicated by the effect of group, the between-subjects factor ($F = 2{\cdot}83$, d.f. = 1, $P = 0{\cdot}09$) but was significant in the ITT analysis ($F = 6{\cdot}10$, d.f. = 1, $P = 0{\cdot}01$). The behavior of the two treatments was homogeneous across the time (groups-by-time interaction, Greenhouse–Geisser correction; $F = 0{\cdot}93$, d.f. = 2·24, $P = 0{\cdot}40$). In addition, a one-way repeated measures ANOVA showed a significant effect of both treatments on the Hamilton Depression rating scale scores ($P < 0{\cdot}0001$). In both groups *post hoc* comparisons showed a significant change from week 1, on the Hamilton Depression rating scale scores. The difference between the two treatments was not significant at the endpoint (OC analysis) (week 6) ($t = 1{\cdot}79$, d.f. = 35, $P = 0{\cdot}08$) but was significant in the ITT analysis ($t = 2{\cdot}58$, d.f. = 46, $P = 0{\cdot}01$). The changes at the endpoint compared with baseline were: $-20{\cdot}3 \pm 8{\cdot}12$ (mean ± SD) and $-16{\cdot}82 \pm 11{\cdot}08$ for nortriptyline and fluoxetine, respectively. A significant difference was not observed on the change of scores of the Hamilton Depression rating scale at week 6 compared with baseline in the two groups in the OC analysis ($t = 1{\cdot}09$, d.f. = 35, $P = 0{\cdot}27$) whereas in ITT analysis the difference was significant ($t = 2{\cdot}01$, d.f. = 46, $P = 0{\cdot}04$).

**Table 2.** Number of patients with side-effects.

| Side effects | Nortriptyline | Fluoxetine | *P* |
|---|---|---|---|
| Vomiting | 3 | 7 | 0·28 |
| Drowsy | 81 | 7 | 0·18 |
| Diarrhea | 1 | 5 | 0·10 |
| Abdominal pain | 7 | 3 | 0·28 |
| Nausea | 3 | 10 | 0·04* |
| Appetite changes | 5 | 13 | 0·03* |
| Blurred vision | 15 | 5 | 0·007** |
| Constipation | 10 | 2 | 0·01** |
| Dry mouth | 18 | 6 | 0·001*** |
| Headache | 6 | 15 | 0·02* |
| Urinary retention | 4 | 1 | 0·34 |
| Tremor | 9 | 11 | 0·77 |
| Tingling in hands or feet | 4 | 5 | 1·00 |
| Feeling tense inside | 7 | 5 | 0·50 |
| Sweating | 6 | 4 | 0·72 |
| Trouble sleeping | 2 | 4 | 0·66 |
| Sexual disorders | 1 | 5 | 0·18 |
| Seeing double | 8 | 3 | 0·16 |
| Restlessness | 2 | 5 | 0·41 |
| Orthostatic hypotension | 9 | 4 | 0·19 |
| Heart racing | 2 | 3 | 1·00 |
| Electrocardiograph abnormalities | 1 | 4 | 0·34 |
| Heart pounding | 4 | 5 | 1·00 |
| Pulse rate problems | 5 | 3 | 0·70 |
| Hypertension | 9 | 8 | 1·00 |
| Dizziness | 10 | 11 | 1·00 |
| Numbness of hands or feet | 8 | 7 | 1·00 |
| Itching | 4 | 3 | 1·00 |

### *Clinical complications and side-effects*

Twenty-eight side-effects were observed over the trial. The difference between the nortriptyline and fluoxetine in the frequency of side-effects was not significant except for blurred vision, constipation, dry mouth, headache, nausea, and appetite changes (Table 2). In the nortriptyline group nine patients had hypertension. Seven of them had diastolic hypertension and two patients had both systolic and diastolic hypertension. In fluoxetine group eight patients had hypertension. Six of them had diastolic hypertension and two patients had both systolic and diastolic hypertension. In the nortriptyline group the only ECG abnormality was because of sinus arrhythmias whereas in the fluoxetine group four cases of ECG abnormalities were because of QT and QRS interval prolongation and T inversion. The difference between the nortriptyline and fluoxetine in the frequency of QTc prolongation was not significant ($P = 0{\cdot}48$).

## DISCUSSION

Depression is an international public health issue with impairment in social and occupational functioning, increased psychiatric and medical comorbidity, and an increased risk of mortality among depressed individuals as consequences (2, 3, 18).

There is an impression among psychiatrists that SSRIs may not work as well as TCAs in severe depression and/or melancholia (5) and a general belief that SSRIs are superior to the TCAs regarding side-effects and in particular cardiovascular adverse effects (15, 19, 20). The present study suggests that nortriptyline is more effective than fluoxetine in this group of major depressed patients. No significant differences were observed between dropout rates in the two groups but anticholinergic side-effects were significantly more common with nortriptyline than fluoxetine but there was no significant difference in cardiovascular effects in particular QTc prolongation. Indeed, QTc prolongation was observed only in the fluoxetine group in this study. However, the difference was not significant ($P = 0{\cdot}48$). In conclusion, the results of the current study provide evidence in favor of an efficacy advantage nortriptyline over fluoxetine in the treatment of moderate to severe depression. However, this conclusion should be tempered by the small sample size. However, even if nortriptyline is more effective than fluoxetine for this patient group, other factors such as anticholinergic effects in particular for elderly patients must be considered in the selection of an antidepressant medication.

## ACKNOWLEDGEMENTS

This study formed part of the postgraduate thesis of Dr Faraji. The Authors wish to thank Dr Margaret Tejerizo for invaluable help.

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