# Combination of citalopram and nortriptyline in the treatment of severe major depression: a double-blind, placebo-controlled trial

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**Objective:** Depression is a major health problem and is not only under-recognized and undertreated but is associated with significant morbidity and mortality. It has been suggested that combination therapy rapidly reduces depressive symptoms in patients with moderate-to-severe depression more effectively than monotherapy; however, this is controversial. Serotonergic and noradrenergic enhancement may be synergistic and more effective than serotonergic enhancement alone in the management of depression. The objective of this double-blind, placebo-controlled study was to investigate the efficacy and tolerability of the combination of citalopram and nortriptyline for the treatment of moderate-to-severe major depression. **Methods:** A total of 45 patients, who met the Diagnostics and Statistical Manual of Mental Disorders-IV criteria for major depressive disorder based on the clinical interview were included in the study. Patients had a baseline Hamilton Depression Rating Scale score of at least 20. In this trial, patients were randomly assigned to receive nortriptyline 50 mg/day plus citalopram 40 mg/day (group 1) or placebo plus citalopram 40 mg/day (group 2), for the 8-week, double-blind, placebo-controlled trial. **Results:** Both protocols significantly decreased the Hamilton Depression Rating Scale score over the trial period, but the combination of nortriptyline and citalopram showed significant superiority over citalopram alone in the treatment of moderate-to-severe major depressive disorder (t = 3.34; degrees of freedom = 36; p = 0.001). The difference between the two groups in the frequency of side effects was not significant. **Conclusions:** The results of this study suggest that the combination of nortriptyline and citalopram is more effective than citalopram alone in the treatment of depression. This advantage probably results from serotonin and noradrenergic reuptake inhibition.

Major depressive disorder (MDD) is one of the most common psychiatric disorders. Patients with this disorder show depressed mood or loss of interest as a key symptom, accompanied by five or more of the following symptoms:

- Changes in weight or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feeling of guilt or worthlessness
- Difficulty in concentration or indecisiveness
- Thoughts of death or suicide

This disorder virtually always results in impaired interpersonal, social and occupational functioning. Lifetime prevalence of MDD is approximately 15%, and can be as high as 25% for women [1,2]. Forecasts suggest that by the year 2020, unipolar major depression could increase in world rank order from the fourth to the second leading cause of disabling-adjusted life years [3]. The main neurochemical theories regarding the pathogenesis of depression involve dysfunction of either norepinephrine or serotonin neurotransmitters [4], the enhancement of which is also believed to mediate, at least in part, the therapeutic effects of antidepressants [5]. The current popularity of the selective serotonin-reuptake inhibitors (SSRIs) for the treatment of depression should not conceal the fact that noradrenergic neurons also seem to influence depressed mood, therefore, selective noradrenergic-reuptake inhibitors (NRIs) such as reboxetine, appear to be at least as effective as SSRIs [6,7]. Improvements in social adjustment have also been reported to be more favorable with reboxetine than with fluoxetine [8]. Antidepressant monotherapy is used more often than other therapies to achieve symptom remission in depressed patients [9], but a significant portion of patients (approximately a third) treated with a single antidepressant exhibit suboptimal or delayed clinical response to these medications [10,11]. Serotonergic and noradrenergic enhancement may be synergistic and more effective than serotonergic

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enhancement alone in treating depression. Many studies have reported that venlafaxine (the dual serotonin–norepinephrine-reuptake inhibitor [SNRI]) was significantly more effective than SSRIs in improving depression, perhaps due to enhancement of both serotonin and norepinephrine. In addition, venlafaxine may induce remission earlier than SSRIs [12–17]. However, some studies contradict this hypothesis [18], but increasing evidence suggests that, in some depressed patients, SNRIs may provide benefits of treating a broader range of target symptoms than single-acting agents such as SSRIs [19]. Combinations of antidepressants with both serotonergic and noradrenergic activity may be especially effective and thus useful in treating refractory patients and severely depressed patients [20–23]. A major depressive episode can be categorized as severe based on depressive symptoms, scores on the Hamilton Depression Rating Scale (HAM-D), need for hospitalization, functional capacity and level of suicidality. Potential complications of untreated severe depression include suicide, self-mutilation and refusal to eat, and treatment resistance. Combination therapy has been reported to be more effective in severe major depression [24].

On the basis of this background, the aim of this double-blind, placebo-controlled study was to investigate the efficacy and tolerability of the combination of citalopram and nortriptyline for the treatment of moderate-to-severe major depression. The combination of nortriptyline and citalopram was selected because nortriptyline is one of the noradrenergic-based tricyclic antidepressants (TCAs) with a tolerable side-effect profile and citalopram is the most selective SSRI [1].

## Methods

### *Trial organization*

This was an 8-week, double-blind, randomized trial, undertaken at the outpatient clinic of Roozbeh Psychiatric Hospital (Tehran, Iran), from September 2003 to December 2004. This study was approved by the Ethics Committee of the Tehran University of Medical Sciences.

### *Participants*

After obtaining informed consent and discontinuing all psychotropic medications for 2 weeks, 45 out-patients (27 female and 18 male) aged 18–54 years were enrolled in the study. All subjects met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for MDD, based on the structured clinical interview for DSM-IV and had a baseline HAM-D (17 item) score of at least 20 [25,26]. The HAM-D is the most widely used physician-administrated rating scale for depression. It summates 17 individual item scores to provide a total score indicative of the severity of depression. Patients with a history of other psychiatric disorders, history of bipolar disorder, personality disorder, anxiety disorder, substance abuse, alcoholism and organic brain disorders, were excluded. Also, patients were excluded if they were psychotic or posed a significant risk of suicide at any time during the trial. Pregnant or lactating women were excluded. All patients were free of unstable medical disorders, including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine or hematological illnesses. All patients gave a complete medical and psychiatric history and were given a physical examination before entry into the study. A total of 23 patients were assigned in a random fashion to nortriptyline 50 mg/day plus citalopram 40 mg/day (group 1) and 22 patients to placebo plus citalopram 40 mg/day (group 2) for an 8-week, double-blind, placebo-controlled trial. The dosage of citalopram (in both groups) was titrated up to 40 mg/day over 3 days and the dosage of nortriptyline (in group 1) was titrated up to 50 mg/day over 3 days. Patients didn't receive other psychopharmacological drugs during the trial and they were not permitted to have psychotherapy. At each scheduled visit, a resident of psychiatry, using a standardized protocol for the HAM-D before administration, assessed all patients at 0, 2, 4, 6 and 8 weeks after the initiation of medication. The principal measure of the outcome was the 17-item HAM-D. The mean decrease in HAM-D score from the baseline was used as the main outcome measure of depression response to treatment. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry at weeks 2, 4, 6 and 8.

### *Statistical analysis*

Using data from our pilot study and considering $\alpha = 0.05$ and $\beta = 0.2$, the final difference between the two groups, at least a score of 5 on the HAM-D, S = 5 and power = 0.8, the sample

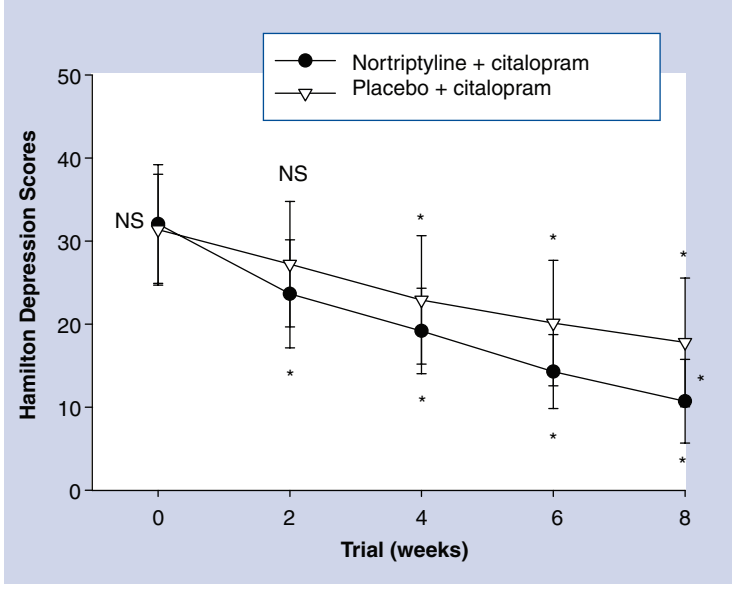
**Table 1. Demographic and clinical characteristics of 45 patients with moderate-to-severe depression.**

| | Nortriptyline + citalopram (n = 23) | Placebo + citalopram (n = 22) |
|---|---|---|
| Women | 9 | 9 |
| Men | 14 | 13 |
| Age (years) (mean ± SD) | 33.63 ± 11.34 | 32.31 ± 9.97 |
| Duration of illness (months) (mean ± SD) | 10.31 ± 7.69 | 10.84 ± 5.82 |
| HAM-D score at baseline (mean ± SD) | 30.80 ± 4.16 | 31.20 ± 5.07 |
| Number of previous episodes | 3.22 ± 0.74 | 3.33 ± 0.82 |
| Medication history | Fluoxetine: 15; nortriptyline: 5; citalopram: 3 | Fluoxetine: 13; nortriptyline: 4; citalopram: 5 |

*HAM-D: Hamilton Depression Rating Scale.*

size was calculated for at least 15 patients in each group. A two-way, repeated-measures ANalysis Of VAriance (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 performed for HAM-D scores. In addition, a one-way, repeated-measures ANOVA with a two-tailed, *post hoc* Tukey mean comparison test was performed on the changes in the HAM-D scores from baseline. Results are presented as mean ± standard error of the mean (SEM) differences and were considered significant with a p-value of 0.05 or less. To compare the demographic data and frequency of adverse events between the protocols, Fisher's exact test was performed. Intention-to-treat (ITT) analysis with last observation carried forward (LOCF) procedure was carried out.

**Figure 1. Mean ± standard deviation of the two protocols on the Hamilton Rating Scale for depression.**




*<0.001. The horizontal symbols were used to express statistical significance versus their respective baseline value and the vertical symbol is for between-subjects comparison.

## Results

Initially, 94 potential study candidates were identified. However, 49 patients did not meet study inclusion and exclusion criteria. Therefore, 45 patients were randomized into the study (23 patients in group 1 and 22 patients in group 2). 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**). Four patients from group 1 and three from group 2 dropped out of the study, leaving 38 patients who completed the trial.

### *Efficacy: combination therapy versus monotherapy*

The mean ± SD scores of the two groups of patients are shown in **Figure 1**. There were no significant differences between the two groups at week 0 (baseline) on the HAM-D ($t = 0.3$; $df = 36$; $p = 0.76$). Both groups showed a significant improvement over the 8 weeks of treatment (Greenhouse–Geisser corrected: $p < 0.001$). The difference between the two protocols was significant, as indicated by the

effect of group, the between-subjects factor ($F = 4.1$; $df = 1$; $p = 0.04$). The behavior of the two treatments was not homogeneous across the time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 7.19$; $df = 1.72$; $p = 0.002$). In addition, a one-way repeated measures ANOVA demonstrated a significant effect of both treatments on the HAM-D scores ($p < 0.001$). In group 1 only, *post hoc* comparisons showed a significant change at week 2 compared with week 0, on the HAM-D scores ($p < 0.001$). The difference between the two treatments was significant at the end point (week 8; $t = 3.34$; $df = 36$; $p = 0.001$). There was significant difference between the two treatments in terms of the percentage of responders (at least 50% drop in the HAM-D score) (group 1: 65% [15/23] and group 2: 31.81%; [7/22]; $p = 0.03$). In addition, it was observed a significant difference regarding remission rate (score ≤7; group 1: 21.70% [5/23] and group 2: 0%; [0/22]; $p = 0.04$).

### *Clinical complications & side effects*

In total, 28 side effects were observed over the trial. The difference between the two groups in the frequency of side effects was not significant (**Table 2**). Nevertheless, the frequency of dry mouth in group 1 was more than group 2.

## Discussion

The current therapeutic goal in the treatment of major depression is to improve the quality of life by normalizing mood, increasing and reversing the functional and social disabilities associated with depression and reducing suicide rates. In moderate-to-severe depression, pharmacotherapy may be the treatment of choice.

**Table 2. Number of patients with side effects in two groups.**

| Side effect | Nortriptyline + citalopram (n = 19) | Citalopram + placebo (n = 19) |
|---|---|---|
| Dizziness | 4 | 4 |
| Fatigue | 6 | 3 |
| Weakness | 4 | 4 |
| Confusion | 2 | 1 |
| Headache | 4 | 5 |
| Insomnia | 2 | 5 |
| Sedation | 7 | 6 |
| Constipation | 8 | 8 |
| Diarrhea | 1 | 3 |
| Nausea | 1 | 2 |
| Vomiting | 1 | 1 |
| Anorexia | 3 | 5 |
| Weight gain | 4 | 2 |
| Orthostatic – hypotension | 3 | 1 |
| Bradycardia | 0 | 0 |
| Tachycardia | 3 | 3 |
| Skin rash | 3 | 2 |
| Dry mouth | 9 | 5 |
| Urinary retention | 3 | 3 |
| Visual disturbance | 4 | 2 |
| Impotence | 0 | 0 |
| Decrease of libido | 3 | 3 |
| Tremor | 3 | 1 |
| Anorgasmia | 1 | 2 |
| Sweating | 7 | 4 |
| Paresthesia | 5 | 3 |

*All p-values were nonsignificant.*

However, some patients do not respond to a single agent and almost all antidepressants take approximately 3–4 weeks to display any significant therapeutic effect [1,2]. It has been reported that the superior efficacy and rapid onset of action of venlafaxine is due to a combination of effects on both serotonin and norepinephrine reuptake. There are several studies that support the effectiveness of the combination of SSRIs and TCAs [27–30]. It has been reported that this combination is a rapid and effective strategy for the treatment of depression [31]. In this study, only 50 mg/day of nortriptyline increased the efficacy of citalopram in the treatment of severe depression. The combination of citalopram and nortriptyline at these doses did not induce any severe side effects. However, this conclusion should be tempered by the small sample size and short duration time. As this study indicates, one of the advantages of this combination is better and earlier improvement. The results indicate that a combination of citalopram and nortriptyline could induce a significant reduction in the HAM-D scores as early as 2 weeks after the initiation of medication. In summary, the current findings support the hypothesis that antidepressants with a dual effect on norepinephrine and serotonin will be more effective than SSRIs alone.

## Conclusion

This study demonstrates that the combination of a noradrenergic agent, such as nortriptyline, and a serotonergic agent, such as citalopram, is an effective treatment for severe depression. This is in line with several studies that indicate the therapeutic use of combinations of SSRIs and TCAs in refractory depression. Also, one of the advantages of this combination is a rapid onset of decreasing symptoms.

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**Executive summary**

- Depression is a major health problem and is not only under-recognized and undertreated but is associated with significant morbidity and mortality.
- The main neurochemical theories regarding pathogenesis of depression involve dysfunction on either the norepinephrine or serotonin neurotransmitters.
- Combination therapy has been reported to be more effective in severe major depression.
- The combination of noradrenergic agents, such as nortriptyline, and a serotonergic agent such as citalopram, is an effective treatment for moderate-to-severe depression.

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