Original Article

Combination of Citalopram and Nortriptyline in Treatment of Moderate to Severe Major Depression: A Double-blind, Placebo- controlled Trial

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Objective: Depression is a major health problem, which is not only underrecognized and undertreated, but is also associated with significant morbidity and mortality. It has been suggested that combination therapy rapidly reduces depressive symptoms in patients with moderate to severe depression and is more effective than monotherapy; but this suggestion remains 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.
Method: 45 patients, who met the DSM-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 (group1) or placebo plus citalopram 40 mg/day (group2), for an 8 week, double-blind, placebo-controlled trial.
Results: Both protocols significantly decreased the score of Hamilton Depression Rating Scale over the trial period, but the combination of nortriptyline and citalopram showed a significant superiority over citalopram alone in the treatment of moderate to severe major depressive disorder ($t = 3.34$, $d.f. = 36$, $P = 0.001$). The difference between the two groups in the frequency of side effects was not significant.
Conclusion: The results of this study suggest that combination of nortriptyline and citalopram is more effective than citalopram alone in the treatment of depression. This advantage is probably the result of reuptake inhibition of both serotonin and norepinephrine

Key words:
Antidepressant, Citalopram, Combination drug therapy, Depression, Nortriptyline

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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 and thought of death or suicide. This disorder virtually always results in impaired interpersonal, social and occupational functioning. Lifetime prevalence of MDD is about 15 percent, perhaps as high as 25 percent for women (1, 2). Forecasts suggest that by year 2020, unipolar major depression could increase in world rank order from the fourth to the second leading cause of disability adjusted life years (3).

The main neurochemical theories regarding the pathogenesis of depression involve dysfunction of either the noradrenaline or serotonin neurotransmitter systems (4), the enhancement of which is also believed to mediate, at least in part, the therapeutic effects of antidepressants (5). The current popularity of 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 seem 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 one 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 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 nor epinephrine. In addition, venlafaxine may induce remission earlier than SSRIs (12-17). Although some studies contradict this hypothesis (18), increasing evidence suggests that in some depressed patients, SNRIs may provide the benefit of treating a broader range of target symptoms compared to single acting agents such as SSRIs (19). Combination of medications with both serotonergic and noradrenergic activity may be especially effective and thus useful in treating patients with refractory depression and severely depressed patients (20).

A major depressive episode can be categorized as severe based on depressive symptoms, scores on the Hamilton Depression Rating Scale, need for hospitalization, functional capacity and level of suicidality. Potential complications of untreated severe depression include suicide, self-mutilation, refusal to eat and treatment resistance. Combination therapy has been reported to be effective in severe major depression (21).

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 treatment of moderate to severe major depression. We selected the combination of nortriptyline and citalopram because nortriptyline is a noradrenergic-based tricyclic antidepressants with tolerable side effects profile and citalopram is the most selective SSRI (1).

Material and 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 ethics committee of Tehran University of Medical Sciences.

Participants

After obtaining informed consent and discontinuing all psychotropic medications for 2 weeks, 45 outpatients (24 female and 14 male) between 18 and 54 years of age were enrolled in the study. All subjects met the Diagnostic and Statistical Manual of Mental Disorders, Forth edition (22) (DSM-IV) criteria for MDD, based on the Structured Clinical Interview for DSM-IV and had a baseline Hamilton Rating Scale for Depression (HAM-D, 17 item) (23) score of at least 20. 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 history of other psychiatric disorders such as bipolar disorder, personality disorder, anxiety disorder, substance abuse and alcoholism, as well as those with history of 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 as well. 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 physically examined before entring the study.

Twenty-three patients were assigned in a random fashion to nortriptyline 50 mg/day plus citalopram 40 mg/day (group 1), 22 patients to placebo plus citalopram 40 mg/day (group 2) for 8 weeks. The dosage of citalopram (in both groups) was titrated up to 40 mg/day over three days and the dosage of nortriptyline (in group 1) was titrated up to 50 mg/day over three days. Patients did not receive other psychopharmacological drugs during the trial and they were not permitted to have psychotherapy.

At each scheduled visit, a resident in psychiatry assessed subjects using a standardized protocol for the HAM-D before administration. Patients were also assessed at weeks 0, 2, 4, 6 and 8 after the start 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 response to treatment. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident in psychiatry at weeks 2, 4, 6 and 8.

Statistical analysis

Using data from our pilot study and considering α=0.05 and β=0.2, the final difference between the two groups, at least a score of 5 on the Hamilton Depression Rating Scale, σ=5 and power=0.8, the sample size was calculated at least 15 patients in each group. A two-way repeated measure Analysis of Variance (ANOVA) (time−treatment interaction) was used. The two groups as a between-subject factor (group) and the five measurements during treatment as the within subject factor (time) were considered. This was done for Hamilton Depression Rating Scale scores. . In addition, a one-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison test was performed on the changes in the Hamilton Depression Rating Scale scores from baseline. Results are presented as mean ± SEM and differences were considered significant with $P \leq 0{\cdot}05$. 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.

Results

Initially 94 potential study candidates were identified. However, 49 patients did not meet the 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

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

	Nortriptyline+ Citalopram (group 1)N=23	Citalopram Placebo (group 2) N=22	P
Age (year) (mean±SD)	33.63 ± 11.34	32.31 ±9.97	0.7
Gender	Male: 9 Female: 14	Male: 9 Female: 13	1.00
Duration of illness (month)(mean±SD)	10.31± 7.69	10.84 ±5.82	0.81

Table 2- Number of patients with side- effects in two groups. ns= non significant

Adverse reactions	Nortriptyline+ Citalopram N=19	Citalopram+ Placebo N=19	P
Dizziness	4	4	ns
Fatigue	6	3	ns
Weakness	4	4	ns
Confusion	2	1	ns
Headache	4	5	ns
Insomnia	2	5	ns
Sedation	7	6	ns
Constipation	8	8	ns
Diarrhea	1	3	ns
Nausea	1	2	ns
Vomiting	1	1	ns
Anorexia	3	5	ns
Weight gain	4	2	ns
Orthostatic - Hypotension	3	1	ns
Bradycardia	0	0	ns
Tachycardia	3	3	ns
Skin rash	3	2	ns
Dry mouth	9	5	ns
Urinary retention	3	3	ns
Visual disturbance	4	2	ns
Impotence	0	0	ns
Decrease of libido	3	3	ns
Tremor	3	1	ns
Anorgasmia	1	2	ns
Sweating	7	4	ns
Paresthesia	5	3	ns

0.76). Both groups identified among 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 immunotherapy

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 Hamilton Depression Rating Scale (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

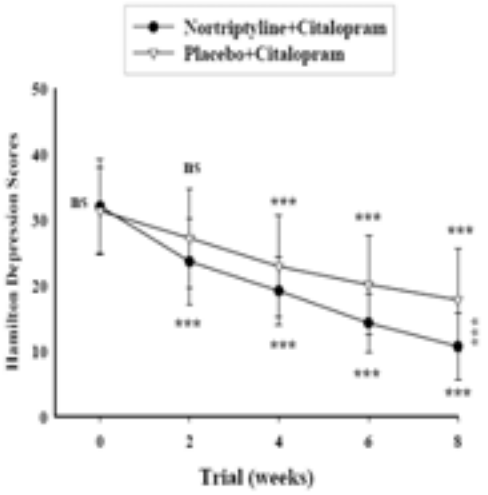

Figure 1- Mean ± SD of the two protocols on the Hamilton rating scale for depression. ns= non-significant and *<0.001. The horizontal symbols were used to express statistical significance versus their respective baseline value and the vertical symbol is for between subjects comparison**

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 two treatments was not homogeneous across 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 showed a significant effect of both treatments on the Hamilton Depression Rating Scale scores (P<0.001). Only in group 1, post hoc comparisons showed a significant change at week 2 compared to
week 0, on the Hamilton Depression Rating Scale scores (P<0.001). The difference between the two treatments was significant at the endpoint (week 8) (t=3.34, d.f=36, P=0.001).

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Clinical complications and side effects

In total, 28 side effects were observed in the course of 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, 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. But some patients do not respond to a single agent and almost all antidepressants take about 3 to 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 effects on both serotonin and nor epinephrine reuptakes. There are several studies that support the effectiveness of combination of SSRI and TCA (24-27). It has been

reported that this combination is a rapid and effective strategy for the treatment of depression (28). In this study a dose of only 50 mg/day 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 with the small sample size and short time of duration. As this study indicates, one of the advantages of this combination is a better and earlier improvement. The results indicate that a combination of citalopram and nortriptyline could induce a significant reduction in the scores of HAM-D as early as 2 weeks after the medication is started.

Conclusion

This study shows that the combination of the noradrenergic agents such as nortriptyline and a serotonergic agent such as citalopram is an effective treatment for moderate to severe depression. Also, one of the advantages of this combination is a rapid onset of decreasing symptoms.

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