Comparing the Efficacy of add-on Nortryptiline With Triiodothyronine in the Management of Citalopram-Resistant Depression

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Objective: To manage a treatment resistant depression, clinicians may add a second medication to the first antidepressant drug. The aim of the current research was to study the outcome of augmentation of citalopram with nortryptiline or triiodothyronine in a randomized clinical trial.

Methods: We selected 48 adult outpatients with a diagnosis of non-psychotic major depressive disorder who had not responded to 12 weeks citalopram therapy (40 mg per day). They were randomly allocated to two groups. One group received nortryiptiline (at a dose of up to 150 mg per day) and the other triiodothyronine (T3) (at a dose of up to 50 µg per day). The remission of depression was defined as a score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HRSD-17).

Results: After 8 weeks, the nortriptyline group had a higher remission rate (33.33 %) than the triiodothyronine group (17.64%). The nortriptyline group, however, had a higher dropout rate due to experiencing more side effects.

Conclusion: Augmentation of citalopram with nortryptiline seems to be effective in the management of treatment resistant depression. However, one should strike a balance between the efficacy and the tolerability of this approach, as there is a higher chance of experiencing side effects by the patients.

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Introduction

The lack of efficacy of an antidepressant in treating at least 20% of depressed patients has prompted the investigators to conduct various research projects to explore other strategies of dealing with treatment resistant depression. One of these strategies is adding an adjunctive agent to pre-existing antidepressant. These can include lithium, sleep deprivation, light therapy, ECT, thyroid hormone (T3) and amisulpride (1,2). Some researchers have shown that to treat a major depressive disorder, clinician often requires more than one medication to achieve a remission (3-10). Frequently, a second medication is added to augment the first drug (6-8). There is evidence to prove the effectiveness of lithium or thyroid hormone in augmenting tricyclic antidepressants (11,12). These strategies can also be potentially useful in treating patient resistant to serotonin selective reuptake inhibitors (SSRIs) (13,14).

The efficacy of nortriptyline and citalopram has been compared with each other. The remission rate to a therapeutic plasma level of nortriptyline appears to be higher than the remission rate to a standard dose of citalopram, especially in those with endogenous or psychotic features. On the other hand, citalopram appears to be better tolerated (15). However, there are limited data to assess the effect of combination of them in patients with treatment-resistant depression. Furthermore, the choice of treatment after failure of SSRIs in the treatment of depression largely depends on the preferences of the physician. The STARD (Sequenced Treatment Alternatives to Relieve Depression) trials set out to rationalize the treatment of depression after the failure of citalopram. When subjects who were unresponsive or intolerant to citalopram were switched to sustained-release bupropion (14), sertaline or extended-release venlafaxine, remission rates were similar (16).

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Current study compares the efficacy of nortriptyline with triiodothronine when added to a therapeutic dose of citalopram.

Materials and Methods

Subjects

A total of 48 patients (27 women and 21 men with an age range of 18 to 60) from psychiatric outpatient clinics of two teaching hospitals (Avecina and Ghaem) in Mashhad (Iran) took part in the study in 2005. Seven subjects dropped out of the study due to adverse events (table 1). All patients met DSM-IV criteria for non-psychotic major depression disorder. To enter the study, a patient's thyroid-stimulating hormone (TSH) value had to be within the normal range. Another inclusion criteria was no improvement in depressive symptoms after 8 weeks treatment with 40 mg/day of citalopram.

Table 1. Demographic characteristics of the participants

Characteristics	Both groups N=48	Nortriptyline group N=28	Triiodothyronine group N=20
Age (years ± SD)	39.8±18.2	38.2±18.3	40.18.8±18.4
Education (years ± SD)	9.18±4.4	8.90±5.3	9.55±4.9
Male/female (n)	21/27	12/16	9/11
Employment status (n)			
Employed	34	20	14
Non- employed	12	8	4
Retired	2	0	2
Marital status (n)			
Married	38	21	17
Single	1	1	0
Divorced or separated	8	6	2
Widowed	1	0	1
Age at first episode (mean-years) ±SD	33.43±15.23	34.37±15.15	32.65±11.87
HRDS-17 Scores at study entry (±SD)	16.2±5.40	15.87±9.18	16.43±4.23

Exclusion criteria

Subjects with any other DSM-IV diagnosis requiring psychological or pharmacological treatment were excluded from the study. Alcohol and substance dependence or use within 1 month prior to and use of psychotropic medication within 3 months prior to start of the study were other exclusion criteria. Women of childbearing potential who were without adequate contraception were also excluded from the study.

Informed written consent was obtained from all subjects. The ethics committee of Mashhad University of Medical Sciences (Mashad, Iran) approved the protocol. The trial was performed in accordance with the declaration of Helsinki.

Assessment and intervention

Subjects (who were already on 4o mg of citalopram) were randomized into two groups. One group (N=28) received nortritptyline (150mg/day) and the other triiodothyronine (50µg/day, N=20). The add on medications were initiated at low dose and then titrated up to the final dose over a period of 4 weeks. The dose then remained the same till the end of the study. During the trial, the citalopram dose was kept unchanged at 40 mg/day. Lorazepam up to 4mg/day was permitted on an as required regime (prn) to tackle extreme agitation or insomnia during the first two weeks of the study. Four patients could no continue the trial because they developed side effects to nortriptyline (sedation, drowsiness and gastrointestinal upset). Three patients withdrew from the triiodothyronine group because of a worsening in their symptoms.

All subjects underwent a medical examination and a series of laboratory tests (blood count, fasting blood sugar, liver function tests, kidney function tests, thyroid function test and urine analysis) at base line. Vital signs and side effects to medications were monitored at base line, on weekly interval for the first 4 weeks and then at the end of the trial at 8th week.

A psychiatrist, using structured clinical interview for DSM-IV (SCID), interviewed the patients and their family at baseline and at the final visit. A single psychiatrist performed all ratings to reduce inter-rater error. In addition, patients along with their families completed a questionnaire providing information on demographic characteristics and past medical and drug histories. Depressive symptoms were evaluated by a psychologist using the 17-item Hamilton Rating Scale for Depression (HRSD-17) (17). A remission was defined as a score of 7 or

less on the HRSD-17. The primary outcome measure was baseline versus endpoint change in the HRDS-17 scores. Both the psychiatrist and the psychologist were blind to the treatment groups throughout the study period.

Statistical analysis:

We performed the statistical analysis on all patients including those who had dropped out. A t-test was used for comparisons of depression scores between groups. For all analyses, $p<0.05$ was defined as statistically significant. All statistical analyses were performed using statistical package for social sciences (SPSS) version 11.

Results

Seven patients were dropped out of the study tolerability and adverse events are shown in table 2.

Table 2 . Tolerability and adverse events

	Nortriptyline group N=28	Triiodothyronine group N=20
Worsening of depression	0	3
Sedation and drowsiness	3	0
Gastrointestinal distress	1	0

There were no statistically significant differences between two groups regarding age, gender or educational level. The mean of baseline depression score was similar in both groups (table 1). However, a significant change in total mean scores was observed following treatment in both groups ($p<0.05$) (table 3). The mean change of total depression score was greater in nortriptyline group compared to triiodothyronine group ($p<0.05$).

Table 3 . Treatment outcomes

	Nortriptyline group N=24	Triiodothyronine group N=17
HRDS-17 remission rate at the end of study (%) *	33.33%	17.64%
HRDS-17 Scores at the end of study (±SD) *	7.3±5.70	11.45±4.55

*= P<0.005

Discussion

Our study shows that the remission rate measured by a reduction in HRSD-17 scores was greater in nortriptyline group (33.33%) than triiodothyronine group (17.64%). Other studies shows the addition of triiodothyronine (T3) helps relieve depressive symptoms in non-hypothyroid major depressive disorder patients who failed to respond to an adequate course of standard SSRI antidepressant treatments(18). Hypothalamic-pituitary-thyroid axis (HPT) and L-triiodothyronine (L-T3) uptake into erythrocytes and membrane lipids have a role in the development and treatment of affective disorders. The change in the function of the membrane transporter for L-T3 in RBC in depression is probably connected with alteration of membrane fluidity and/or transporter-lipid interactions (19).

Other studies have shown that the addition of citalopram to nortriptyline led to clinical improvement (20,21). There is enough evidence that the antidepressant effects are mediated by both serotonin (5-HT) and norepinephrine (NE) (22). That is why in some studies, researchers have tried to augment the efficacy of SSRIs by adding an antipsychotic to the preexisting regime (23). Also serotonin-norepinephrine reuptake inhibitors (SNRIs) may be used as an alternative treatment for depressed patients who do not tolerate or respond adequately to treatment with a conventional antidepressant (24). Because the diffusion of NE may be spatially limited by serotonin transporters, the SSRIs, despite their selectivity, might enhance not only serotonergic but also noradrenergic neurotransmission, which might contribute to their antidepressant action (25). Furthermore, other studies show that NE plays an important role in mediating acute behavioral and neuro-chemical actions of many antidepressants, including most SSRIs (26) and use of nortriptyline might augment this process.

Our study has several limitations. Firstly, due to the relatively small sample size, the power of the study is limited. Secondly, there was no placebo control group in the study. In our study seven patients could not complete the trial due to the side effects. In addition, subjects were selected from academic

psychiatric outpatient clinics and may not be representative of community patients. Our study results cannot be generalized to patients with psychotic symptoms. Finally, we could not monitor the blood levels of the drugs due to financial restraints.

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