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Brief report

Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania

Zohreh Amrollahi [a], Farzin Rezaei [b], Bahman Salehi [c], Amir-Hossein Modabbernia [a], Azad Maroufi [b], Gholam-Reza Esfandiari [b], Mehrangiz Naderi [c], Fariba Ghebleh [c], Seyed-Ali Ahmadi-Abhari [a], Majid Sadeghi [a], Mina Tabrizi [d], Shahin Akhondzadeh [a,*]

[a] Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
[b] Qods Hospital, Kurdistan University of Medical Sciences, Sanandaj, Iran
[c] Shaheed Hashemi Senejani Hospital, Arak University of Medical Sciences, Arak, Iran
[d] Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: Considerable amount of biochemical data supports the potential involvement of protein kinase C in the pathophysiology and treatment of bipolar disorder. The aim of this double-blind, placebo-controlled study was to investigate the efficacy and tolerability of tamoxifen as an adjunct to lithium for the treatment of acute mania in hospitalized bipolar patients.

Methods: Eligible participants were 40 inpatients, between the ages of 19 and 49 years with current manic episode. Patients were randomly allocated to lithium (1–1.2 mEq/L) + tamoxifen 80 mg/day (group A) or lithium (1–1.2 mEq/L) + placebo (group B) for a 6-week, double-blind, placebo-controlled study. The principal measure of outcome was the Young Mania Rating Scale. The raters used standardized instructions for Young Mania Rating Scale.

Results: Young Mania Rating Scale scores improved with tamoxifen. The difference between the two protocols was significant as indicated by the effect of the group, the between-subjects factor ($F=5.41$, $df=1$, $p=0.02$). A significant difference was observed on the Positive and Negative Syndrome Scale total score at week 6 in the two groups. The difference between the two groups in the frequency of side effects was not significant except for fatigue that occurred more often in the tamoxifen group.

Limitations: Tamoxifen is an antagonist of estrogen receptor as well.

Conclusion: The results demonstrate that the combination of tamoxifen with lithium was superior to lithium alone for the rapid reduction of manic symptoms. The combined use of tamoxifen with lithium was well tolerated in these acutely manic patients.

1. Introduction

Protein kinase C (PKC) represents a family of enzymes highly enriched in brain, where it plays a major role in regulating both pre- and post-synaptic aspects of neurotransmission (DiazGranados and Zarate, 2008). Abundant evidence has accumulated to show that activation of PKC enhances release of dopamine, a neurotransmitter implicated in the manic syndrome (DiazGranados and Zarate, 2008). A converging body of preclinical data has shown that chronic use of lithium and valproate, at therapeutic concentrations, regulates the PKC signaling cascade (Zarate et al., 2007). This has led to the investigation of the potential

* Corresponding author. Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran 13337, Iran. Tel.: +98 21 55412222; fax: +98 21 55419113.
E-mail address: s.akhond@neda.net (S. Akhondzadeh).

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antimanic efficacy of tamoxifen, which at sufficient doses inhibits PKC (Zarate and Manji, 2009). Tamoxifen clearly crosses the blood–brain barrier, has efficacy in the treatment of malignant gliomas, and is fairly well tolerated even at high doses (up to 200 mg / day) (DiazGranados and Zarate, 2008). Tamoxifen, among the least toxic of anticancer agents, is the most widely used hormonal therapy for breast cancer, and has been approved as a chemopreventive agent in women at high risk for breast cancer (DiazGranados and Zarate, 2008). A small number of trials have suggested possible efficacy of tamoxifen in mania (Bebchuk et al., 2000; Kulkarni et al., 2006; Zarate et al., 2007; Yildiz et al., 2008). The four reported trials were in different designs such as open label, montherapy, add-on therapy or placebo-controlled trial (Bebchuk et al., 2000; Kulkarni et al., 2006; Zarate et al., 2007; Yildiz et al., 2008). Although the results with tamoxifen as an antimanic agent are encouraging, they need to be confirmed in further studies. The aim of this double-blind, placebo-controlled study was to investigate the efficacy and tolerability of tamoxifen as an adjunct to lithium for the treatment of acute mania in hospitalized bipolar patients.

2. Methods

2.1. Trial organization

This was a 6-week, parallel-group, placebo-controlled trial undertaken at three teaching psychiatric hospitals in Iran from March 2010 to May 2010.

3. Participants

Eligible participants were 40 inpatients, between the ages of 19 and 49 years with current manic episode (with or without psychotic features) as diagnosed by means of the Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Version (SCID-P) (American Psychiatric Association, 2000). In addition, a score of at least 20 points on the Young Mania Rating Scale was required representing at least a moderate-to-severe mania (Young et al., 1978). Neurological or other medical impairment; the need for ongoing treatment with other psychoactive medications and/or current substance dependence; mental retardation (IQ<70); history of renal or liver function impairments; history of coagulopathy, deep vein thrombosis, or pulmonary embolus; known sensitivity to tamoxifen; QTC>450 ms at screening, seizure disorder requiring medication; participation in an investigational drug trial within 30 days before the start of the trial; known sensitivity to lithium or tamoxifen; use of depot neuroleptics within one cycle before study entry; laboratory values outside the normal range; and women of childbearing potential who were without adequate contraception were the exclusion criteria. The protocol was approved by the Institutional Review Board of Tehran University of Medical Sciences. The trial was performed in accordance with the Declaration of Helsinki. Written informed consents were obtained before entry into the study. This trial is registered with the Iranian Clinical Trials Registry (IRCT1138901151556N12).

4. Study design

Forty patients were randomly allocated to lithium (1–1.2 mEq/L)+ tamoxifen or lithium (1–1.2 mEq/L) + placebo for a 6-week, double-blind, placebo-controlled study. The starting dose of tamoxifen citrate was 20 mg twice daily (40 mg/day). Thereafter, daily doses were adjusted upward by 10 mg to achieve 80 mg/day in twice-daily divided doses for all subjects. Concomitant lorazepam use was restricted to a maximum dose of 2 mg/day for the first 4 days of treatment and thereafter by up to 1 mg/day for the next 6 days. Lorazepam use was stopped after the initial 10 days and was not dispensed within 8 h of the administration of the mania rating scale. Patients were assessed by psychiatrist at baseline and at 7, 14, 28 and 42 days after start of medical therapy. All psychotropic medications, with the exception of benzodiazepines, were discontinued at least 48 h before randomization.

5. Outcome

The principal measure of the outcome was the Young Mania Rating Scale (YMRS) (Young et al., 1978; Akhondzadeh et al., 1999, 2003, 2006). The mean decrease in Young Mania Rating Scale score from baseline was used as the main outcome measure of response of mania to treatment. The secondary outcome measures were the Hamilton Depression Rating Scale (HAMD-17) and the Positive and Negative Syndrome Scale (PANSS) (Hamilton, 1960; Kay et al., 1987). High inter-rater reliability for the SCID [intraclass correlation coefficient (ICC) = 0.90], YMRS (ICC = 0.90), PANSS (ICC = 0.89) and HAMD-17 (ICC = 0.85) were obtained. Patients were randomized to receive tamoxifen or placebo in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until data analysis.

6. Safety measures

Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on day 3, 7, 14, 21, 28 and 42 (Table 1). Laboratory tests obtained included a complete blood count with differential and liver and renal function tests.

7. Statistical analysis

A two-way repeated measure analysis of variance (time–treatment interaction) was used. The two groups as a between-subjects factor (group) and the four measurements during treatment as the within-subjects factor (time) were considered. This was done for Young Mania Rating Scale scores. In addition, a one-way repeated measure analysis of variance with a two-tailed post hoc Bonferroni mean comparison test was performed on the change of Mania Rating Scale scores from baseline. To compare the score reduction of Young Mania Rating Scale at week 6 with baseline, an unpaired two-sided Student's *t*-test was used. Results are presented as mean ± SD differences and were considered significant with $p \leq 0.05$. To compare the baseline

Table 1
Baseline data.

	Tamoxifen group	Placebo group	*p*
Gender	Male: 8, Female: 12	Male: 7, Female: 13	1.00
Age (Mean ± SD)	30.45 ± 9.68 (year)	30.95 ± 8.66 (year)	0.86
Marital status	Single: 11, married: 6, divorced: 3	Single: 12, married: 7, divorced: 1	1.00
Level of education	Under diploma: 11, diploma: 6, higher diploma: 3	Under diploma: 12, diploma: 7, higher diploma: 1	1.00
Length of illness	9.25 ± 8.68 (year)	8.90 ± 5.333 (year)	0.88
Current episode, days	33.25 ± 18.65	34.12 ± 19.14	0.87
Smoking	10	9	1.00
Current episode	Mania: 5, psychotic: 14, mixed: 1	Mania: 6, psychotic: 13, mixed: 1	1.00
Previous medication use	Lithium: 20, valproate: 10, carbamazepine: 8, olanzapine: 8, risperidone:5, typical antipsychotic: 5	Lithium: 20, valproate: 11, carbamazepine:6, olanzapine: 10, risperidone:7, typical antipsychotic: 6	1.00
Life time alcohol and drug use	13	12	1.00
Previous number of episode	Mania: 6, depressive: 2, mixed: 0	Mania: 7, depressive: 1, mixed: 0	1.00

data and frequency of adverse events between the protocols, Fisher's exact test was performed. Intention-to-treat analysis with last observation carried forward procedure was performed. Fisher's exact test was used to compare the treatment groups on the proportion of responders and remitters at endpoint. Responders demonstrated an at least 50% improvement in YMRS scores from baseline to week 1 and endpoint and remitters had an YMRS score of 7 or less at endpoint (Chengappa et al., 2003).

8. Results

Sixty potential study candidates were initially identified. However, 20 patients did not meet study inclusion criteria. Therefore, 40 bipolar patients were randomized in this study. One patient from the tamoxifen group and two from the placebo group were dropped out of the study, leaving 37 patients who met the DSMIV criteria for mania and currently experiencing a manic episode (Fig. 1). No significant differences were identified between patients randomly assigned to the group A or B condition with regard to basic demographic data (Table 1).

9. Tamoxifen versus placebo: YMRS

The mean ± SD scores of the two groups of patients are shown in Fig. 2. There were no significant differences between the two groups on day 0 (baseline) in the Young Mania Rating Scale ($t = 012$, $df = 38$ and $p = 0.79$). The difference between the two protocols was significant as indicated by the effect of group, the between subjects factor ($F = 5.41$, $df = 1$, $p = 0.02$). The behavior of the two treatments was not similar across time (groups-by-time interaction, Greenhouse–Geisser correction; $F = 4.00$, $df = 2.10$ and $p = 0.02$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the Young Mania Rating Scale ($p < 0.0001$). In both groups, post hoc comparisons showed a significant change compared with baseline from day 7 on the Young Mania Rating Scale. The difference between the two protocols was significant at the endpoint (day 42) ($t = 3.23$, $df = 38$; $p = 0.002$). The changes at the endpoint compared with baseline were −29.80 ± 7.36 (mean ± SD) and −23.05 ± 7.95 for groups A and B, respectively. A significant difference was observed in the change of scores of the Young Mania Rating Scale on day 42 compared to baseline in the two groups ($t = 2.78$, $df = 38$, $p = 0.008$). There was significant difference between the two treatments in terms of percentage of responders at week 1 and endpoint (at least 50% reduction in the Young Mania Rating Scale score) (tamoxifen group 50 %, 10 of 20 and placebo group: 15%, 3 of 20; $p = 0.04$) (tamoxifen group 95%, 19 of 20 and placebo group 70%, 14 of 20; $p = 0.09$). Ninety percent of the patients in the tamoxifen group (18 of 20) and 55% in the placebo group (11 out 20) were remitted after 6 weeks (an YMRS score of 7 or less). The difference was significant ($p = 0.03$).

10. Tamoxifen versus placebo: PANSS and HAMD-17

The mean ± SD scores of the two groups of patients on PANSS and HAMD-17 at week 0 are shown in Table 2. There were no significant differences between the two groups on day 0 (baseline) in the PANSS and HAMD-17 ($t = 0.20$; $df = 38$; $p = 0.84$ and $t = 0.40$; $df = 38$; $p = 0.68$ respectively).

A significant difference was observed on the PANSS total score at week 6 in the two groups ($t = 2.55$; $df = 38$; $p = 0.01$). The difference between the two groups in the HAMD-17 at week 6 was not significant ($t = 0.20$; $df = 38$; $p = 0.84$).

11. Clinical complications and side effects

Fifteen side effects were observed over the trial. The difference between the two groups in the frequency of side effects was not significant except for fatigue that occurred more often in the tamoxifen group (Table 3).

12. Discussion

The present study shows Young Mania Rating Scale scores improvement with tamoxifen over the 6-week double-blind placebo-controlled trial. Clinical characteristics of the patients, such as sex, age, and duration of illness, did not differ between the groups and cannot explain differences in the therapeutic outcome. Therapy with 80 mg/day of tamoxifen was well tolerated, and no clinically important side effects except fatigue were observed. The efficacy of tamoxifen to obtain a greater improvement in patients with mania

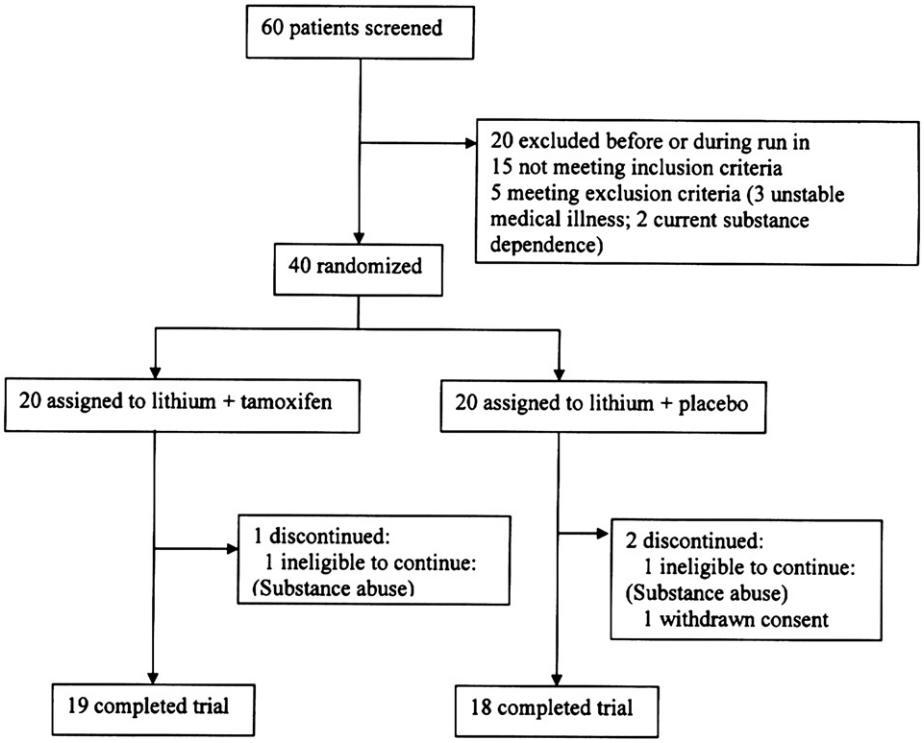

Fig. 1. Trial profile.

seems to support the hypothesis that PKC inhibition has an important role in the treatment of mania. The results of the present study are in line with 4 published trials. Bebchuk et al. (2000) in a single-blind, open-label, add-on (some patients were administered no other medications) study on 7 subjects, reported that tamoxifen may have efficacy in the treatment of acute mania (Bebchuk et al., 2000). The maximal dosage of tamoxifen was 80 mg/day. In a 4-week, three-arm, double-blind, lithium and/or valproate add- on study, in women involving 13 women with a 40 mg fixed dose of tamoxifen compared with medroxyprogesterone or placebo, tamoxifen 40 mg/day was found to have superior anti-manic effects compared to placebo (Kulkarni et al., 2006). In a 3-week, double-blind, placebo-controlled study ($n=16$), tamoxifen (up to 140 mg/day) was superior to placebo in acute mania. Lorazepam (up to 2 mg/day) was permitted for the first 10 days of the blinded phase. Significant improvement was seen as early as day 5 in YMRS scores. No significant improvement was seen in MADRS scores (Zarate et al., 2007).

In a recent 3-week, double-blind, placebo-controlled study ($n=66$), tamoxifen (up to 80 mg/day) was superior to placebo in acute mania. Lorazepam (up to 5 mg/day) was permitted for the entire duration of the study (Yildiz et al., 2008). Significant improvement in YMRS was reported at week 3. However, the present study added tamoxifen to lithium and the follow- up was longer compared to

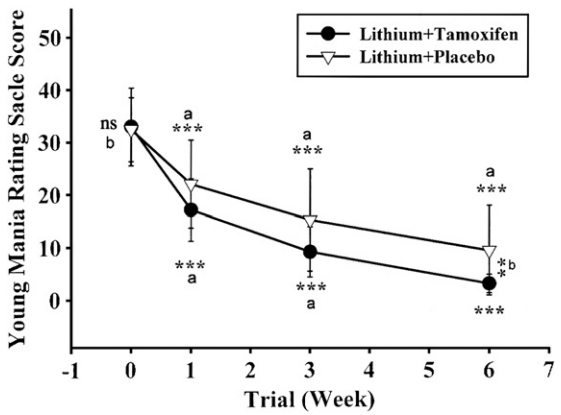

Fig. 2. Mean ± SD of the two protocols on the Young Mania Rating Scale. $^{**}p<0.01$; $^{***}p<0.001$ and ns = nonsignificant. a indicates week versus baseline and b indicates tamoxifen versus placebo.

Table 2
Summary of primary and secondary outcome measurers at baseline and endpoint.

	Week 0	*p*	Week 6	*p*
Young Mania Rating Scale				
Lithium + tamoxifen	32.95 ± 7.41	0.79	3.15 ± 1.78	0.002
Lithium + placebo	32.40 ± 6.07		9.45 ± 8.50	
Positive and Negative Syndrome Scale (total score)				
Lithium + tamoxifen	75.10 ± 18.65	0.84	45.16 ± 11.85	0.01
Lithium + placebo	73.90 ± 19.16		56.32 ± 15.42	
Hamilton Depression Rating Scale-17				
Lithium + tamoxifen	7.15 ± 2.20	0.68	6.18 ± 1.95	0.84
Lithium + placebo	7.45 ± 2.33		6.30 ± 1.80	

Table 3
Number of patients with side effects over the six weeks of trial.

Side effects	Tamoxifen	Placebo	*p*
Day time drossiness	14 (70%)	12 (60%)	0.74
Morning drossiness	13 (65%)	10 (50%)	0.52
Constipation	3 (15%)	6 (30%)	0.45
Dizziness	6 (30%)	5 (25%)	1.00
Restlessness	13 (65%)	10 (50%)	0.52
Stiffness	5 (25%)	5 (25%)	1.00
Slowed movement	5 (25%)	4 (20%)	1.00
Tremor	11 (55%)	12 (60%)	1.00
Increased appetite	8 (40%)	5 (25%)	0.50
Decreased appetite	5 (25%)	4 (20%)	1.00
Nervousness	7 (35%)	7 (35%)	1.00
Blurred vision	5 (25%)	3 (15%)	0.69
Fatigue	8 (40%)	1 (5%)	0.01
Diarrhea	2 (10%)	1 (10%)	1.00
Dry mouth	9 (45%)	6 (30%)	0.51

previously reported studies. The most important findings of this study are that tamoxifen may induce a rapid effect as early as day 7. Based on our hypothesis, attenuating PKC activity not only represents a very important facet in the treatment of manic behavior, but that a direct acting PKC inhibitor would also have rapid effects (Zarate and Manji, 2009). The main limitation of this study is that tamoxifen is an antagonist of estrogen receptor as well (Zarate and Manji, 2009). The results demonstrate that the combination of tamoxifen with lithium was superior to lithium alone for rapid reduction of manic symptoms.

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Conflict of interest statement

We declare no conflict of interest.

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