

# Protein Kinase C Inhibition in the Treatment of Mania

## *A Double-blind, Placebo-Controlled Trial of Tamoxifen*

Ayşegül Yıldız, MD; Sebnem Guleryuz, MD; Donna Pauler Ankerst, PhD;  
Dost Öngür, MD, PhD; Perry F. Renshaw, MD, PhD

**Context:** Findings that protein kinase C (PKC) activity may be altered in mania, and that both lithium carbonate and valproate sodium inhibit PKC-associated signaling in brain tissue, encourage development of PKC inhibitors as candidate antimanic agents.

**Objective:** To perform a controlled test of antimanic efficacy of the centrally active PKC inhibitor tamoxifen citrate.

**Design:** Three-week, randomized, double-blind, placebo-controlled, parallel-arms trial.

**Setting:** A university medical center inpatient psychiatric unit in Izmir, Turkey.

**Patients:** Sixty-six patients aged 18 to 60 years, diagnosed as having *DSM-IV* bipolar I disorder on the basis of the Structured Clinical Interview for *DSM-IV*, currently in a manic or mixed state, with or without psychotic features, with initial scores on the Young Mania Rating Scale (YMRS) greater than 20.

**Intervention:** Treatment with tamoxifen or identical placebo tablets for up to 3 weeks. Adjunctive lorazepam was allowed up to 5 mg/d.

**Main Outcome Measures:** Primary: change in YMRS scores; secondary: change in Clinical Global Impressions–Mania scores, weekly ratings of depression and psychosis, and adjunctive use of lorazepam.

**Results:** The 21-day trial was completed by 29 of 35 subjects randomized to receive tamoxifen (83%) and 21 of 31 given placebo (68%) ( $P = .25$ ). Intent-to-treat analysis of available measures on all 66 subjects indicated that tamoxifen treatment yielded mean decreases in scores on the YMRS and Clinical Global Impressions–Mania of 5.84 and 0.73 point per week, respectively, compared with mean increases of 1.50 and 0.10 point per week, respectively, with placebo; both drug-placebo contrasts differed significantly ( $P < .001$ ).

**Conclusions:** Tamoxifen demonstrated antimanic properties and was remarkably well tolerated. The findings encourage further clarification of the role of PKC in the pathophysiologic mechanism of bipolar I disorder and development of novel anti-PKC agents as potential antimanic or mood-stabilizing agents.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00411203 and isrctn.org Identifier: ISRCTN97160532

*Arch Gen Psychiatry.* 2008;65(3):255-263

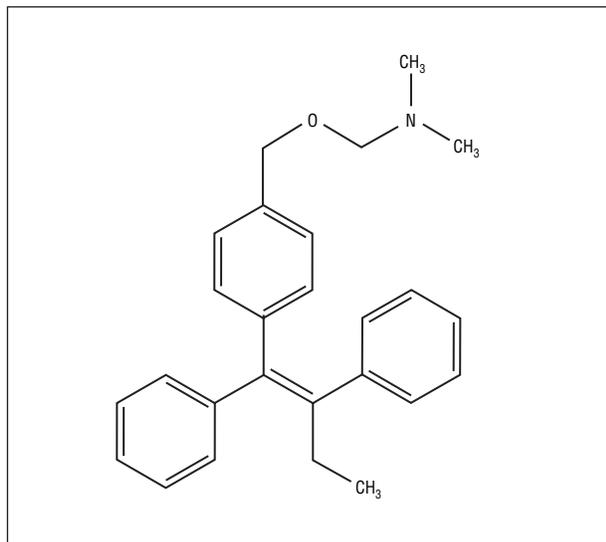
**Author Affiliations:**  
Department of Psychiatry, Dokuz Eylül University Medical School, Izmir, Turkey (Dr Yıldız); Department of Psychiatry, Harvard Medical School, and McLean Hospital, Boston, Massachusetts (Drs Yıldız, Öngür, and Renshaw); Emergency Department, Altın Ordu Hospital, Izmir (Dr Guleryuz); and Institute for Medical Informatics, Biometry, and Epidemiology, Munich, Germany (Dr Ankerst).

**P**ROTEIN KINASE C (PKC) IS A family of enzymes that phosphorylate neurotransmitter receptors, intracellular signaling molecules, transcription factors, and cytoskeletal proteins.<sup>1</sup> Protein kinase C translocates from cytosol to the cell membrane on activation by diacylglycerol or its analogues.<sup>1-3</sup> Several

### *See also page 252*

lines of evidence implicate abnormal PKC activity in bipolar disorder (BPD). Higher basal and stimulation-induced PKC activity has been found in platelets of manic patients than in those of normal control sub-

jects.<sup>4-6</sup> Associated increases in the ratio of platelet PKC membrane to cytosol in response to chemical stimuli were diminished after long-term treatment of patients with BPD with lithium carbonate or divalproex sodium.<sup>4,6</sup> Postmortem studies have found higher basal and stimulation-induced PKC activity in frontal cortex tissue from patients with BPD than in frontal cortex tissue from normal controls.<sup>7,8</sup> Long-term treatment of rats with lithium carbonate or valproate sodium decreased cytoplasm-to-membrane translocation of PKC and reduced PKC stimulation-induced release of serotonin from cerebral cortical and hippocampal tissue.<sup>1,9-11</sup> Psychostimulants, which can trig-



**Figure 1.** Molecular structure of tamoxifen. Molecular weight is 371.5; given as the citrate salt, 563.6.

ger manic episodes in susceptible persons and induce manialike excited behaviors (eg, motor hyperactivity, increased consumption of reward, and increased conditioned place preference) in rodents, activate PKC.<sup>12</sup>

Disruption of PKC function in the nucleus accumbens and ventral tegmental area of forebrain results in blockade of manialike behaviors in animal models, similar to the effects of antimanic and mood-stabilizing drugs including lithium carbonate and divalproex.<sup>3,12,13</sup> Studies in PKC- $\gamma$  knockout mice showed reduced morphine-induced conditioned place preference, and PKC- $\epsilon$  knockout mice demonstrate reduced ethanol self-administration.<sup>12,14</sup> Also, high PKC activity in prefrontal cerebral cortex has been associated with impaired behavioral and electrophysiologic measures of working memory in nonhuman primates.<sup>15</sup> Pretreatment of monkeys and rats with lithium carbonate or valproate and the PKC inhibitor chelerythrine blocked such impairment of working memory.<sup>15</sup> These findings suggest that excessive PKC activation can disrupt prefrontal cortical regulation of behavior, possibly contributing to such dysfunctions as distractibility, impaired judgment, impulsivity, and disorganized thought disorder, all of which are characteristic of patients with BPD, particularly when manic.<sup>15</sup> These preclinical findings strongly suggest that PKC signaling in brain represents a highly plausible target for mood-stabilizing drugs.

Tamoxifen (**Figure 1**) is a selective estrogen receptor modulator, widely used in the prophylactic treatment of breast cancer.<sup>16,17</sup> It is also the only known centrally active PKC inhibitor available for human use.<sup>16,17</sup> In rodents, tamoxifen has significantly reduced amphetamine-induced hyperactivity, normalized amphetamine-induced visits to the center of an open field (risk-taking behavior), and reduced hedonialike amphetamine-induced conditioned place preference.<sup>18</sup> There is also preliminary clinical experience with tamoxifen for the treatment of manic patients. A single-blind, 4- to 15-day, pilot trial of 5 manic men and 2 manic women given tamoxifen citrate (20-80 mg/d), with or without other psycho-

tropic medications, suggested antimanic effects.<sup>16</sup> A small double-blind, controlled trial adding tamoxifen citrate (n=5; 40 mg/d), medroxyprogesterone acetate (n=4), or placebo (n=4) to lithium carbonate or divalproex treatment for 4 weeks in manic women found greater antimanic effects with tamoxifen than with placebo or medroxyprogesterone.<sup>17</sup> Given this background, we now report on results of a randomized, double-blind, placebo-controlled trial adequately powered to test the efficacy of tamoxifen in the treatment of mania.

## METHODS

### SUBJECTS

Patients aged 18 to 60 years, diagnosed as having DSM-IV type I BPD currently in a manic or mixed episode, with or without psychotic features, were admitted to the psychiatric inpatient unit at Dokuz Eylül University Medical Center in Izmir, Turkey, for this single-site trial. Study subjects were recruited between April 7, 2003, and June 28, 2006, from all over Turkey; often, these patients were seeking expert evaluation and treatment for illnesses that had not responded well to previous treatment efforts. Diagnoses were based on the Structured Clinical Interview for DSM-IV,<sup>19</sup> administered by one of us (A.Y.), and on all other clinical information available from medical records and family interviews. After approval of the study protocol by the Turkish Ministry of Health Central Review Board and the Local Ethical Committee of the Dokuz Eylül University Medical Center, the study was reviewed with each potential subject and at least 1 first-degree relative, both of whom gave written informed consent for participation.

Subject screening included medical and psychiatric history, physical examination, and laboratory assays of serum hepatic enzymes, thyrotropin, human chorionic gonadotropin, urea nitrogen, and creatinine, and screening for substance abuse, as well as routine hematologic and chemical studies. In view of ethical, clinical, and safety considerations, a protocol-required drug-free period was limited to 1 day before randomization (benzodiazepines were continued to the day of randomization and converted to equivalent doses of lorazepam, later adjusted clinically), although some patients had been unmedicated for longer times, as indicated later in this article.

Subject inclusion criteria were (1) diagnosis of type I BPD in a current episode of mania or mixed state, all meeting DSM-IV diagnostic criteria; (2) age 18 to 60 years; and (3) Young Mania Rating Scale (YMRS)<sup>20</sup> total score greater than 20 found twice at screening and baseline. Subjects were excluded for (1) being or planning to become pregnant, or breastfeeding; (2) history of coagulopathy, deep vein thrombosis, or pulmonary embolus; (3) known sensitivity to tamoxifen; (4) presence of any substance of abuse at screening, active substance abuse within 2 weeks, or substance dependence within 2 months; (5) DSM-IV diagnosis of schizophrenia, dementia, delirium, seizure disorder, obsessive-compulsive disorder, or *International Statistical Classification of Diseases, 10th Revision* major and clinically unstable cardiac, hepatic, or renal disease; (6) use of any other investigational drug within 30 days; and (7) current clinically significant suicidal or homicidal ideation or plans.

### TREATMENT

Subjects entering the study were randomly assigned 1:1 to receive tamoxifen or identical placebo tablets in double-blind fashion for 3 weeks, with computer-generated codes used to create randomization kits (prepared by ARGEFAR Corp, Izmir, a

contract research organization). The starting dosage of tamoxifen citrate was 20 mg twice daily (40 mg/d). Thereafter, daily doses were adjusted upward by 10 mg to achieve 80 mg/d in twice-daily divided doses for all subjects; similar tablet-count adjustments were applied to placebo dosing, based on pairing of tamoxifen- and placebo-treated subjects by a computer-generated random schedule. Concomitant use of oral lorazepam (2.5-mg rapidly dissolving tablets) was allowed during the study as clinically indicated, up to a protocol-defined maximum of 5 mg (2 tablets) per 24 hours. In addition, use of lorazepam was avoided after the initial 12 days whenever possible and was not given within 12 hours of scheduled mania ratings. Subjects experiencing symptomatic worsening and agitation not controlled by study medications were "rescued" with risperidone but dropped from the protocol, and ratings from their last assessment before the rescue intervention were included for analysis.

## CLINICAL MANAGEMENT

For safety, and owing to the severity of their initial illnesses, all subjects were hospitalized throughout the 3 weeks of the trial and were discharged thereafter only if their Clinical Global Impressions–Bipolar Version Severity of Mania (CGI-Mania)<sup>21</sup> score was 3 or less and they had a 50% or greater reduction in their YMRS scores from baseline. To maximize subject retention and protocol adherence, at least 1 close adult relative remained in the hospital with each patient throughout the trial, and patients were provided individualized food preferences and enriched recreational activities.

## CLINICAL ASSESSMENT

Assessment ratings included the YMRS, CGI-Mania, 17-item Hamilton Depression Rating Scale (HAM-D-17),<sup>22</sup> Montgomery-Åsberg Depression Rating Scale (MADRS),<sup>23</sup> and Positive and Negative Syndrome Scale (PANSS)<sup>24</sup> for psychotic symptoms, as well as an ad hoc adverse effect questionnaire. The rating scales were administered in semistructured interviews each week. All ratings were carried out by 1 of us (A.Y.), who had been certified in the use of each rating scale by the Massachusetts General Hospital Bipolar Disorder Research Program (Boston, Massachusetts), demonstrated high reliability (intraclass correlation coefficient,  $\geq 0.90$ ), and who was held blind to treatment but considered all available clinical information on symptomatic status. The rater attempted to guess treatment assignments at the end of the study while unaware of the assigned treatments. Vital signs were monitored and recorded daily, and weight was monitored weekly.

## POWER CALCULATIONS

*Response* was defined as a 50% or greater reduction in YMRS total score from baseline to 3 weeks. Response was used to estimate required study sample size based on power calculations to achieve 80% power to detect a difference of 40%, assuming 15% and 55% response rates for placebo and tamoxifen, respectively, and a 28% to 30% dropout rate, and using exact power for the Fisher exact test at a 2-tailed  $\alpha$  level of 5%. On the basis of these considerations, randomization kits were prepared for 70 subjects. *Remission* to virtual euthymia was defined as achieving a final YMRS total score of 12 or less at 3 weeks.

## DATA ANALYSIS

We used  $\chi^2$  and 2-sample *t* tests to compare baseline categorical and continuous characteristics between treatment arms, and

the Wilcoxon nonparametric test to compare pretrial medication-free days. Response and remission rates were compared by Pearson  $\chi^2$  with continuity correction at week 3, and at the end point for subjects with 1 or more postbaseline observations. Numbers needed to treat (NNTs) for measures of response and remission, defined as the number of patients required to treat to prevent a single nonresponse (or nonremission), were calculated as the inverse of the placebo minus tamoxifen nonresponse (or nonremission) rates.

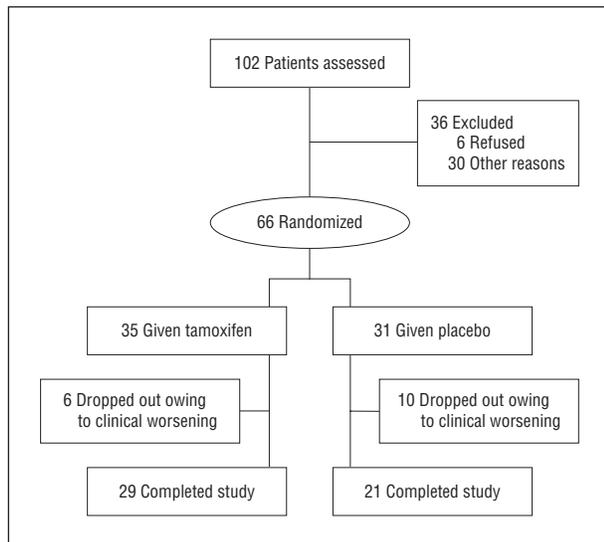
The primary outcome measure was weekly change in YMRS; this measure, as well as weekly change in all other scores (CGI-Mania, PANSS, HAMD-17, and MADRS), were analyzed under the intent-to-treat principle based on normal linear mixed-effect models for longitudinal data fit by maximum likelihood. These models contained 4 fixed parameters and 2 random effects. The fixed parameters included an intercept, a parameter for the effect of week on study (baseline and weeks 1, 2, and 3), treatment arm (tamoxifen vs placebo), and an interaction between treatment arm and week of study. Random intercept and week effects, 1 per subject, were also included, and these were assumed to follow a normal distribution with mean 0 and variance covariance matrix D. Covariates, such as age at randomization, age at onset, and sex, were tested for inclusion in the model, each separately, as either a main effect or an interaction with study week and included in the model when statistically significant ( $P < .05$ ). The linear mixed model analyses, based on all 66 randomized participants and all available data, were valid under a missing-at-random data mechanism, which implies that the probability of dropout at any time point depends only on observed outcome measures up until the time point.<sup>25,26</sup>

Results from the intent-to-treat linear mixed model are presented as average change in ratings per week of study with standard error for each study arm (parameter for the covariate week for the placebo arm vs the sum of the parameters for covariates week and interaction between week and treatment arm for the tamoxifen arm), with *P* values for a test of the null hypothesis of no difference in average change between treatments. Cohen *d* (CD) measure of effect size for the difference between tamoxifen and placebo was defined as the difference in average change per week between placebo and tamoxifen divided by the standard deviation of change per week for an individual patient and was estimated from parameter estimates from the mixed model, with standard deviation estimated from the asymptotic variance-covariance matrix of the parameters from the mixed model. All statistical tests required 2-sided  $P < .05$  for significance.

## RESULTS

### PATIENT CHARACTERISTICS

A total of 66 patients (**Figure 2**), all with normal results of baseline screening medical assessments and laboratory values, were randomized to receive tamoxifen ( $n=35$ ) or placebo ( $n=31$ ); 16 dropped out before completion of the 21-day protocol, for a completion rate of 76% overall (68% [21 of 31] with placebo and 83% [29 of 35] with tamoxifen;  $\chi^2_1=1.31$ ,  $P=.25$ ). Subjects randomized to receive tamoxifen and placebo were well matched at baseline for demographic and clinical characteristics and initial symptom ratings (**Table 1** and **Table 2**). However, tamoxifen-treated subjects were somewhat less likely to have received psychotropic medicines in the month before randomization, with more medication-free days (Table 1).



**Figure 2.** Flow of study subjects with *DSM-IV* mania or mixed states from entry to completion of 3-week randomized, double-blind trial of tamoxifen citrate vs placebo.

### TREATMENT EFFECTS

The intent-to-treat assessments of changes in symptom ratings indicated statistically significant differences between the treatment arms per week of the trial (Table 2, **Figure 3**). Patients randomized to receive tamoxifen experienced an average (SE) decrease of 5.84 (0.64) YMRS points per week, whereas among placebo-treated subjects ratings increased slightly, by 1.50 (0.73), a statistically significant difference ( $t_{157} = -7.59$ ,  $P < .001$ ,  $CD = 1.05$  [0.14]). Moreover, responses with tamoxifen were consistently superior to those with placebo on individual YMRS items (**Table 3**).

Changes in CGI-Mania scores (a principal secondary outcome measure) followed similar patterns, changing by  $-0.73$  (0.09) point per week with tamoxifen vs  $+0.10$  (0.10) with placebo ( $t_{157} = -6.00$ ,  $P < .001$ ,  $CD = 0.77$  [0.13]).

Among other secondary outcome measures, PANSS total scores, which are likely to reflect manic as well as psychotic symptoms, also showed greater improvement with tamoxifen ( $-6.79$  [1.10] points per week) and slight worsening with placebo ( $+3.80$  [1.25]) ( $t_{157} = -6.37$ ,  $P < .001$ ,  $CD = 0.82$  [0.13]). Outcomes for the PANSS positive subscale scores followed similar trends:  $-3.51$  (0.55) points per week with tamoxifen vs  $+1.65$  (0.62) with placebo ( $t_{157} = -6.21$ ,  $P < .001$ ,  $CD = 0.79$  [0.13]), as did PANSS general subscale scores:  $-3.25$  (0.61) with tamoxifen vs  $+2.25$  (0.69) with placebo ( $t_{157} = -5.98$ ,  $P < .001$ ,  $CD = 0.78$  [0.13]), whereas PANSS negative subscale ratings showed low scores and little change with either treatment. Changes in depression ratings also tended to be greater in tamoxifen- than in placebo-treated subjects, based on the HAM-D-17 ( $-0.67$  [0.33] point per week with tamoxifen vs  $-0.14$  [0.37] with placebo, a 4.8-fold difference;  $CD = 0.15$  [0.14]) or MADRS scores ( $-0.81$  [0.35] point per week with tamoxifen vs  $-0.13$  (0.38) with placebo, a 6.2-fold difference;  $CD = 0.20$  [0.15]). However, these differences were not statisti-

**Table 1. Characteristics of Subjects Randomized to Receive Tamoxifen vs Placebo**

Characteristic	Tamoxifen Citrate (n = 35)	Placebo (n = 31)	P Value <sup>a</sup>
Age, median (range), y			
At randomization	29.0 (18-60)	36.0 (18-54)	.54
At onset of illness	21.0 (13-47)	25.0 (16-48)	.06
Previous No. of episodes/subject, median (range) <sup>b</sup>			
Total	4 (1-42)	3 (1-41)	.52
Mania	3 (0-22)	3 (0-36)	.54
Mixed	0 (0-5)	0 (0-6)	.53
Depressive	1 (0-20)	0.5 (0-7)	.06
Sex, No. (%)			.82
Female	18 (51)	16 (52)	
Male	17 (49)	15 (48)	
Current episode, No. (%)			.76
Mania	12 (34)	8 (26)	
Mixed	1 (3)	1 (3)	
Psychotic features	22 (63)	22 (71)	
Education, No. (%)			.93
< High school	6 (17)	6 (19)	
High school or more	29 (83)	25 (81)	
Marital status, No. (%)			.49
Married	16 (46)	10 (32)	
Single	16 (46)	15 (48)	
Divorced	2 (6)	5 (16)	
Widowed	1 (3)	1 (3)	
Psychotropics used in pretrial month, No. (%)			
Lithium carbonate	9 (26)	13 (42)	.16
Valproate sodium	4 (11)	6 (19)	.50
Antidepressant	7 (20)	6 (19)	.95
Modern antipsychotic	14 (40)	13 (42)	.87
Older antipsychotic	10 (29)	14 (45)	.16
Any psychotropic agent	26 (74)	29 (94)	.04
≥ 2 Psychotropics	17 (49)	18 (58)	.44
Pretrial treatment status			
Medication-free days, median (range) <sup>c</sup>	7 (1-600)	3 (1-450)	.01
No mood stabilizer or antipsychotic in pretrial week, No. (%)	18 (51)	10 (32)	.12
No mood stabilizer or antipsychotic in pretrial month, No. (%)	11 (31)	2 (6)	.01

<sup>a</sup>Statistics are based on analysis of variance for continuous variables and contingency tables for categorical measures.

<sup>b</sup>Two patients (1 randomized to receive tamoxifen; 1, to placebo) were excluded because of lack of reliable counts of previous episodes of illness.

<sup>c</sup>One previously untreated patient (tamoxifen arm) was excluded.

cally significant ( $t_{159} = -1.07$ ,  $P = .29$ , and  $t_{157} = -1.33$ ,  $P = .19$ , respectively).

Paralleling improvements in mania, there was much less use of lorazepam among subjects randomized to receive tamoxifen. Daily doses of lorazepam (mean [SD]) averaged 25.2 (16.1) mg per 21 days (1.2 [0.8] mg/d) with tamoxifen vs 41.8 (36.0) mg per 21 days (2.0 [1.7] mg/d) with placebo ( $t_{33} = 2.19$ ,  $P = .04$ ). Moreover, all subjects used less lorazepam as the trial progressed, and the rate of decrease was 2.5 times greater with tamoxifen. Patients in the placebo group decreased their lorazepam use by 1.15 (0.57) tablets per week ( $-2.9$  [1.4] mg/wk); pa-

**Table 2. Summary of Completion Rates and Outcome Measures by Trial Week**

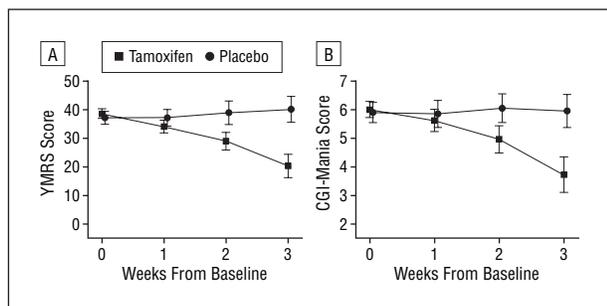
Measure	Baseline	Week 1	Week 2	Week 3
Provided data, No. (%)				
Tamoxifen citrate (n = 35)	35 (100)	32 (91)	29 (83)	29 (83)
Placebo (n = 31)	31 (100)	26 (84)	22 (71)	21 (68)
YMRS				
Tamoxifen				
Mean (SD)	38.6 (5.0)	34.1 (6.2)	29.1 (8.5)	20.3 (11.2)
Range	29.0-49.0	18.0-47.0	13.0-43.0	4.0-43.0
95% CI	36.9-40.3	31.9-36.3	25.8-32.3	16.0-24.6
Placebo				
Mean (SD)	37.2 (6.6)	37.2 (7.5)	38.9 (9.7)	40.1 (10.4)
Range	24.0-49.0	22.0-49.0	16.0-54.0	13.0-51.0
95% CI	34.7-39.6	34.2-40.2	34.6-43.2	35.4-44.8
CGI-Mania				
Tamoxifen				
Mean (SD)	6.0 (0.9)	5.6 (1.1)	5.0 (1.3)	3.7 (1.7)
Range	4.0-7.0	3.0-7.0	2.0-7.0	1.0-7.0
95% CI	5.7-6.3	5.2-6.0	4.5-5.5	3.1-4.4
Placebo				
Mean (SD)	5.9 (1.0)	5.8 (1.2)	6.0 (1.2)	6.0 (1.4)
Range	4.0-7.0	3.0-7.0	3.0-7.0	3.0-7.0
95% CI	5.5-6.3	5.3-6.3	5.5-6.6	5.3-6.6
HAMD-17				
Tamoxifen				
Mean (SD)	7.3 (5.5)	5.8 (4.7)	4.6 (3.4)	5.2 (5.3)
Range	0.0-28.0	0.0-22.0	0.0-13.0	0.0-24.0
95% CI	5.4-9.1	4.0-7.4	3.3-5.9	3.2-7.2
Placebo				
Mean (SD)	6.1 (3.8)	5.0 (3.3)	5.4 (2.4)	5.3 (2.4)
Range	0.0-16.0	0.0-16.0	1.0-10.0	0.0-11.0
95% CI	4.7-7.5	3.6-6.3	4.3-6.5	4.2-6.4
MADRS				
Tamoxifen				
Mean (SD)	7.5 (5.9)	7.1 (4.7)	5.7 (3.3)	5.4 (5.6)
Range	0.0-29.0	0.0-21.0	2.0-15.0	0.0-25.0
95% CI	5.7-9.8	5.4-8.8	4.4-6.9	3.3-7.6
Placebo				
Mean (SD)	6.2 (3.6)	5.4 (3.5)	5.5 (2.6)	5.7 (2.6)
Range	1.0-18.0	1.0-20.0	0.0-11.0	1.0-12.0
95% CI	4.9-7.6	4.0-6.8	4.4-6.7	4.5-6.9
PANSS total				
Tamoxifen				
Mean (SD)	68.2 (13.0)	63.8 (16.0)	54.9 (15.2)	47.8 (13.5)
Range	45.0-99.0	38.0-112.0	33.0-97.0	32.0-75.0
95% CI	63.8-72.7	58.0-69.6	49.1-60.7	42.7-53.0
Placebo				
Mean (SD)	66.5 (14.3)	69.4 (15.2)	72.0 (18.7)	76.9 (21.2)
Range	42.0-100.0	39.0-104.0	41.0-104.0	43.0-114.0
95% CI	61.3-71.8	63.3-75.6	63.7-80.2	67.2-86.5

Abbreviations: CGI-Mania, Clinical Global Impressions–Mania; CI, confidence interval; HAMD-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

tients in the tamoxifen group reduced their lorazepam use by 2.89 (0.49) tablets per week ( $-7.2 [1.2]$  mg/wk) ( $t_{99} = -2.31, P = .02$ ). Use of lorazepam was similar in both groups in the first study week in the tamoxifen and placebo arms (2.3 [1.6] mg/d vs 2.6 [1.8] mg/d;  $t_{56} = 0.78, P = .44$ ), but less with tamoxifen in week 2 (1.2 [0.9] mg/d vs 2.1 [1.8] mg/d;  $t_{28} = 2.15, P = .04$ ), as well as week 3 (0.2 [0.5] mg/d vs 1.9 [2.5] mg/d;  $t_{21} = 3.11, P = .005$ ).

We also performed mixed-model analyses adjusting for baseline mania and depression ratings, age at onset, current age, and sex, and none had a significant effect on the contrast of responses during treatment with tamoxifen vs

placebo. Using a logistic model with randomization to tamoxifen vs placebo as the dependent variable, we also found no effect of relevant covariates descriptive of the subject sample on the randomization process, except age at onset (**Table 4**). We also tested for effects of possibly relevant covariates on treatment response and found randomization to tamoxifen, more weeks in treatment, higher initial mania score, and less use of lorazepam to be statistically significantly associated, with a modest effect of younger current age and a higher initial MADRS score, but no effect of days without psychotropic treatment before the trial or of sex (**Table 5**).



**Figure 3.** Ratings of mania, as defined in the “Methods” section, based on total Young Mania Rating Scale (YMRS) (A) or Clinical Global Impressions–Mania (CGI–Mania) scores (B) (means with 95% confidence intervals) by weeks of treatment with tamoxifen citrate (n=35) vs placebo (n=31).

**Table 3. Average Change per Week in YMRS Item Scores<sup>a</sup>**

YMRS Items (Score Range)	Tamoxifen Citrate (n = 35)	Placebo (n = 31)	P Value
Elevated mood (0-4)	-0.45 (0.06)	-0.06 (0.07)	<.001
Increased motor activity/energy (0-4)	-0.40 (0.07)	0.01 (0.08)	<.001
Sexual interest (0-4)	-0.25 (0.08)	0.10 (0.09)	.004
Sleep (0-4)	-0.45 (0.07)	0.06 (0.08)	<.001
Irritability (0-8)	-0.70 (0.12)	0.21 (0.14)	<.001
Speech (0-8)	-0.79 (0.11)	-0.02 (0.12)	<.001
Language-thought disorder (0-4)	-0.38 (0.06)	0.04 (0.07)	<.001
Content (0-8)	-0.89 (0.12)	0.18 (0.13)	<.001
Disruptive-aggressive behavior (0-8)	-0.67 (0.11)	0.34 (0.13)	<.001
Appearance (0-4)	-0.29 (0.07)	0.24 (0.08)	<.001
Insight (0-4)	-0.57 (0.08)	0.22 (0.09)	<.001

Abbreviation: YMRS, Young Mania Rating Scale.

<sup>a</sup>Data are mean (SE) score changes, based on intent-to-treat linear mixed model described in the “Methods” section.

## RATES OF RESPONSE AND REMISSION

Rates of response (patients with  $\geq 50\%$  reduction in YMRS scores from baseline to trial completion at 3 weeks) were 48% (14 of 29) with tamoxifen vs 5% (1 of 21) with placebo ( $\chi^2=9.01$ ,  $P=.003$ , NNT=2.30). Responder rates at the end point were 44% (14 of 32) with tamoxifen vs 4% (1 of 26) with placebo ( $\chi^2=9.92$ ,  $P=.002$ , NNT=2.51). Moreover, among subjects given no mood-stabilizer treatment during the week before randomization, 46% (12 of 26) responded with tamoxifen vs 5% (1 of 22) with placebo at the end point ( $\chi^2=8.45$ ,  $P=.004$ ). Finally, for subjects free of all psychotropic medicines during the week before randomization, corresponding rates of responders were 61% (11 of 18) with tamoxifen vs 10% (1 of 10) with placebo ( $\chi^2=4.93$ ,  $P=.03$ ).

Rates of clinical remission (YMRS score  $\leq 12$  after completing the 3-week trial) were 28% (8 of 29) with tamoxifen vs none (0 of 21) with placebo ( $\chi^2=5$ ,  $P=.03$ , NNT=3.63). Rates of euthymia at end point were 25% (8 of 32) with tamoxifen vs none (0 of 26) with placebo ( $\chi^2=5.58$ ,  $P=.02$ , NNT=4). No patient achieved remis-

**Table 4. Multivariate Logistic Regression Model of Randomization to Tamoxifen vs Placebo<sup>a</sup>**

Covariate	Odds Ratio (95% CI)	z Score	P Value
Pretrial days without treatment	1.01 (1.00-1.01)	+1.46	.14
Baseline HAMD-17 score	1.11 (0.93-1.32)	+1.17	.24
Previous rapid cycling	0.17 (0.01-4.67)	-1.05	.29
Age at intake	1.03 (0.96-1.10)	+0.87	.39
Current psychotic features	0.60 (0.16-2.26)	-0.76	.45
Previous episodes, y	1.27 (0.64-2.54)	+0.69	.49
Mixed vs manic episode	0.39 (0.01-10.4)	-0.57	.57
Age at onset, y	0.91 (0.84-1.00)	-2.04	.04
Male sex	1.20 (0.40-3.57)	+0.33	.74
Initial YMRS score	1.02 (0.88-1.18)	+0.24	.81
Initial PANSS total score	1.00 (0.94-1.06)	-0.06	.96

Abbreviations: CI, confidence interval; HAMD-17, 17-item Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

<sup>a</sup>Randomization to tamoxifen citrate vs placebo was not appreciably biased by covariates.

**Table 5. Multivariate Regression Model of Response to Experimental Treatments<sup>a</sup>**

Covariate	Coefficient (95% CI)	t	P Value
Randomization to tamoxifen citrate	+9.98 (+4.83 to +15.12)	+3.88	<.001
Weeks of treatment	+6.30 (+3.46 to +9.14)	+4.44	<.001
Higher initial YMRS score	+0.87 (+0.40 to +1.33)	+3.72	<.001
Less lorazepam use, mg/d	-4.83 (-7.02 to -2.64)	+4.42	<.001
Younger age	-0.23 (-0.41 to -0.05)	-2.51	.02
Higher initial MADRS score	+0.46 (+0.01 to +0.92)	+2.04	.05
Pretrial days without treatment	+0.01 (-0.01 to +0.02)	+0.85	.40
Male sex	+0.96 (-3.55 to +5.46)	+0.43	.67

Abbreviations: CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

<sup>a</sup>Treatment response (percentage change per week in total YMRS score from intake to last assessment) was strongly associated with randomization to tamoxifen even with adjustment for stated covariates, as well as with longer treatment exposure, higher initial mania scores, and less need for adjunctive lorazepam; weakly associated with higher initial depression score; and unrelated to days without treatment before randomization and to sex.

sion or even clinical response ( $\geq 50\%$  improvement) before day 21 of the trial.

## ADVERSE EVENTS

Two patients experienced a serious adverse effect during the trial in that one given tamoxifen (at day 18) and another given placebo (at day 13) attempted suicide; neither was in a mixed state or depression, but in both patients, suicidal thinking was closely associated with delusions. Adverse events of minor or moderate severity were noted in similarly low rates in both trial arms: 7 of 35 tamoxifen-treated patients (20%) and 3 of 31 placebo-

treated subjects (10%) ( $\chi^2=1.36$ ,  $P=.24$ ). Their complaints included dermatologic changes and other non-specific somatic symptoms. With tamoxifen these were headache (2 cases), worsening of acne (2), dry skin (1), urticaria (1), flushing (1), and loss of appetite (1); placebo-associated symptoms were eczematous rash, excessive sweating, and headache (1 case each). Body weight was similar at randomization to tamoxifen (mean [SD], 73.4 [18.0] kg) and placebo (69.8 [11.1] kg). Both groups experienced similar, minor weight losses during the trial (tamoxifen,  $0.23\pm 0.11$  kg/wk; placebo,  $0.29\pm 0.12$  kg/wk). Finally, there were no consistent changes in blood pressure, pulse rate, or laboratory values during the trial in either treatment group.

## COMMENT

This is, to our knowledge, the first reported randomized, double-blind, placebo-controlled trial with adequate statistical power to test for antimanic effects of tamoxifen. The study was encouraged by an earlier single-blind pilot trial<sup>16</sup> and a small trial of adding tamoxifen or placebo to standard antimanic treatments.<sup>17</sup> Similar to lithium carbonate and valproate, which also have anti-PKC effects, tamoxifen was effective in men and women in manic or mixed states, with excellent tolerability (Tables 2, 3, 4, and 5; Figure 3).<sup>27</sup> Our findings require replication and encourage further consideration of novel agents with central anti-PKC activity.

The antimanic properties of tamoxifen may be mediated by pharmacodynamic effects related to inhibition of cerebral PKC, as suggested by findings summarized in the introduction to this article. Secondary effects of PKC inhibition include attenuated stimulation of adenylyl cyclase,<sup>28</sup> downregulation of myristoylated alanine-rich C-kinase substrate,<sup>1,29,30</sup> inhibition of glycogen synthase kinase-3 $\beta$ ,<sup>31,32</sup> and regulation of gene expression by activator protein 1.<sup>1,28,33-37</sup> In addition, the antiestrogenic activity of tamoxifen might decrease PKC activity indirectly, whereas estrogens, which increase PKC activity in the brain, may exacerbate mania and increase risk of postpartum episodes of BPD.<sup>38-40</sup>

Response rates ( $\geq 50\%$  improvement of mania ratings, typically within 3-4 weeks) in short-term trials of lithium carbonate and divalproex have been consistently 46% to 52%,<sup>27</sup> similar to the 48% rate observed in this trial of tamoxifen. In previous pilot studies of tamoxifen, response rates in mania were even higher, 71% within 2 weeks<sup>16</sup> and 80% within 4 weeks,<sup>17</sup> as might be expected in less well-controlled circumstances. A recent pilot study with 16 manic patients at the National Institute of Mental Health found changes in YMRS scores that were similar to the present findings ( $-18.3$  [4.29] with tamoxifen and  $+4.67$  [4.08] [slight worsening] with placebo over 3 weeks).<sup>41</sup>

Responses in the placebo arm of the present trial were remarkably poor compared with most other short-term, controlled trials in mania,<sup>42,43</sup> although differences in improvement with drug vs placebo were similar to the present findings.<sup>43-46</sup> Only 5% of our subjects randomized to placebo showed 50% or greater improvement in YMRS

scores, with an overall nonsignificant mean increase in final YMRS scores of 7.8% (Table 2). Unfavorable outcomes with placebo may be attributable in part to 5 "outliers" with major worsening (by 34%-85%) of YMRS scores. These unusual subjects were very ill and had received antipsychotic medications at chlorpromazine-equivalent daily doses of 1390 [SD, 680] mg, sometimes along with lithium carbonate at 1000 mg/d (3 cases) or divalproex sodium at 2000 mg/d (1 case), up to 21 days before randomization. These conditions may well have contributed to their worsening without the protection of an effective antimanic agent and might have contributed to the contrast in responses to tamoxifen vs placebo. However, by comparison, there also were at least 6 similarly previously treated and very ill patients in the tamoxifen arm, but they showed substantial improvements in mania ratings (by 51%-90%).

In previous trials in mania (averaging 3 weeks), involving varied numbers of collaborating sites, response rates in placebo arms have averaged about 23%.<sup>42</sup> However, in other single-site trials in mania, placebo-associated response rates have averaged only 11%,<sup>44,45,47</sup> with slight symptomatic worsening with placebo in both the present and new National Institute of Mental Health single-site trials.<sup>41</sup> Thus, the poor response to placebo may be associated with a hard-to-treat population likely to be found in single-site studies in contrast to large multisite studies. These observations suggest that local differences in subject characteristics or circumstances of treatment can affect outcomes, even in randomized trials. For example, most of our subjects had been referred for study specifically for having been proved difficult to treat by their referring physicians. Their initial YMRS ratings (averaging 38 and as high as 49 of a maximum possible score of 60) were high, as was the prevalence of psychotic features (67%). Particular features of the present trial also may have influenced placebo-associated outcomes. First, we sought to limit potential unreliability of clinical assessments based on relatively infrequent (weekly) self-reports<sup>48</sup> by including daily clinical assessments by investigators and observations by clinical staff and family members remaining with each subject throughout the trial, all of which may have influenced the reported formal weekly assessments. Second, efforts to limit dropouts included an enriched environment, with individualized diets, extra recreational activities, and daily presence of family members, resulting in completion rates of 83% with tamoxifen and 68% with placebo, which are at least as high as in other comparable trials.<sup>46,49-51</sup> However, such environmental enrichment might also have been overstimulating to some, especially unmedicated, subjects, and it is conceivable that blinding was compromised by the unusually detailed, daily knowledge of each subject. However, this potential confound seems unlikely because the blinded rater guessed the assigned treatments at less than chance levels.

It is also likely that pharmacodynamic "carryover" and "discontinuation" effects of recent pretrial treatment influence outcomes in such short-term trials. Such effects would, however, be expected to exert competing lessening or enhancing of responses to either tamoxifen or placebo, with an indeterminate net impact.<sup>27,52,53</sup> For ex-

ample, relatively abrupt discontinuation of previous medication might contribute to low levels of improvement with placebo but might also tend to limit benefits of tamoxifen. Many subjects randomized to receive placebo (68%) or tamoxifen (49%) had recently been exposed to antimanic or antipsychotic treatments (Table 1). However, we found that the number of days without antimanic medication was unrelated to treatment response (Table 5). Most contemporary trials involving acute, major mental illnesses involve relatively brief "wash-out" and treatment-free run-in periods, typically of only several days.<sup>46,49,54-56</sup> Nevertheless, redesign of such trials so as to minimize drug-discontinuation or carryover effects would require slow and prolonged discontinuation of previous treatments and prolonged drug-free periods and raise major clinical and ethical concerns, but they would also lack empirical guidance as to the optimal conditions required.

Finally, it is important to underscore a major limitation of all such short-term trials of innovative treatments for mania: they may demonstrate technical "efficacy" (greater symptomatic improvement than with placebo) but usually are too brief to quantify clinically important rates of syndromal, symptomatic, or functional recovery, which typically evolve over several months.<sup>37</sup> In the present trial, 88% of all subjects remained symptomatic at the end of 3 weeks; even with tamoxifen, the 3-week YMRS score averaged 20.3 (11.2), or 53% of the baseline average of 38.6 (5.0).

In conclusion, tamoxifen demonstrated highly significant antimanic effects similar in magnitude and timing to those reported for lithium carbonate and divalproex, and it was remarkably well tolerated. Given extensive experimental indications of a role of PKC inhibition in the actions of lithium and divalproex, and the central anti-PKC activities of tamoxifen (among other effects), we propose the PKC system as a plausible target for novel mood-stabilizing treatments and for efforts to identify the pathophysiologic mechanism of BPD.

**Submitted for Publication:** January 6, 2007; final revision received September 10, 2007; accepted September 11, 2007.

**Correspondence:** Ayşegül Yildiz, MD, Department of Psychiatry, Dokuz Eylül University, Huzur Mah. Saffet Baba Sok, No. 27/12 PK: 35320 Narlıdere, Izmir, Turkey (agul\_yildiz@hotmail.com).

**Author Contributions:** Dr Yildiz (principal investigator) and Dr Ankerst (study statistician) were responsible for integrity and analysis of reported data.

**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by research grant 02T-162 from the Stanley Medical Research Institute (to Dr Yildiz).

**Role of the Sponsor:** The Stanley Medical Research Institute had no influence on the design, conduct, or analysis of this study.

**Previous Presentation:** Preliminary findings were presented at the 19th Congress of the European College of Neuropsychopharmacology; September 19, 2006; Paris, France; the Fifth European Stanley Conference on Bipolar Disorder; October 6, 2006; Barcelona, Spain; the 62nd

Annual Meeting of the Society of Biological Psychiatry, May 17, 2007; San Diego, California; and the 160th Annual Meeting of American Psychiatric Association; May 21, 2007; San Diego.

**Additional Contributions:** Ross J. Baldessarini, MD, provided invaluable consultation on analysis, interpretation, and presentation of findings. We also received valuable advice from Nese Boztok, PharmD, and Isik Tuglular, MD. Our Turkish psychiatric colleagues, Elif Onur, MD, Atil Mantar, MD, Selcuk Simsek, MD, Mevhibe Tumuklu, MD, Ahmet Ayer, MD, Ayhan Oteyuzoglu, MD, Dogan Isik, MD, Omer Aydemir, MD, Secil Incekas, MD, Sermin Yalin, MD, Neslihan Emir, MD, and Erdem Yaka, MD, provided patient referrals; Hasan A. Yesiloglu, PhD, provided technical support; and Kubra Turgut provided administrative assistance. We thank the Psychiatry Unit nursing staff at Dokuz Eylül University and Hasan Tinzaztepe, Ozgur Taylan Yucel, Sukru Sahin, Yakup Ipek, Mehmet Kuluk, and Serdar Salis for contributions to patient care, and the study participants and their very supportive families.

## REFERENCES

- Manji HK, Lenox RH. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry*. 1999;46(10):1328-1351.
- Quiroz JA, Gould TD, Manji HK. Molecular effects of lithium. *Mol Interv*. 2004;4(5):259-272.
- Zarate CA, Singh J, Manji HK. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry*. 2006;59(11):1006-1020.
- Friedman E, Wang HY, Levinson D, Connell TA, Singh H. Altered platelet protein kinase C activity in bipolar affective disorder, manic episode. *Biol Psychiatry*. 1993;33(7):520-525.
- Wang HY, Markowitz P, Levinson D, Undie AS, Friedman E. Increased membrane associated protein kinase C activity and translocation in blood platelets from bipolar affective disorder patients. *J Psychiatr Res*. 1999;33(2):171-179.
- Hahn CG, Umapathy J, Wang HY, Koneru R, Levinson DF, Friedman E. Lithium and valproic acid treatments reduce PKC activation and receptor-G protein coupling in platelets of bipolar manic patients. *J Psychiatr Res*. 2005;39(4):355-363.
- Wang HY, Friedman E. Enhanced protein kinase C activity and translocation in bipolar affective disorder brains. *Biol Psychiatry*. 1996;40(7):568-575.
- Wang H, Friedman E. Increased association of brain protein kinase C activity with the receptor for activated C kinase-1 (RACK1) in bipolar affective disorder. *Biol Psychiatry*. 2001;50(5):364-370.
- Wang HY, Friedman E. Lithium inhibition of protein kinase C activation-induced serotonin release. *Psychopharmacology (Berl)*. 1989;99(2):213-218.
- Manji HK, Etcheberrigaray R, Chen G, Olds JL. Lithium decreases membrane-associated protein kinase C in hippocampus: selectivity for the alpha isozyme. *J Neurochem*. 1993;61(6):2303-2310.
- Chen G, Manji HK, Hawver DB, Wright CB, Potter WZ. Chronic sodium valproate selectively decreases protein kinase C  $\alpha$  and  $\epsilon$  in vitro. *J Neurochem*. 1994;63(6):2361-2364.
- Einat H, Manji HK. Cellular plasticity cascades: genes to behavior pathways in animal models of bipolar disorder. *Biol Psychiatry*. 2006;59(12):1160-1171.
- Steketee JD. Intra-A10 injection of H7 blocks the development of sensitization to cocaine. *Neuroreport*. 1994;6(1):69-72.
- Narita M, Aoki T, Ozaki S, Yajima Y, Suzuki T. Involvement of protein kinase C $\gamma$  isoform in morphine-induced reinforcing effects. *Neuroscience*. 2001;103(2):309-314.
- Birnbaum SG, Yuan PX, Wang M, Vijayraghavan S, Bloom AK, Davis DJ, Gobeske KT, Sweatt JD, Manji HK, Arnsten AFT. Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. *Science*. 2004;306(5697):882-884.
- Bebchuk JM, Arfken CL, Dolan-Manji S, Murphy J, Hasanat K, Manji HK. A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. *Arch Gen Psychiatry*. 2000;57(1):95-97.
- Kulkarni J, Garland KA, Scaffidi A, Headey B, Anderson R, de Castella A, Fitzger-

- ald P, Davis SR. A pilot study of hormone modulation as a new treatment for mania in women with bipolar affective disorder. *Psychoneuroendocrinology*. 2006; 31(4):543-547.
18. Einat H, Yuan P, Szabo ST, Dogra S, Manji HK. Protein kinase C inhibition by tamoxifen antagonizes manic-like behavior in rats: implications for the development of novel therapeutics for bipolar disorder. *Neuropsychobiology*. 2007; 55(3-4):123-131.
  19. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
  20. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429-435.
  21. Spearing MK, Post R, Leverich G, Brandt D, Nolen W. Modification of the Clinical Global Impressions Scale for use in bipolar illness: the CGI-BP. *Psychiatry Res*. 1997;73(3):159-171.
  22. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278-296.
  23. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.
  24. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.
  25. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.
  26. Little RJA. Modeling the drop-out mechanism in repeated-measures studies. *J Am Stat Assoc*. 1995;90(431):1112-1121.
  27. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. *J Clin Psychiatry*. 1998;59(Suppl 6):13-19.
  28. Chen G, Masana M, Manji HK. Lithium regulates PKC-mediated intracellular cross-talk and gene expression in the CNS in vivo. *Bipolar Disord*. 2000;2(3, pt 2): 217-236.
  29. Lenox RH, Watson DG, Patel J, Ellis J. Chronic lithium administration alters a prominent PKC substrate in rat hippocampus. *Brain Res*. 1992;570(1-2):333-340.
  30. Watson DG, Lenox RH. Chronic lithium-induced down-regulation of MARCKS in immortalized hippocampal cells: potentiation by muscarinic receptor activation. *J Neurochem*. 1996;67(2):767-777.
  31. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A*. 1996;93(16):8455-8459.
  32. Chen G, Huang LD, Jiang YM, Manji HK. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. *J Neurochem*. 1999;72(3): 1327-1330.
  33. Chen G, Yuan PX, Jiang YM, Huang LD, Manji HK. Valproate robustly enhances AP-1 mediated gene expression. *Brain Res Mol Brain Res*. 1999;64(1):52-58.
  34. Jope RS. Anti-bipolar therapy: mechanism of action of lithium. *Mol Psychiatry*. 1999;4(2):117-128.
  35. Yuan P, Chen G, Manji HK. Lithium activates the c-Jun NH<sub>2</sub>-terminal kinases in vitro and in the CNS in vivo. *J Neurochem*. 1999;73(6):2299-2309.
  36. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter [published correction appears in *Lancet*. 2000; 356(9247):2104]. *Lancet*. 2000;356(9237):1241-1242.
  37. Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, Manji HK. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *J Neurochem*. 1999;72(2):879-882.
  38. Payne JL. The role of estrogen in mood disorders in women. *Int Rev Psychiatry*. 2003;15(3):280-290.
  39. Young RC, Moline M, Kleyman F. Hormone replacement therapy and late-life mania. *Am J Geriatr Psychiatry*. 1997;5(2):179-181.
  40. Kumar C, Mclvor RJ, Davies T, Brown N, Papadopoulos A, Wieck A, Checkley SA, Campbell IC, Marks MN. Estrogen administration does not reduce rate of recurrence of affective psychosis after childbirth. *J Clin Psychiatry*. 2003;64(2):112-118.
  41. Zarate CA, Manji HK. Efficacy of a PKC inhibitor (tamoxifen) in the treatment of acute mania: double-blind, placebo-controlled study [abstract]. *Biol Psychiatry*. 2007;61(8)(suppl 1):S7.
  42. Keck PE, Welge JA, McElroy SL, Arnold LM, Strakowski SM. Placebo effect in randomized, controlled studies of acute bipolar mania and depression. *Biol Psychiatry*. 2000;47(8):748-755.
  43. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry*. 2007;64(4):442-455.
  44. Pope HG Jr, McElroy SL, Keck PE Jr, Hudson JI. Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry*. 1991;48(1): 62-68.
  45. Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, Heath J. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry*. 1998; 37(2):171-178.
  46. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania. *Br J Psychiatry*. 2005;187:229-234.
  47. Janicak PG, Sharma RP, Pandey G, Davis JM. Verapamil for the treatment of acute mania: a double-blind, placebo-controlled trial. *Am J Psychiatry*. 1998;155(7):972-973.
  48. Rush AJ, Post RM, Nolen WA, Keck PE, Suppes T, Altshuler L, McElroy SL. Methodological issues in developing new acute treatments for patients with bipolar illness. *Biol Psychiatry*. 2000;48(6):615-624.
  49. Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol*. 2005;15(1):75-84.
  50. Gopal S, Steffens DC, Kramer ML, Olsen MK. Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy. *J Clin Psychiatry*. 2005;66(8):1016-1020.
  51. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol*. 1999;14(6):339-343.
  52. Baldessarini RJ, Suppes T, Tondo L. Lithium withdrawal in bipolar disorder: implications for clinical practice and experimental therapeutics research. *Am J Ther*. 1996;3(7):492-496.
  53. Baldessarini RJ, Tondo L, Faedda GL, Viguera AC, Baethge C, Bratti I, Hennen J. Latency, discontinuation, and re-use of lithium treatment. In: Bauer M, Grof P, Müller-Oerlinghausen B, eds. *Lithium in Neuropsychiatry: The Comprehensive Guide*. London, England: Taylor & Francis; 2006:465-481.
  54. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, Sanger T, Risser R, Zhang F, Toma V, Francis J, Tollefson GD, Breier A; Olanzapine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2000;57(9):841-849.
  55. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, Petty F, Centorrino F, Wang R, Grundy SL, Greaney MG, Jacobs TG, David SR, Toma V; Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry*. 1999;156(5):702-729.
  56. Hirschfeld RM, Keck PE Jr, Kramer M, Karcher K, Canuso C, Eerdekens M, Grossman F. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2004;161(6): 1057-1065.
  57. Chengappa KNR, Hennen J, Baldessarini RJ, Kupfer DJ, Yatham LN, Gershon S, Baker RW, Tohen M. Recovery and functional outcomes following olanzapine treatment for bipolar I mania. *Bipolar Disord*. 2005;7(1):68-76.