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(54) Title: USE OF THE PROTEIN KINASE C INHIBITOR TAMOXIFEN FOR THE TREATMENT OF BIPOLAR DISORDER

(57) Abstract: Bipolar subjects with manic/mixed episode were randomly assigned to receive either tamoxifen (80mg/day) or identical placebo tablets in 1:1 ratio for three weeks. At the end of three weeks of trial tamoxifen treatment has been shown to have strong anti-manic properties. Protein kinase C inhibition seems to be one of the direct targets of lithium and valproate, The existing effective treatments in bipolar disorder/mania. These findings may lead to delineation of the underlying pathophysiology of bipolar disorder and development of novel therapeutics.

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USE OF THE PROTEIN KINASE C INHIBITOR TAMOXIFEN FOR THE TREATMENT OF BIPOLAR DISORDER

5 **FIELD OF INVENTION:**

In this study, Tamoxifen citrate has been compared to placebo for treatment of acute mania. Tamoxifen (Gador® OR Nolvadex®) is widely used for prophylaxis and treatment of breast cancer, and it's mechanism of action has similarities to the mechanism of action of Lithium and Valproate, which are the standard
10 treatments for bipolar disorder/mania. For this reason it has been thought that Tamoxifen may also have an antimanic effect in bipolar patients. In this trial we aimed to investigate the antimanic effects of Tamoxifen in a large sample, which includes 50 bipolar patients. According to the findings of this study, there will be a significant progress in the understanding and treatment of bipolar illness.

15 Among the other treatment alternatives we have lithium and valproate as the most commonly used standard treatments for bipolar disorder. These drugs are known as the mood stabilizers, and they have the greatest success rates in treatment of bipolar illness among the existing treatment strategies. However, a significant amount of bipolar patients either fail to respond the standard
20 treatments with lithium and/or valproate or respond only partially. For this reason, new and better treatment strategies for bipolar disorder need to be developed by the researchers. This study is designed to serve for that purpose and will have a significant contribution on the progress of science for bipolar disorder.

25 **Background of the Invention:**

Bipolar disorder (BD) is a chronic mental illness that affects 1-2% of the adult population^{1,2} and is associated with a substantial risk of suicide among those affected^{1,3}.

Although, the efficacy of lithium and more recently valproate as mood stabilizing
30 agents have generated a large body of clinical and experimental findings in BD, it has become increasingly appreciated that a substantial minority of patients fail to respond, or respond only partially, to these agents.^{4,5} Thus, a critical task

becomes the development of newer therapeutic agents that will have a quicker, more potent, and more specific mode(s) of action with fewer side effects.⁴

While precise mechanisms underlying this disorder that affects millions is yet to be delineated, it has become increasingly clear that elucidation of the signaling pathways affected in BD will greatly facilitate not only the development of novel, improved therapeutics but our understanding of the pathophysiology underlying this intriguing disorder.⁴

It is known that signaling pathways are in a pivotal position in the brain, and they affect the functional balance between multiple neurotransmitter systems. Thus, it is likely that dysregulation of cellular signaling networks in the brain underlies the oscillations observed in mood disorders (such as the disruption of sleep and motor, cognitive and psychological function), and the so-called mood stabilizers work by compensating for this dysregulation in critical regions of the brain.⁶ In keeping with this, recent findings from in vivo proton magnetic resonance spectroscopy studies suggest that while inhibition of inositol monophosphatase (IMPase) may represent an initiating lithium effect, reducing myo-inositol levels per se is not associated with therapeutic response.^{7,8} Accordingly, it is likely that some of the initial actions of lithium may occur with a relative reduction of myo-inositol; this reduction of myo-inositol initiates a cascade of secondary changes in the protein kinase C (PKC) signaling pathway and gene expression in the brain, effects that are ultimately responsible for lithium's mood stabilizing efficacy.^{7,8} Indeed, evidence accumulating from various laboratories has clearly demonstrated that lithium, at therapeutically relevant concentrations, exerts major effects on the PKC signaling cascade.^{4, 9-11} PKC exists as a family of closely related subspecies, has a heterogeneous distribution in brain (with particularly high levels in presynaptic nerve terminals), and plays a major role in the regulation of neuronal excitability, neurotransmitter release, long-term alterations in gene expression and plasticity. Recently, it has been shown that chronic lithium produces isozyme-selective decreases in PKC α , and PKC ϵ . Moreover, it has been found that the structurally highly dissimilar, second mood stabilizer agent- valproate produces effects on the PKC signaling pathway that are strikingly similar to those of lithium's.^{4,11,12} Additionally, it has been

demonstrated that chronic lithium and also valproate dramatically reduce myristoylated alanine-rich C kinase substrate (MARCKS), which is the most prominent substrate for PKC in brain, and implicated in regulating long-term neuroplastic events.^{12,13}

- 5 There exist other direct and indirect evidence supporting a role for PKC in pathophysiology and treatment of bipolar disorder. Friedman and associates (1993), investigated PKC activity and translocation in response to serotonin in platelets obtained from bipolar disorder subjects before and during lithium treatment.¹⁴ They found that the ratios of membrane-bound to cytosolic PKC
10 activities were elevated in platelets obtained from the manic subjects, compared with patients with schizophrenia and healthy controls. In addition, serotonin stimulated platelet PKC translocation was found to be enhanced in manic subjects. Moreover, lithium treatment for up to 2 weeks resulted in reduction in cytosolic and membrane-associated PKC activities and in an attenuated PKC
15 translocation in response to serotonin. Recently, same laboratory found elevated levels of some PKC isozymes in brains obtained at postmortem from bipolar disorder patients compared to controls.^{15,16}

Regulation of the levels of PKC α and ϵ in areas of rat brain by typical and atypical antipsychotics; increments in PKC activity by amphetamine; and
20 blockade of the biochemical and behavioral responses to amphetamine and cocaine by PKC inhibitors are the other findings implicating PKC signaling system in the pathophysiology of BD.^{4,6}

Based upon the above documented evidence suggesting involvement of protein kinase C signaling pathway in BD, Bebchuk JM et al (2000), have postulated that
25 the attenuation of protein kinase C activity might play a major role in the antimanic effects of lithium and valproate and undertook a pilot feasibility study to test the hypothesis that a direct PKC inhibitor would possess antimanic efficacy.¹⁷ In a single blind pilot (only 7 patients; single blind and underpowered) study of a protein kinase C inhibitor-tamoxifen in treatment of acute mania, they
30 reported significant (in some case rapid and striking) improvement of manic symptoms in 5-14 days. The tamoxifen was well tolerated; only one patient has reported any adverse effects attributable to the medication, namely mild flushing

on dose titration.¹⁷

Tamoxifen citrate is the only relatively selective PKC inhibitor available for human use. It is a synthetic nonsteroidal antiestrogen, has been widely used in the treatment of breast cancer.¹⁸ Many of its effects are clearly due to estrogen receptor antagonism¹⁸ but it is also a potent protein kinase C inhibitor¹⁹⁻²¹ that crosses the blood-brain barrier¹⁹. Other than Bebchuk and colleague's study, there have been no previous published studies designed to specifically investigate the potential mood altering effects of tamoxifen, although mild to moderate depression has been described in patients receiving long term tamoxifen for breast cancer.²²

Placebo-controlled, double-blind, randomized clinical trials have been recognized as the standard by which to establish a drug's safety, efficacy, and dose-relationships in most major psychiatric illnesses.²³ The justifications for using placebo control groups in such trials are the fluctuating natural course of most psychiatric illnesses, the wide variability in placebo response across patient groups, and the influence of psychosocial factors on treatment response.^{24,25} There have been four potential alternatives to use of placebo control group proposed in studies of acute mania.^{26,27} These are add-on studies, variable dose designs, establishing a priori threshold effect size with active comparison control, and comparisons with historical controls. However, as recently reviewed by Keck and colleagues (2000), mania is in fact associated with substantial placebo response and placebo-controlled studies are a viable and necessary standard by which to develop new antimanic agents.²³ The authors conclude that randomized, double blind, placebo controlled, parallel group trial in acute bipolar mania remains the "GOLD STANDARD" to determine whether a drug has antimanic properties.²³ After the Helsinki Declaration, in recent years, experts in the field have clearly stated the exceptionality of the psychiatric field in terms of placebo use by emphasizing the necessity of placebo control especially in the clinical trials of mania and depression in an evidence based manner.

Moreover, providing that a drug is efficacious in acute bipolar mania has classically been the first step in determining whether a drug is a mood stabilizer. The optimum duration of acute mania trials is unclear. However, in all the positive

studies to date drug separation from placebo have occurred by day 7 to 21. Thus, there seems little justification for extending a placebo-controlled study in patients with acute mania beyond 21 days.²³ In this study we proposed a 3 week randomized double blind trial of tamoxifen-citrate or identical appearing placebo treatment in acute mania or mixed states in adults with Bipolar I Disorder. By providing data derived from the physiological response of the system (PKC signaling cascade) in affected individuals and addressing the critical dynamic interaction with a pharmacologic agent that may potentially modify the clinical expression of the pathophysiology; this tamoxifen-citrate trial in acute mania will be a promising step in bipolar research.

Recently, our group has detected several factors for which bipolar women seemed to have higher vulnerability than bipolar men. These are;

1. Lifetime history of psychosis was found to be more common in bipolar women⁴¹
2. Bipolar women who were exposed to antidepressant drugs before their first manic/hypomanic episode had higher rates of rapid cycling than the ones who were not, whereas there was no such association in bipolar men⁴²
3. We found a significant association between rapid cycling and early age of onset in bipolar females but not in males. Rapid cycling was more common in women than men⁴³

Given the antiestrogen effect of tamoxifen in the light of the above findings it will be interesting to look for any possible effect of gender in treatment response, since bipolar women may benefit from the antiestrogen effect in addition to the PKC inhibition.

SUMMARY OF THE INVENTION

Method:

Subjects are 50 adults diagnosed with bipolar affective disorder by using DSM-IV criteria, most recent episode manic or mixed, with or without psychotic features. All the diagnosis is based on the Structured Clinical Interview for the DSM-IV, administered by a trained investigator (PI).

A minimum total score of at least 20 on the Young-Mania Rating Scale (Y-MRS)²⁸ are required at the screening visit and on the day of randomization

(baseline).

After the protocol explained to the bipolar patient to be included in the trial and their at least one first degree relative, patient and the relative are asked to give written informed consent for participation in the protocol.

- 5 Subject screening includes medical and psychiatric history, physical examination, and laboratory screen including LFT's, TSH, HCG, BUN, Cr, and serum toxicology. Blood samples are collected from the patients included in the study for the measurements of the PKC activity and PKC translocation in response to serotonin under the influence of tamoxifen at baseline and after the first week of
10 treatment. To evaluate the brain chemistry of the patients, magnetic resonance imaging/spectroscopy are applied to the study patients under the influence of midazolam/fentanyl sedation both in the manic state at baseline and study end point as well as after eutymia has been achieved. All psychotropic medication therapy (except benzodiazepines) are tapered during the screening period and
15 discontinued at least 1 day before randomization.

- Subjects successfully screened who meet inclusion and exclusion criteria are randomly assigned to receive the protein kinase C inhibitor, tamoxifen or identical placebo tablets in a 1:1 ratio and a double blind fashion for 3 weeks. Computer-generated codes are used to create randomized blocks of clinical trial material
20 kits before study startup (randomization blocks are prepared by the ARGEFAR, a contract research organization). Each kit contains all clinical trial material to be used by a patient throughout the 3-week study. The starting dose of tamoxifen is 20 mg bid. After the first day of therapy, daily dose is adjusted upward, by 10 mg increments per day up to 80 mg/d in divided doses. Similar daily dose
25 adjustments are applied for the placebo group. Concomitant use of lorazepam is allowed during double blind therapy as clinically indicated. Lorazepam use is avoided after the initial 12 days after randomization, whenever possible. Subjects are monitored weekly during the 3 week double blind trial. Young Mania Rating Scale (YMRS), Clinical Global Impressions-Bipolar Version of Severity of Illness (CGI-BP)²⁹ mania score, Hamilton Depression Rating Scale (HAM-D)³⁰ and
30 Positive and Negative Syndrome Scale (PANSS)³¹, and side effect questionnaire (SEs) are administered by semi-structured interviews at each week.

Inclusion Criteria:

1. Diagnosis of bipolar affective disorder I, most recent episode, manic or mixed based on the structural clinical interview for DSM-IV
2. Ages 18-65
- 5 3. Young Mania Rating Score > 20 at screening and baseline
4. Providing informed consent

Exclusion Criteria:

1. Currently pregnant, planning to become pregnant, or breast feeding
2. History of any coagulopathies, deep vein thrombosis, pulmonary embolus³²⁻²⁹
- 10 3. A history of hypersensitivity to tamoxifen
4. Drug screen positive for any drug of abuse at screening, active substance abuse in the past 2 weeks or substance dependence in the past 2 months (except nicotine and caffeine)
5. Diagnosis of schizophrenia, dementia, delirium, seizure disorder, obsessive
- 15 compulsive disorder, or major cardiac, hepatic or renal disease that is unstable or that requires constant medical care
6. Administration of any investigational drug in the last 30 days
7. Clinically significant suicidal or homicidal ideation

Outcome Measures:

- 20 Assessment tools include Y-MRS, HAM-D, CGI-BP, and PANSS. Responders are defined as those subjects who demonstrate a 50 % or greater improvement over baseline in the Y-MRS score in the 3 week trial. The principle investigator, who is trained in the rating instruments and blind to treatment, performed all study assessments on a weekly basis by using all available clinical information.
- 25 The primary efficacy variable is defined as the reduction from baseline of the Y-MRS total score after 3 weeks of therapy. Response is defined as at least 50 % improvement from baseline to the endpoint in the Y-MRS total score.
- Following hypotheses are proposed to be tested;
1. There will be greater reduction in ratings of manic or mixed mood symptoms
- 30 with tamoxifen citrate compared to placebo.
2. A greater proportion of subjects will respond to tamoxifen citrate when compared to placebo.

Statistical methods used:

For the five studies demonstrating lithium superior to placebo in treatment of acute mania pooled response rates indicated that 87 out of 124 patients (70 %) experienced at least partial improvement with lithium.⁴⁰ Pooled response rates to valproate from the three double blind, parallel-design trials indicated that 54 % of patients displayed a significant reduction in manic symptoms. Keck et al (2000) reviewed all the acute mania studies to date and reported the mean effect size for drug-treated patients as 0.9-1.1.²³ In the preliminary trial made by Bebchuk et al (2000) response rate to tamoxifen was 71% as defined by at least 50 % reduction in Y-MRS score.¹⁷

Keck et al in the above mentioned work reported the mean percentage of placebo responders in all studies as 23% with an effect size of 0.4. Analysis of variables potentially associated with placebo response found that presence of patients with rapid cycling course in relatively longer duration trials (via confounding effect of spontaneous remissions), and large multi-center trials (via larger variation in inter rater reliability across many study sites) are the factors contributing to high placebo response in acute mania.²³

Since this trial involves a single site with a relatively short study period, we were expecting a lower response rate in the placebo arm. Given that all the study assessments were performed by only one investigator (PI who is trained in the rating instruments), washout period was just 24 hours, and majority of patients were severely psychotic, placebo response rate was expected to be even lower. Based on the above documented response rates in the trials of acute mania we have predicted a 55-70% positive response rate in the tamoxifen arm, defined as at least 50 % reduction in Y-MRS score.

Power analysis has revealed that with 25 patients on placebo and 25 patients on tamoxifen there will be an 80% chance of detecting a significant difference at a two sided .05 significance level if the response rate in placebo group is 0.15 and the response rate of tamoxifen is 0.55.

Total scores from rating scales are derived from the individual items; if any single item is missing, the total score is treated as missing. All statistical evaluations are

made by using SPSS 13.0. Mean baseline scores for each group are compared using the independent samples Student's t test. Lorazepam use in each group is compared on a weekly basis using the independent samples Student's t test. Response rates as defined by $\geq 50\%$ improvement in the Y-MRS scores are compared by using the Chi-Square test. Statistical significance in the change scores of the Y-MRS, HAM-D, CGI-BP, and PANSS within and in between the groups are assessed by using the paired and unpaired samples Student's t test as appropriate. Drug effects are analyzed using repeated measures analysis of variance (ANOVA). Since in this study, most patients could complete the trial, analysis on an 'intent to treat basis' is not required.

Patient population enrolled & baseline characteristics table:

Age:

	Drug	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-Tailed)
Age	Placebo	21	36,90	12,720	2,776	0,529
	Tamoxifen	29	34,55	13,127	2,438	

Gender:

		Drug		Total
		Placebo	Tamoxifen	
Gender	Female	12	15	27
	Male	9	14	23
Total		21	29	50

Education:

		Drug	
		Placebo	Tamoxifen
Education	None	0	1
	Primary School	3	1
	Secondary School	1	2
	High School	9	13
	University 2 years	3	1
	University 4 years	4	11
	Degreeafter university	1	0
Total		21	29

Marriage:

		Drug		Total
		Placebo	Tamoxifen	
Marriage	Married	6	13	19
	Single	10	13	23
	Divorced	4	2	6
	Widowed	1	1	2
Total		21	29	50

5 Current Episode:

		Drug		Total
		Placebo	Tamoxifen	
CurrentEp	Manic Ep	5	11	16
	PsychoticManic Ep	15	17	32
	Mixed Ep	1	1	2
Total		21	29	50

Baseline Disease Severity for the Study Groups:

	Drug	N	Mean	Std. Deviation
YMRSbaseline	Tamoxifen	29	38,38	5,095
	Placebo	21	34,90	6,441
HAM17baseline	Tamoxifen	29	6,66	4,522
	Placebo	21	5,19	3,341
HAM23baseline	Tamoxifen	29	6,69	4,560
	Placebo	21	5,24	3,330
PANSSbaseline	Tamoxifen	29	67,79	13,415
	Placebo	21	64,38	15,526
Positbaseline	Tamoxifen	29	25,48	6,911
	Placebo	21	23,86	7,303
Negatbaseline	Tamoxifen	29	7,14	,743
	Placebo	21	7,33	1,528
Genelbaseline	Tamoxifen	29	35,17	7,354
	Placebo	21	32,62	7,256
CgiManiabaseline	Tamoxifen	29	5,97	,906
	Placebo	21	5,62	1,071
CgiDepbaseline	Tamoxifen	29	1,41	,907
	Placebo	21	1,19	,680
CgiGenbaseline	Tamoxifen	29	5,66	,721
	Placebo	21	5,48	,928
Age	Tamoxifen	29	34,55	13,127
	Placebo	21	36,90	12,720

Results:**Efficacy:**

Among the 67 patients randomized, 50 (74.6%) completed the three weeks of the trial and adhered to protocol. In the tamoxifen group 14 out of 29 (48%) patients achieved a positive response, defined as $\geq 50\%$ improvement in Young Mania Rating Scale-YMRS, compared to only 1 out of 21 (5%) patients in the placebo group ($\chi^2_{df,1}=9.01$, $p=0.003$). The tamoxifen group had a mean 18.07 (standard deviation, $SD=11.21$) decrease ($t=8.681$, $df=28$, $p<0.001$), whereas the placebo group had a mean 5.19 ($SD=9.38$) increase ($t=-2.535$, $df=20$, $p=0.02$) in YMRS at three weeks compared to baseline. ANOVA repeated measures indicated significance for change in YMRS and Clinical Global Impressions-CGI mania with respect to time between tamoxifen and placebo groups ($F=13.584$, $p=0.001$; $F=6.427$, $p=0.015$, respectively).

Response Rate according to the YMRS (≥ 50 improvement over baseline in the YMRS score):

	Drug		Total
	Placebo	Tamoxifen	
ResponseRateYMRS	20	15	35
	1	14	15
Total	21	29	50

Lorazepam use for the study groups:

	Drug	N	Mean	Std.Deviation	Sig. (2-tailed)
Lorazepam 1stweek	Tamoxifen	29	6,069	4,3337	0,270
	Placebo	21	7,595	5,3189	
Lorazepam 2ndweek	Tamoxifen	29	3,414	2,4314	0,046
	Placebo	21	5,976	5,2021	
Lorazepam 3dweek	Tamoxifen	29	,569	1,2154	0,005
	Placebo	21	5,310	6,8983	

Table 1: Baseline and endpoint (end of 3 weeks) Young Mania Rating Scale (YMRS), Positive and Negative Syndrome Scale (PANSS), Positive Syndrome Scale, Clinical Global Impressions (CGI)-Mania, and Hamilton Depression Rating Scale (HAMD) scores of manic patients in tamoxifen and placebo arms.

5 Δ = Change in score.

Assessment tool	Tamoxife n N=29 Scores (Baseline) vs Scores (3 week)	Placebo N=21 Scores (Baseline) vs Scores (3 week)	Statistical Method Used	Statistical Test Value	P value
YMRS	38.38 $\pm$ 5.1 vs 20.31 $\pm$ 11.2	34.90 $\pm$ 6.4 vs 40.1 $\pm$ 10.4	Paired t test for Tamoxifen group Paired t test for Placebo group	t=8.681, df=28 t=-2.535, df=20	p< 0.001 p= 0.02
Δ YMRS	18.07 $\pm$ 11.2	- 5.19 $\pm$ 9.38	Independent samples t test	t=7.74, df= 48	p< 0.001
YMRS (at baseline, week 1, 2, and 3; only baseline & week 3 is given here)	38.38 $\pm$ 5.1 vs 20.31 $\pm$ 11.2	34.90 $\pm$ 6.4 vs 40.1 $\pm$ 10.4	ANOVA Repeated Measures	F= 13.584	p= 0.001
PANSS (at baseline, week 1, 2, and 3; only baseline & week 3 is given here)	67.79 $\pm$ 13.4 vs 47.83 $\pm$ 13.5	64.38 $\pm$ 15.5 vs 76.86 $\pm$ 21.2	ANOVA Repeated Measures	F= 9.628	p= 0.003
Positive Symptom Scale (at baseline, week 1, 2, and 3; only baseline & week 3 is given here)	25.48 $\pm$ 6.9 vs 15.14 $\pm$ 7.0	23.86 $\pm$ 7.3 vs 29.48 $\pm$ 11.1	ANOVA Repeated Measures	F= 9.642	p= 0.003

CGI-Mania(at baseline, week 1, 2, and 3; only base-line & week 3 is given here)	5.97 ± 0.9 vs 3.72 ± 1.7	5.62 ± 1.1 vs 5.95 ± 1.4	ANOVA Repeated Measures	F= 6.427	p= 0.015
HAMD-17(at baseline, week 1, 2, and 3; only base-line & week 3 is given here)	6.66 ± 4.5 vs 5.17 ± 5.4	5.19 ± 3.3 vs 5.33 ± 2.4	ANOVA Repeated Measures	F= 0.051	p= 0.822

What new insights this finding brings to the science:

Existing evidence suggests that two structurally dissimilar antimanic agents, lithium and valproate, attenuate Protein Kinase C-PKC function in a therapeutically relevant time frame, whereas promanic psychostimulants activate PKC. Although best known for its antiestrogenic properties, tamoxifen is also a potent PKC inhibitor at high concentrations. This is the first double-blind placebo-controlled study showing antimanic properties of tamoxifen in bipolar patients. This promising finding by leading to elucidation of the direct targets of lithium and valproate offers the potential not only for development of new target specific antimanic agents but also to delineate the underlying pathophysiology of bipolar disorder.

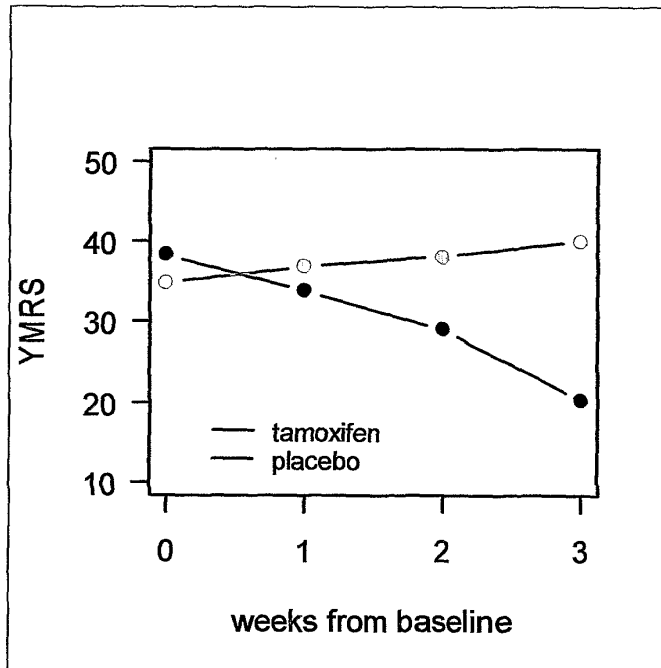
In most instances, an effective agent has first been discovered clinically as in the case with lithium and valproate, and this consequently initiated research into its potential mechanisms of action. Now, this relation became bidirectional, as the PKC inhibitor: tamoxifen, have been tested in acute mania based on the proposed mechanism of action of the existing mood stabilizer drugs. Many pre-clinical studies have priory suggested that PKC signaling is a target of mood stabilizing drugs, however, it has been difficult to establish the clinical relevance of these findings. Now, the present data demonstrating clinical efficacy of a PKC inhibitor-tamoxifen in treatment of bipolar disorder/mania proves that PKC signaling is a target of mood stabilizing drugs and this pathway can be used for development of targeted treatment strategies for bipolar disorder. Eventually,

targeted treatment strategies for patients with bipolar disorder will be possible.

DRAWINGS/FIGURES:

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Figure 1.

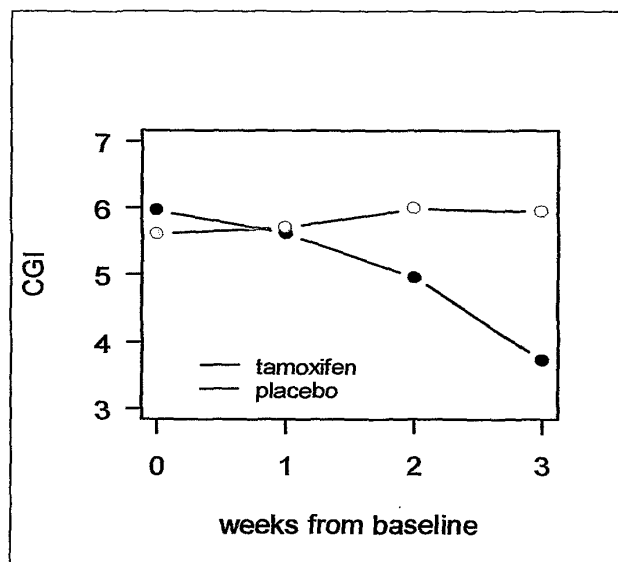


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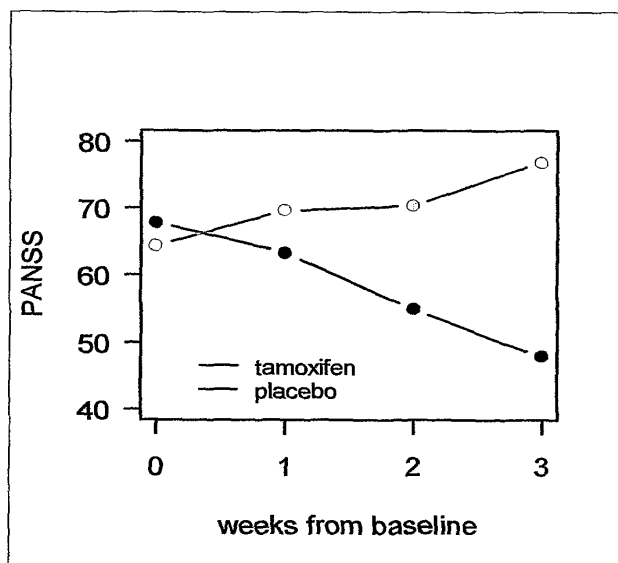
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Figure 2.



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Figure 3.



Brief Description of the Drawings:**Figure 1. Change in YMRS scores in tamoxifen & placebo groups:**

- 5 The primary efficacy variable is defined as the reduction from baseline of the Young Mania Rating Scale (YMRS) total score after 3 weeks of therapy. This figure shows that there is greater reduction the YMRS total score measuring manic or mixed mood symptoms in the tamoxifen citrate group as compared to the placebo group.

10

Figure 2. Change in CGI Mania scores in tamoxifen & placebo groups:

This figure shows that there is greater reduction in the Clinical Global Impressions-Bipolar Version of Severity of Illness (CGI-BP) mania score in the tamoxifen citrate group as compared to the placebo group.

15

Figure 3. Change in PANSS scores in tamoxifen & placebo groups:

This figure shows that there is greater reduction in the Positive and Negative Syndrome Scale (PANSS) score in the tamoxifen citrate group as compared to the placebo group.

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CLAIMS:

1. Any kind of existing pharmacological agent OR its derivatives OR New compounds to be developed for treatment of Bipolar Disorder wherein said
5 compounds work through the Protein Kinase C signaling pathway.

2. Any kind of existing pharmacological agent OR its derivatives OR New compounds to be developed for treatment of Bipolar Disorder wherein said compounds have anti-estrogenic properties.
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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2007/000063

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/138 A61K31/00 A61P25/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BEBCHUK J M ET AL: "A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania." ARCHIVES OF GENERAL PSYCHIATRY JAN 2000, vol. 57, no. 1, January 2000 (2000-01), pages 95-97, XP008084309 ISSN: 0003-990X cited in the application the whole document ----- -/--	1,2
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *Z* document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
8 October 2007		18/10/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Cielen, Elsie

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	MANJI HUSSEINI K ET AL: "Modulation of CNS signal transduction pathways and gene expression by mood-stabilizing agents: Therapeutic implications" JOURNAL OF CLINICAL PSYCHIATRY, vol. 60, no. SUPPL. 2, 1999, pages 27-39, XP008084310 ISSN: 0160-6689 abstract page 32, column 2, paragraph 1	1,2
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X	WO 2005/030143 A (UNIV YALE [US]; ARNSTEN AMY F T [US]; BIRNBAUM SHARI G [US]) 7 April 2005 (2005-04-07) page 1, paragraphs 1,2 page 3, paragraphs 3,5 claims 1,4,10 ----- -/--	1,2

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International application No
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P,X	ZARATE CARLOS A JR ET AL: "Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study." BIPOLAR DISORDERS SEP 2007, vol. 9, no. 6, September 2007 (2007-09), pages 561-570, XP002453973 ISSN: 1398-5647 abstract page 563, column 1, paragraph 2 - column 2, paragraph 3 page 564, column 1, paragraph 3 - column 2, paragraph 2 page 568, column 1, paragraph 3 - column 2, paragraph 2 page 569, column 1, paragraph 3	1,2

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Information on patent family members

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