REVIEW ARTICLE

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The Use of Tamoxifen as a Potential Treatment for Bipolar Disorder

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ABSTRACT

Bipolar disorder (BD) is a chronic mental disease that substantially affects the patient's quality of life and causes significant morbidity and mortality. Although there are a variety of available treatments, therapeutic intervention is not beneficial in many cases and recurrence rates remain high. Recent data suggested tamoxifen, a drug with a wide range of activities, as a potential treatment for reducing manic symptoms of BD. Tamoxifen's therapeutic effect on bipolar mania has not been fully elucidated, but it is believed to biochemically operate on protein kinase C (PKC) inhibition. In this article, we review preclinical and clinical studies investigating the efficacy of tamoxifen as a potential treatment for bipolar manic patients.

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BIPOLAR DISORDER

Bipolar disorder (BD) is a chronic mental disease, characterized by alternating episodes of mania and depression of varying severity, each radical state impairing social and personal functioning.[1] The manic episodes include symptoms such as euphoria, aggressive behavior, and increased motor and sexual activity. Depression episodes are characterized by feelings of worthlessness, suicidal thoughts, altered appetite, and decreased interest in pleasurable activities, among other features.[1] BD affects approximately 1% of the world population and is the sixth leading cause of disability.[2] The substantial morbidity and mortality rates associated with BD are not only a result of the illness itself and its immediate ramifications, but are also due to the rampant comorbidity quotient among this population; they are high risk for a wide range of medical illnesses, especially cardiovascular diseases and metabolic disorders.[3,4] Several hypotheses have been proposed explaining the biological basis of BD; however, a clear pathophysiological mechanism remains elusive.

The pharmacotherapy of BD consists of various medications, including salts of the monovalent cation lithium, antiepileptic drugs (e.g., valproate, carbamazepine, and lamotrigine), and antipsychotics (e.g., chlorpromazine, haloperidol, clozapine, olanzapine, and quetiapine).[1,5-7] Mood-stabilizers and antipsychotic drugs are given during acute episodes of the disease as well as for preventing recurrence of mood symptoms (maintenance therapy). Occasionally, other treatments are added to help stabilize the patient during the acute and the chronic phases of the disease.[1,5-7]

A variety of cellular pathways are affected by mood-modulating drugs,[1,8-10] making it difficult to elucidate which of them is most relevant to their therapeutic efficacy. Given that the mechanism of mood-modulating drugs is poorly understood, the development of better-suited medication is complex.

Although medications such as lithium, valproate, and antipsychotic drugs were proven as effective agents in treating bipolar patients,[1,5,6,11] there are many patients who do not respond to these treatments, some experiencing severe side effects increasing the burden of the disease, and in turn, impelling low-adherence to treatment.[12,13] Many patients suffer high recurrence rates and chronicity of symptoms.[5-7,14] In addition, the effectiveness of most of these medications is minimal in some areas, such as ameliorating cognitive function and suicidal thoughts.[15] Thus, finding adequate and better-tolerated treatments for BD is an urgent need.[16] In recent years, intracellular signaling cascades have been studied extensively, revealing that the protein kinase C (PKC) signaling pathway is an important factor in the pathophysiology and treatment of BD.[17-26] In this review,

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we focus on the non-selective PKC inhibitor tamoxifen as a potential treatment for BD.

PKC

PKC is a family of kinases among the largest superfamilies of several highly conserved proteins regulating a vast range of cellular activities.[27] Proteins from this family are widely distributed throughout the human body. Abnormal activity in PKC signaling may result in severe alterations in physiological functions, leading to diseases such as cancer, Parkinson's disease, Alzheimer's disease, immune and infectious disorders, among others.[28]

Numerous studies have shown that there is an association between alterations in the PKC signaling pathway and the pathophysiology of BD.[29-31] PKC regulates neuronal signaling by affecting excitability, neurotransmitter release, receptor regulation, synaptic remodeling, and gene expression.[32] It was found to be highly expressed in the prefrontal cortex, hippocampus, and amygdala--brain regions that are involved in regulation of emotions and mood.[33]

TAMOXIFEN

Tamoxifen is an effective antitumor agent with low toxicity,[34,35] and as such, it is an extensively used drug in all stages of breast cancer and is also given in cases where women are at high risk for breast cancer.[36] It was first approved by the United States Food and Drug Administration in 1977 for the treatment of women in advanced stages of breast cancer.[37] The antitumor properties of tamoxifen are attributed to its competitive blocking of estrogen receptors.[38] As a result of tamoxifen binding to the estrogen receptor, there is consequent inhibition of estrogen-regulated gene expression; growth factors and angiogenic factors that are normally regulated by estrogen are demonstrably inhibited as well. The result of this cascade is blocking of the cell cycle in the G1 phase and an interruption in cell proliferation rate.[39,40]

In synthesis with its effect on estrogen receptors, tamoxifen appears to have additional cellular causata. For example, at certain concentrations, tamoxifen inhibits PKC.[41] The inhibition of PKC activity is by two independent pathways--allosteric inhibition, and inhibition of the fully stimulated enzyme through binding to its active site instead of ATP.[41] Tamoxifen was also found to be a competitive inhibitor of calmodulin-dependent enzymes such as cAMP phosphodiesterase.[42] The mechanism of this inhibition is not yet clear, and it is not known whether tamoxifen binds to calmodulin itself or to the calmodulin binding site of cAMP phosphodiesterase.[43] Both PKC and calmodulin play critical roles in transmembrane signaling and cell growth regulation.[44,45] The interactions of tamoxifen with PKC and the calmodulin-cAMP phosphodiesterase suggest different pathways of biological processes that are not estrogen receptor-dependent.[46]

METHODS

This is a narrative review. The search strategy was designed by the authors and conducted based on criteria as follows: using the keyword tamoxifen in conjunction with each one of the following words: BD, mania, depression, mental illness, psychiatry, PKC. We searched for published articles in PubMed, Google, and Google Scholar up to December 2020. The search was limited to studies published in English.

ANTI-MANIC EFFECTS OF TAMOXIFEN

Preclinical Studies

There are several animal behavioral models that mimic human mania. Mania-like behavior is achieved by pharmacological (administration of stimulants such as amphetamine), environmental (rodent sleep deprivation, the resident intruder test, and the dominant–submissive behavior paradigms), and genetic interventions.[47] Although these models do not fulfill all validity criteria, they are considered a valuable tool for the screening of new mood-stabilizing compounds.[28] Several studies have shown that treatment with tamoxifen decreased mania-like effects induced by amphetamine in rats, similar to lithium and valproate.[48-50] Tamoxifen-treated rats showed a decrease in PKC activity, which was accompanied by a reduction in amphetamine-induced hyperactivity and risk-taking behavior (a parameter of mania-like behavior in rodents).[48-51] It was found that amphetamine enhanced the activity of PKC, whereas pretreatment with tamoxifen eliminated the effect of amphetamine on PKC and on rats' behavior.[48] Another substrate of PKC that plays an important role in manic-like behavior is myristoylated alanine-rich C kinase substrate (MARCKS).[52] Rats submitted to amphetamine induction and sleep deprivation showed an increase in MARCKS phosphorylation in the frontal cortex, suggestive of an important role of MARCKS in manic-like behavior.[52] Valvassori et al.[53] demonstrated that intracerebroventricular injection of ouabain, a specific inhibitor of the Na^+/K^+-adenosine-triphosphatase, caused an increase in MARCKS phosphorylation in the frontal cortex and hippocampus of rats, inducing manic-like behavior. Tamoxifen reversed the ouabain-induced increase in MARCKS phosphorylation in rats' frontal cortex and the behavioral changes.[53] Subsequent studies showed that despite the positive effects of tamoxifen on ouabain-induced mania-like behavior, it did not reverse the oxidative damage caused by ouabain.[54] These results suggest that the antimanic effects of tamoxifen are not due to inhibition of oxidative stress.

Moreover, the administration of amphetamine is associated with mitochondrial damage and inhibition of creatine kinase.[55-58] Treatment with tamoxifen reversed the mitochondrial damage and inhibition of creatine kinase induced by amphetamine.[49] Interestingly, the mood stabilizers lithium and valproate—which conjointly inhibit PKC[8,22]—also attenuated mitochondrial damage,[59] but did not reverse the inhibition of creatine kinase.[56] It was shown that creatine kinase is involved in the estrogen receptor cascade, indicating that tamoxifen may treat mania via PKC inhibition and via estrogen receptor as well.[60] However, Pereira et al.[61] showed that, in contrast to tamoxifen, other anti-estrogenic drugs (such as medroxyprogesterone and clomiphene) did not reverse amphetamine-induced hyperactivity, either in acute or in chronic administration, suggesting that the antimanic effect of tamoxifen derives mainly from its PKC inhibitory activity rather than its anti-estrogenic effect.

A possible explanation for the link between mitochondrial damage and BD may be the fact that mitochondrial activity is coupled with the tricarboxylic acid (TCA) cycle. Hence, the inactivation of any step in the cycle can impair mitochondrial activity. Valvassori et al.[62] showed that the administration of amphetamine inhibited the TCA cycle enzymes and that tamoxifen treatment reversed this effect of amphetamine. In addition, a negative correlation between amphetamine-induced hyperactivity and the activity of TCA cycle enzymes was observed.

Evaluation of other biochemical targets of lithium, such as glycogen synthase kinase (GSK)-3β, PKC, protein kinase A (PKA), cAMP response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) in the amygdala and in different areas of the anterior limbic brain showed increased PKC and GSK-3β levels and decreased phospho-GSK-3β, PKA, NGF, BDNF, and CREB levels in amphetamine-treated mice.[51] Treatment with lithium and tamoxifen reversed these amphetamine-induced effects, indicating their influence on cellular plasticity cascades in addition to their effect on behavior.[51] Contrastingly, a study evaluating the effects of long-term treatment (28 days) with tamoxifen reported decreased levels of BDNF in the hippocampus of both male and female rats and decreased levels of NGF in the hippocampus of female rats, suggesting that long-term tamoxifen treatment may lead to negative cellular effects and possibly cognitive impairments.[63]

The effect of tamoxifen on mania-like behavior was also examined under the paradoxical sleep deprivation (PSD)-induced hyperactivity model. Tamoxifen and lithium administrated separately and combined reversed PSD-induced hyperactivity.[64] PSD was also found to trigger hippocampal cell proliferation deficits and the effect was reversed by the PKC inhibitors tamoxifen and chelerythrine.[65] Interestingly, depressive-like behavior and reduction of cell proliferation in the hippocampus were seen after chronic administration of tamoxifen in healthy rats.[66]

Furthermore, it was shown that amphetamine induces 50 kHz ultrasonic vocalizations (USV) in rats,[67-69] and that treatment with lithium, tamoxifen, and myricitrin (a PKC inhibitor) reversed amphetamine-induced USV, suggesting that USV may serve as a sensitive marker to model exaggerated euphoric mood.[70] Another possible positive therapeutic effect of tamoxifen in relation to BD treatment was observed in the study by Tinsgov et al.,[71] in which tamoxifen attenuated lithium-induced polyuria in rats. This suggests that tamoxifen might represent a novel therapeutic approach for patients with lithium-induced nephrogenic diabetes insipidus.

Clinical Studies

The results of the included clinical studies are presented in Table 1. The first study conducted on patients with acute mania was carried out in 2000 by Bebchuk et al.[72] It included 5 male and 2 female subjects, aged 18-65 years, diagnosed with BD and bearing no other psychiatric disorders. Treatment with tamoxifen (up to 80 mg daily) showed a significant decrease in manic symptoms rated by the Young Mania Rating Scale (YMRS). Five of 7 patients had more than a 50% decrease in the YMRS score. The Hamilton Depression Rating Scale (HAMD) did not show a consistent change over time. Overall, the treatment was well tolerated; only 1 patient reported flushing during dose titration.[72] The second study, by Kulkarni et al.,[73] included 13 women with acute BD episodes who participated in a comparative 28-day trial. All patients had a baseline treatment that consisted of lithium, valproate, or both. In this trial, tamoxifen (40 mg/day) was added to the standard treatment and compared to a synthetic progesterone medroxyprogesterone acetate (MPA) (20 mg/day), and a placebo. The tamoxifen group showed a significant decrease in mania symptoms in comparison to the placebo group. The MPA group also showed an improvement.[73] In the next study, 16 patients with BD (14 men and 2 women), aged 18-65 years, were divided randomly into 2 groups.[74] One group received tamoxifen (up to 140 mg/day) and the other received a placebo. On day 5, the tamoxifen-treated group started to show a significant improvement from baseline, demonstrating the rapid effect of tamoxifen in comparison to previously shown effects of mood stabilizers. At the end of the trial, 5 of the 8 patients in the tamoxifen group had more than 50% improvement in the YMRS score, while in the placebo group only 1 patient showed a similar improvement. The treatment was overall well tolerated, except for the loss of appetite which was significantly higher in the tamoxifen group.[74] Another study[75] included 66 patients, aged 18-60 years, diagnosed with bipolar 1 disorder and randomly divided into 2 groups: 1 group received tamoxifen (up

Table 1. Clinical Studies on the Efficacy of Tamoxifen in the Treatment of Bipolar Disorder

Study	Disorder	Study Design	Sample Size	Drug	Duration, Weeks	Test	Adverse Effects	Outcome
Ahmad et al.[79] (2016)	Manic or mixed episode	Double-blind, active-controlled trial	84	Endoxifen or valproate	3	YMRS	No reports	The efficcacy of endoxifen was similar to that of valproate
Fallah et al.[81] (2016)	Manic episode Children, adolescents	Double-blind placebo-controlled RCT	44	Tamoxifen+lithium or placebo+lithium	3	YMRS	Dry mouth	Lithium+tamoxifen was superior to lithium+placebo
Kulkarni et al.[78] (2014)	Manic episode or schizoaffective disorder	3-arm, double-blind RCT	51	Tamoxifen/MPA or placebo adjunct to lithium or valproate	4	CARS-M	No reports	Tamoxifen was superior to placebo. The effect occurred significantly faster in the MPA group in comparison to the tamoxifen/control group
Amrollahi et al.[77] (2011)	Manic episode	Double-blind, placebo-controlled RCT	40	Tamoxifen+lithium or placebo+lithium	6	YMRS	Fatigue	Lithium+tamoxifen was superior to lithium+placebo
Yildiz et al.[75] (2008)	Manic or mixed episode	Double-blind RCT	66	Tamoxifen or placebo	3	YMRS	No reports	Tamoxifen was superior to placebo for the treatment of acute mania
Zarate et al.[74] (2007)	Manic or mixed episode	Double-blind RCT	16	Tamoxifen or placebo	3	YMRS, PANSS	Loss of appetite	Tamoxifen was superior to placebo for the treatment of acute mania
Kulkarni et al.[73] (2006)	Manic episode	3-arm, double-blind RCT	13	Tamoxifen/MPA or placebo adjunct to lithium or valproate	4	CARS-M	No reports	Tamoxifen demonstrated antimanic effects superior to placebo
Bebchuk et al.[72] (2000)	Manic episode	Single-blind, open-label, add-on	7	Tamoxifen (monotherapy or add-on)	2	YMRS	Flushing during dose titration	Preliminary results. Tamoxifen may have efficacy for the treatment of acute mania

MPA, synthetic progesterone medroxyprogesterone acetate; YMRS, Young Mania Rating Scale; CARS-M, Clinician-Administered Rating Scale for Mania; PANSS, Positive and Negative Syndrome Scale.

to 80 mg/day) and the other received a placebo. The tamoxifen group showed a decrease in YMRS every week while the placebo group showed an increase. At the end of the trial, 48% of the tamoxifen group had a 50% or more decrease in YMRS score, as compared to 5% in the placebo group.[75] Significant improvements were also seen in the Positive and Negative Syndrome Scale (PANSS). However, no significant improvements were observed in HAMD-17 and Montgomery-Åsberg Depression Rating Scale (MADRS). Overall, the treatment was well tolerated and there were no reports of any serious adverse events.[75] An interesting case report supported the previous findings attesting for the mood-stabilizing effect of tamoxifen.[76] A 44-year-old woman with a diagnosis of a schizoaffective disorder which manifested after the birth of her second child participated in a 28-day trial of tamoxifen (40 mg/day) treatment. The woman stopped taking her usual medications 3 weeks prior to the beginning of the trial. At the beginning of the trial, she had moderate manic symptoms and moderate depressive symptoms. After 1 week, a reduction in her manic symptoms was observed, and by week 4, the reduction was significant. In addition, the patient's depressive symptoms remained stable (did not increase) during the trial.[76]

Amrollahi et al.[77] tested the efficacy of tamoxifen as an adjunctive treatment to lithium.[77] In the study, 40 patients aged 19-49 years with current manic episodes were randomly assigned to 2 groups for a 6-week trial. The first group received lithium+tamoxifen (80 mg/day) and the second group received lithium+placebo. At the end of the trial, the lithium+tamoxifen group showed a significant improvement in their YMRS scores compared to the lithium+placebo group. There was also a significant difference in the percentage of patients who showed a reduction of 50% or more in the YMRS score; this difference was observed as early as week 1 (50% in the lithium+tamoxifen group, 15% in the lithium+placebo group) and at the end of the trial (95% in the lithium+tamoxifen group, 70% in the lithium+placebo group). At week 6, a significant difference was observed in the PANSS, but not in the HAMD-17 score. Side effects did not differ significantly between the groups, except for fatigue that occurred more frequently in the lithium+tamoxifen group.[77] Another study by Kulkarni et al.[78] reported surprising results. In this 28-day trial, 51 women with a diagnosis of schizoaffective disorder or BD were divided randomly to receive tamoxifen (40 mg/day), MPA (20 mg/day), or a placebo. The experimental treatment was given in addition to standard treatment. All groups showed a reduction in symptoms over time, however, this decrease occurred significantly faster in the MPA group in comparison to the tamoxifen and the control group.[78] In 2016, Ahmad et al.[79] performed a double-blind, active-controlled trial to study the efficacy and safety of endoxifen in the treatment of patients with BD I. Endoxifen is an active metabolite of tamoxifen with higher affinity and specificity to estrogen receptors. Moreover, endoxifen has a 4-fold higher potency in inhibiting PKC activity compared with tamoxifen.[80] In the Ahmad et al.[79] trial, 84 patients with mania or mixed state were treated for 21 days with endoxifen (4 or 8 mg/day) or valproate (extended release tablets of 1000 mg/day) in a 2 : 1 ratio, respectively. A significant decrease in YMRS score was observed in the endoxifen group from day 4 of treatment. The effect remained significant throughout 21 days. The efficcacy of endoxifen in mitigating manic symptoms was found similar to that of valproate. Additionally, endoxifen was well tolerated by patients.[80]

The aforementioned studies explored the effects of tamoxifen in adult patients. In this regard, a study was conducted aiming to measure the effect of tamoxifen in children and adolescents as an adjunctive treatment of lithium.[81] Totally 44 patients aged 9-20 years and diagnosed with acute mania were randomly allocated to treatment with lithium+tamoxifen (up to 40 mg/day) or lithium+placebo. A significant decrease in YMRS score was observed in the adjunctive tamoxifen treatment group compared to the placebo treatment group. The significant difference between the groups was observed after the first week and remained until the end of the trial. No side effects were reported, except dry mouth, in the lithium+tamoxifen group.[81] Two meta-analyses of 5 randomized controlled trials that evaluated the efficacy of tamoxifen on manic episodes concluded that tamoxifen as monotherapy or add-on to the standard therapy is efficacious and generally well tolerated.[30,82] However, the total number of participants was relatively low (N = 186) with only short duration of follow-up (3-6 weeks). The authors therefore conclude that more studies are needed in order to establish its long-term efficacy, side effects, and effective doses.[30,82]

DISCUSSION

The results of the studies summarized above support the hypothesis that the PKC inhibitor tamoxifen has an anti-manic effect in BD patients. Overall, tamoxifen was well tolerated and no severe side effects were reported. Mostly, the therapeutic effects of tamoxifen appeared more rapidly than those seen with lithium or valproate. Although the results of the preclinical and clinical studies are promising, there is a need for future randomized, placebo-controlled studies with larger sample sizes to test the efficacy of tamoxifen monotherapy among BD patients. Moreover, since mood disorders require continued pharmacological treatment throughout patients' lives, it is important to examine the long-term effects of tamoxifen on various body systems. For example, it is necessary to examine the effects of tamoxifen on the occurrence of endometrial cancer,[83-87] depressive symptoms,[88-90] cognitive

impairment,[91-94] and increased risk of thromboembolic events.[84,87] For instance, it has been reported that tamoxifen treatment was associated with an increased risk of endometrial cancer.[83-87] A meta-analysis of the breast cancer prevention trials found that tamoxifen therapy increased the risk of endometrial cancer about 2.4-fold when compared with placebo treatment.[84] In addition, endometrial cancers appear sooner in those administered tamoxifen than in non-tamoxifen users.[86] Research literature addressing the association between depression and tamoxifen suggests that this relationship may exist. Tamoxifen has been reported to affect mood, with some patients needing to discontinue tamoxifen treatment secondary to depression.[88-90] In contrast, other studies found no association between tamoxifen and depression.[95-98] The potential effects of tamoxifen on cognition are uncertain.[91-94,99] Few studies have suggested an association between tamoxifen and cognitive problems in women treated for breast cancer.[91-94] Women on long-term tamoxifen treatment reported diminished cognitive functioning.[94] Furthermore, tamoxifen users showed specific impairments in processing speed,[92] verbal memory,[92,93] and executive functioning,[93] compared to healthy post-menopausal women. However, contradicting findings have also been published.[99] Studies evaluating the side effects of tamoxifen in male breast cancer patients reported a higher tendency to experience side effects and as a result, higher discontinuation rates.[100-102] The most common side effects were a decrease in libido, weight gain, and hot flashes, followed by mood alterations, depression, insomnia, and deep venous thrombosis.[100-102] A fifth of the patients terminated tamoxifen treatment in less than 1 year due to these side effects.[100-102] Therefore, further exploration of the effects of tamoxifen is necessary in order to provide a broader understanding of its therapeutic effect and toxicity profile before it can be recommended as a mainstream treatment for BD.

CONCLUSION

Tamoxifen may be a possible therapeutic intervention in manic bipolar patients. Randomized, placebo-controlled, double-blind trials are nessecary to determine the long-term efficacy and safety of tamoxifen as a treatment for manic bipolar patients.

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REFERENCES

1. Belmaker RH. Bipolar disorder. *N Engl J Med*. 2004;351:476-486. [CrossRef]
2. Murray CJ., Lopez A. D . The Global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020 . 1996. Boston: Harvard School of Public Health. https://apps.who.int/iris/handle/10665/41842.
3. Krishnan KRR. Psychiatric and medical comorbidities of bipolar disorder. *Psychosom Med*. 2005;67:1-8. [CrossRef]
4. Kupfer DJ. The increasing medical burden in bipolar disorder. *J Am Med Assoc*. 2005;293:2528-2530. [CrossRef]
5. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet*. 2016;387:1561-1572. [CrossRef]
6. Sachs GS, Dupuy JM, Wittmann CW. The pharmacologic treatment of bipolar disorder. *J Clin Psychiatry*. 2011;72:704-715. [CrossRef]
7. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry*. 2019;24:198-217. [CrossRef]
8. Chen G, Manji HK, Hawver DB, Wright CB, Potter WZ. Chronic sodium valproate selectively decreases protein kinase C α and ε in vitro. *J Neurochem*. 1994 ;63:2361-2364. [CrossRef]
9. Manji HK, Moore GJ, Chen G. Lithium at 50: Have the neuroprotective effects of this unique cation been overlooked? *Biol Psychiatry*. 1999;46:929-940. [CrossRef]
10. Phiel CJ, Zhang F, Huang EY, et al. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem*. 2001;276:36734-36741. [CrossRef]
11. Goodwin FK, Jamison KR. *Manic-Depressive Illness : Bipolar Disorders and Recurrent Depression*. 2nd ed. Oxford University Press; Oxford; 2007:729-785.
12. Gitlin M. Treatment-resistant bipolar disorder. *Mol Psychiatry*. 2006 March;11:227-240. [CrossRef]
13. Nierenberg AA. A critical appraisal of treatments for bipolar disorder. *Prim Care Companion J Clin Psychiatry*. 2010;12:23-29. [CrossRef]
14. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry*. 2005;162:2152-2161. [CrossRef]
15. Alda M, Hajek T, Calkin C, O'Donovan C. Treatment of bipolar disorder: New perspectives. *Ann Med*. 2009;41:186-196. [CrossRef]
16. Machado-Vieira R, Salvadore G, DiazGranados N, et al. New therapeutic targets for mood disorders. *ScientificWorldJournal*. 2010;10:713-726. [CrossRef]
17. Wang HY, Friedman E. Lithium inhibition of protein kinase C activation-induced serotonin release. *Psychopharmacol (Berl)*. 1989;99:213-218. [CrossRef]
18. Giambalvo CT. Protein kinase C and dopamine transport-2. Effects of amphetamine in vitro. *Neuropharmacology*. 1992 ;31:1211-1222. [CrossRef]
19. Giambalvo CT. Protein kinase C and dopamine transport-1. Effects of amphetamine in vivo. *Neuropharmacology*. 1992 ;31:1201-1210. [CrossRef]

20. Friedman E, Hoau-Yan-Wang, Levinson D, Connell TA, Singh H. Altered platelet protein kinase C activity in bipolar affective disorder, manic episode. *Biol Psychiatry*. 1993;33:520-525. [CrossRef]
21. Gnegy ME, Hong P, Ferrell ST. Phosphorylation of neuromodulin in rat striatum after acute and repeated, intermittent amphetamine. *Brain Res Mol Brain Res*. 1993;20:289-298. [CrossRef]
22. Manji HK, Etcheberrigaray R, Chen G, Olds JL. Lithium decreases membrane-associated protein kinase C in hippocampus: selectivity for the α isozyme. *J Neurochem*. 1993 ;61:2303-2310. [CrossRef]
23. Manji HK, Bersudsky Y, Chen G, Belmaker RH, Potter WZ. Modulation of protein kinase C isozymes and substrates by lithium: the role of myo-inositol. *Neuropsychopharmacology*. 1996 ;15:370-381. [CrossRef]
24. Cervo L, Mukherjee S, Bertaglia A, Samanin R. Protein kinases A and C are involved in the mechanisms underlying consolidation of cocaine place conditioning. *Brain Res*. 1997;775:30-36. [CrossRef]
25. Birnbaum SG, Yuan PX, Wang M, et al. Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. *Science*. 2004;306:882-884. [CrossRef]
26. Lenox RH, Watson DG, Patel J, Ellis J. Chronic lithium administration alters a prominent PKC substrate in rat hippocampus. *Brain Res*. 1992;570:333-340. [CrossRef]
27. Kazi JU, Kabir NN, Soh JW. Bioinformatic prediction and analysis of eukaryotic protein kinases in the rat genome. *Gene*. 2008;410:147-153. [CrossRef]
28. Armani F, Andersen ML, Galduróz JCF. Tamoxifen use for the management of mania: a review of current preclinical evidence. *Psychopharmacol (Berl)*. 2014;231:639-649. [CrossRef]
29. Manji HK, Lenox RH. Long-term action of lithium: a role for transcriptional and posttranscriptional factors regulated by protein kinase C. *Synapse*. 1994;16:11-28. [CrossRef]
30. Talaei A, Pourgholami M, Khatibi-Moghadam H, et al. Tamoxifen: a protein kinase C inhibitor to treat mania a systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Psychopharmacol*. 2016;36:272-275. [CrossRef]
31. Zarate CA, Manji HK. Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder. *CNS Drugs*. 2009;23:569-582. [CrossRef]
32. Amadio M, Battaini F, Pascale A. The different facets of protein kinases C: old and new players in neuronal signal transduction pathways. *Pharmacol Res*. Academic Press; Cambridge. 2006;54:317-325. [CrossRef]
33. Naik MU, Benedikz E, Hernandez I, et al. Distribution of protein kinase M? and the complete protein kinase C isoform family in rat brain. *J Comp Neurol*. 2000;426:243-258. [CrossRef]
34. Powles TJ, Hardy JR, Ashley SE, et al. A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer*. 1989; 60:126-131. [CrossRef]
35. Shagufta A. I., Ahmad I. Tamoxifen a pioneering drug: an update on the therapeutic potential of tamoxifen derivatives. *Eur J Med Chem*. 2018 ;143:515-531. [CrossRef]
36. Jordan VC. Tamoxifen: a personal retrospective. *Lancet Oncol*. 2000;1:43-49. [CrossRef]
37. Cohen MH, Hirschfeld S, Flamm Honig SF, et al. Drug approval summaries: arsenic trioxide, tamoxifen citrate, Anastrazole, paclitaxel, bexarotene. *Oncologist*. 2001;6:4-11. [CrossRef]
38. Osborne C, Elledge R, SAW F. Estrogen receptors in breast cancer therapy. *Sci Med*. 1996;3:32-41.
39. Arteaga CL, Osborne CK. Growth factors as mediators of estrogen/antiestrogen action in human breast cancer cells. *Cancer Treat Res*. 1991;53:289-304. [CrossRef]
40. Lippman ME., Dickson RB, eds. Regulatory mechanisms in breast cancer. *Cancer Treat Res*. Kluwer Academic Publishers, Boston. 2012.
41. O'brian CA, Ward NE, Anderson BW. Role of specific interactions between protein kinase C and triphenylethylenes in inhibition of the enzyme. *J Natl Cancer Inst*. 1988;80:1628-1633. [CrossRef]
42. Huai-De S, Mazzei GJ, Vogler WR, kuo JF. Effect of tamoxifen, a nonsteroidal antiestrogen, on phospholipid/calcium-dependent protein kinase and phosphorylation of its endogenous substrate proteins from the rat brain and ovary. *Biochem Pharmacol*. 1985;34:3649-3653. [CrossRef]
43. Lam HYP. Tamoxifen is a calmodulin antagonist in the activation of cAMP phosphodiesterase. *Biochem Biophys Res Commun*. 1984;118:27-32. [CrossRef]
44. O'Brian CA, Liskamp RM, Solomon DH, Weinstein IB. Inhibition of protein kinase C by tamoxifen . *Cancer Res*. 1985;45:2462-2465.
45. Means AR, Tash JS, Chafouleas JG. Physiological implications of the presence, distribution, and regulation of calmodulin in eukaryotic cells. *Physiol Rev*. 1982; 62:1-39. [CrossRef]
46. O'Brian CA, Ioannides CG, Ward NE, Liskamp RM. Inhibition of protein kinase C and calmodulin by the geometric isomers cis- and trans-tamoxifen. *Biopolymers*. 1990 ;29:97-104. [CrossRef]
47. Sharma AN, Fries GR, Galvez JF, et al. Modeling mania in preclinical settings: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016;66:22-34. [CrossRef]
48. 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;55:123-131. [CrossRef]
49. Moretti M, Valvassori SS, Steckert AV, et al. Tamoxifen effects on respiratory chain complexes and creatine kinase activities in an animal model of mania. *Pharmacol Biochem Behav*. 2011 April ;98:304-310. [CrossRef]
50. Steckert AV, Valvassori SS, Mina F, et al. Protein kinase C and oxidative stress in an animal model of mania. *Curr Neurovasc Res*. 2012;9:47-57. [CrossRef]
51. Cechinel-Recco K, Valvassori SS, Varela RB, et al. Lithium and tamoxifen modulate cellular plasticity cascades in

animal model of mania. *J Psychopharmacol*. 2012;26:1594-1604. [CrossRef]
52. Szabo ST, Machado-Vieira R, Yuan P, et al. Glutamate receptors as targets of protein kinase C in the pathophysiology and treatment of animal models of Mania. *Neuropharmacology*. 2009;56:47-55. [CrossRef]
53. Valvassori SS, Dal-Pont GC, Resende WR, et al. Lithium and tamoxifen modulate behavior and protein kinase C activity in the animal model of mania induced by ouabain. *Int J Neuropsychopharmacol*. 2017;20:877-885. [CrossRef]
54. Dal-Pont GC, Resende WR, Bianchini G, et al. Tamoxifen has an anti-manic effect but not protect the brain against oxidative stress in an animal model of mania induced by ouabain. *J Psychiatr Res*. 2019;113:181-189. [CrossRef]
55. Andreazza AC, Shao L, Wang JF, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. *Arch Gen Psychiatry*. 2010;67:360-368. [CrossRef]
56. Streck EL, Amboni G, Scaini G, et al. Brain creatine kinase activity in an animal model of mania. *Life Sci*. 2008;82:424-429. [CrossRef]
57. Clay HB, Sillivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. *Int J Dev Neurosci*. 2011;29:311-324. [CrossRef]
58. Gigante AD, Andreazza AC, Lafer B, et al. Decreased mRNA expression of uncoupling protein 2, a mitochondrial proton transporter, in post-mortem prefrontal cortex from patients with bipolar disorder and schizophrenia. *Neurosci Lett*. 2011;505:47-51. [CrossRef]
59. Valvassori SS, Rezin GT, Ferreira CL, et al. Effects of mood stabilizers on mitochondrial respiratory chain activity in brain of rats treated with d-amphetamine. *J Psychiatr Res*. 2010;44:903-909. [CrossRef]
60. Somjen D, Katzburg S, Sharon O, et al. The effects of estrogen receptors α- and β-specific agonists and antagonists on cell proliferation and energy metabolism in human bone cell line. *J Cell Biochem*. 2011;112:625-632. [CrossRef]
61. Pereira M, Martynhak BJ, Baretta IP, et al. Antimanic-like effect of tamoxifen is not reproduced by acute or chronic administration of medroxyprogesterone or clomiphene. *Neurosci Lett*. 2011;500:95-98. [CrossRef]
62. Valvassori SS, Bavaresco D V., Budni J, et al. Effects of tamoxifen on tricarboxylic acid cycle enzymes in the brain of rats submitted to an animal model of mania induced by amphetamine. *Psychiatry Res*. 2014;215:483-487. [CrossRef]
63. Valvassori SS, Borges CP, Varela RB, et al. The different effects of lithium and tamoxifen on memory formation and the levels of neurotrophic factors in the brain of male and female rats. *Brain Res Bull*. 2017;134:228-235. [CrossRef]
64. Armani F, Andersen ML, Andreatini R, et al. Successful combined therapy with tamoxifen and lithium in a paradoxical sleep deprivation-induced mania model. *CNS Neurosci Ther*. 2012;18:119-125. [CrossRef]
65. Abrial E, Bétourné A, Etiévant A, et al. Protein kinase C inhibition rescues manic-like behaviors and hippocampal cell proliferation deficits in the sleep deprivation model of mania. *Int J Neuropsychopharmacol*. 2014;18:1-11. [CrossRef]
66. Abrial E, Etievant A, Bétry C, et al. Protein kinase C regulates mood-related behaviors and adult hippocampal cell proliferation in rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;43:40-48. [CrossRef]
67. Burgdorf J, Knutson B, Panksepp J, Ikemoto S. Nucleus accumbens amphetamine microinjections unconditionally elicit 50-kHz ultrasonic vocalizations in rats. *Behav Neurosci*. 2001;115:940-944. [CrossRef]
68. Thompson B, Leonard KC, Brudzynski SM. Amphetamine-induced 50 kHz calls from rat nucleus accumbens: a quantitative mapping study and acoustic analysis. *Behav Brain Res*. 2006;168:64-73. [CrossRef]
69. Wright JM, Gourdon JC, Clarke PBS. Identification of multiple call categories within the rich repertoire of adult rat 50-kHz ultrasonic vocalizations: effects of amphetamine and social context. *Psychopharmacol (Berl)*. 2010;211:1-13. [CrossRef]
70. Pereira M, Andreatini R, Schwarting RKW, Brenes JC. Amphetamine-induced appetitive 50-kHz calls in rats: a marker of affect in mania? *Psychopharmacol (Berl)*. 2014;231:2567-2577. [CrossRef]
71. Tingskov SJ, Hu S, Frøkiær J, et al. Tamoxifen attenuates development of lithium-induced nephrogenic diabetes insipidus in rats. *Am J Physiol Ren Physiol*. 2018;314:F1020-F1025. [CrossRef]
72. Bebchuk JM, Arfken CL, Dolan-Manji S, et al. A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. *Arch Gen Psychiatry*. 2000;57:95-97. [CrossRef]
73. Kulkarni J, Garland KA, Scaffidi A, et al. A pilot study of hormone modulation as a new treatment for mania in women with bipolar affective disorder. *Psychoneuroendocrinology*. 2006;31:543-547. [CrossRef]
74. Zarate CA, Singh JB, Carlson PJ, et al. Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disord*. 2007;9:561-570. [CrossRef]
75. Yildiz A, Guleryuz S, Ankerst DP, Öngür D, Renshaw PF. Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. *Arch Gen Psychiatry*. 2008;65:255-263. [CrossRef]
76. Kulkarni J, Gurvich C, Gilbert H, et al. Hormone modulation: a novel therapeutic approach for women with severe mental illness. *Aust N Z J Psychiatry*. 2008;42:83-88. [CrossRef]
77. Amrollahi Z, Rezaei F, Salehi B, et al. Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. *J Affect Disord*. 2011;129:327-331. [CrossRef]
78. Kulkarni J, Berk M, Wang W, et al. A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania. *Psychoneuroendocrinology*. 2014;43:52-61. [CrossRef]
79. Ahmad A, Sheikh S, Shah T, et al. Endoxifen, a new treatment option for mania: a double-blind, active-controlled trial demonstrates the antimanic efficacy of endoxifen. *Clin Transl Sci*. 2016;9:252-259. [CrossRef]

80. Ali SM, Ahmad A, Shahabuddin S, et al. Endoxifen is a new potent inhibitor of PKC: a potential therapeutic agent for bipolar disorder. *Bioorg Med Chem Lett*. 2010;20:2665-2667. [CrossRef]
81. Fallah E, Arman S, Najafi M, Shayegh B. Effect of tamoxifen and lithium on treatment of acute mania symptoms in children and adolescents. *Iran J Child Neurol*. 2016 ;10:16-25.
82. Palacios J, Yildiz A, Young AH, Taylor MJ. Tamoxifen for bipolar disorder: systematic review and meta-analysis. *J Psychopharmacol*. 2019;33:177-184. [CrossRef]
83. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet*. 1994;343:1318-1321. [CrossRef]
84. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet*. 2003;361:296-300. [CrossRef]
85. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. *Gynecol Oncol*. 2004;94:256-266. [CrossRef]
86. Slomovitz BM, Sun CC, Ramirez PT, et al. Does tamoxifen use affect prognosis in breast cancer patients who develop endometrial cancer? *Obstet Gynecol*. 2004;104:255-260. [CrossRef]
87. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. *J Natl Cancer Inst*. 2005;97:1652-1662. [CrossRef]
88. Cathcart CK, Jones SE, Pumroy CS, et al. Clinical recognition and management of depression in node negative breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat*. 1993;27:277-281. [CrossRef]
89. Thompson DS, Spanier CA, Vogel VG. The relationship between tamoxifen, estrogen, and depressive symptoms. *Breast J*. 1999;5:375-382. [CrossRef]
90. Bourque F, Karama S, Looper K, Cohen V. Acute tamoxifen-induced depression and its prevention with venlafaxine. *Psychosomatics*. 2009;50:162-165. [CrossRef]
91. Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat*. 2000;64:165-176. [CrossRef]
92. Jenkins V, Shilling V, Fallowfield L, Howell A, Hutton S. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? a pilot study. *Psycho Oncol*. 2004;13:61-66. [CrossRef]
93. Schilder CM, Seynaeve C, Beex LV, et al. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. *J Clin Oncol*. 2010;28:1294-1300. [CrossRef]
94. Boele FW, Schilder CMT, De Roode ML, Deijen JB, Schagen SB. Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer. *Menopause*. 2015;22:17-25. [CrossRef]
95. Love RR, Cameron L, Connell BL, Leventhal H. Symptoms associated with tamoxifen treatment in postmenopausal women. *Arch Intern Med*. 1991;151:1842-1847.
96. Day R, Ganz PA, Costantino JP. Tamoxifen and depression: more evidence from the national surgical adjuvant breast and bowel project's breast cancer prevention (p-1) randomized study. *J Natl Cancer Inst*. 2001;93:1615-1623. [CrossRef]
97. Fallowfield L, Fleissig A, Edwards R, et al. Tamoxifen for the prevention of breast cancer: psychosocial impact on women participating in two randomized controlled trials. *J Clin Oncol*. 2001;19:1885-1892. [CrossRef]
98. Lee KC, Ray GT, Hunkeler EM, Finley PR. Tamoxifen treatment and new-onset depression in breast cancer patients. *Psychosomatics*. 2007;48:205-210. [CrossRef]
99. Cella D, Land SR, Chang CH, et al. Symptom measurement in the Breast Cancer Prevention Trial (BCPT) (P-1): psychometric properties of a new measure of symptoms for midlife women. *Breast Cancer Res Treat*. 2008;109:515-526. [CrossRef]
100. Anelli TF, Anelli A, Tran KN, Lebwohl DE, Borgen PI. Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. *Cancer*. 1994;74:74-77. [CrossRef]
101. Visram H, Kanji F, Dent SF. Endocrine therapy for male breast cancer: rates of toxicity and adherence. *Curr Oncol*. 2010;17:17-21. [CrossRef]
102. Pemmaraju N, Munsell MF, Hortobagyi GN, Giordano SH. Retrospective review of male breast cancer patients: analysis of tamoxifen-related side-effects. *Ann Oncol*. 2012;23:1471-1474. [CrossRef]