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Possible Effects of Protein Kinase C (PKC) Inhibition in Breast Cancer Patients Taking Tamoxifen: A Comprehensive Literature Analysis

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ABSTRACT

Tamoxifen is widely used to treat estrogen-dependent breast cancer while also blocking Protein Kinase C (PKC) in the brain. Understanding the potential psychological effects of tamoxifen's PKC inhibition in the brain is essential for improving breast cancer patients' long-term quality of life. This research paper addresses the question: What are the potential neurological and psychological effects that PKC inhibition may have on breast cancer patients taking tamoxifen? To answer this, I conducted a literature analysis by analyzing articles describing the effects of PKC inhibition on different psychological symptoms and disorders and grouped those symptoms and disorders into six different categories: bipolar disorder symptoms, borderline personality disorder symptoms, substance abuse, memory disorder symptoms, schizophrenia symptoms, and hyperalgesia. Through this literature analysis, I was able to explore the identified effects of PKC inhibition in relation to what is currently known about tamoxifen and breast cancer patients. Building on this analysis, the significance of this research demonstrates the fact that understanding how tamoxifen's inhibition of PKC affects psychological variables can help develop safer treatments that protect both the physical and mental well-being of breast cancer patients.

INTRODUCTION

With breast cancer accounting for about 15.5% of all new cancer diagnoses in women, it stands as one of the most common cancers in women in the United States (National Cancer Institute, n.d.). There have been many treatments regarding this illness, but a major focus has been on blocking or counteracting the estrogen that fuels the growth of these tumors. Based on the role of estrogen in promoting breast cancer growth, researchers have experimented with the hormonal treatment tamoxifen, an antiestrogen drug that blocks estrogen activity and slows down the growth of these estrogen-dependent tumors (Howell & Howell, 2023). Historically, the first significant trial of tamoxifen on breast cancer was conducted in 1969, where scientists conducted a single-arm Phase 2 trial with 46 patients, observing a similar response rate to existing breast cancer hormonal treatments, but with lower toxicity (Cole et al., 1971). Based on

additional testing trials conducted over the following years, ranging from 1 to 10 years of therapy, the Early Breast Cancer Trials Collaborative Group concluded 5 years of therapy was an effective adjuvant care (Howell & Howell, 2023). More recent studies supported this benefit: in the ten-year follow-up of the TAM-01 (Lazzeroni et al., 2023), women with intraepithelial neoplasia with breast cancer revealed that low doses of tamoxifen administered daily over three years significantly reduced their cancer. However, even though tamoxifen has clearly improved the outcome for many patients dealing with breast cancer, it can inhibit the protein kinase pathways in the brain, contributing to certain psychological effects on its users (Novick et al., 2021). Investigating the neural and psychological effects of protein kinase C inhibition in breast cancer patients is important to study because tamoxifen, while effective in blocking estrogen receptors to treat breast cancer, also inhibits PKC, a key regulator of neural signaling and mood regulation. In fact, a notable amount of breast cancer survivors report significant mood and memory changes during therapy, signifying the life-altering neurological effects PKC inhibition can have on an individual (Bower 2008). Ultimately, to guide safer therapeutic strategies, understanding the neural and psychological consequences of PKC inhibition is key to improving patient quality of life.

Protein Kinase C

Initially PKC had been discovered in the late 1970s, the proenzyme purified from the bovine brain (Callender & Newton, 2017). Shortly after its discovery, scientists were trying to understand PKC's role in cancer (Koivunen et al., 2006); however, studies signifying PKC inhibitor effects on cancer not only failed but also worsened the outcome of patients (Liu et al., 2022). Highly expressed in the brain and found in the neurons and glial cells, multiple PKC isoenzymes in this family function to suppress survival signaling and are associated with neurodegenerative diseases like Alzheimer's. They essentially play significant roles in brain pathophysiologies, such as alcoholism, opiate addiction, and substance abuse (Callender & Newton, 2017). PKC signaling is overactive in bipolar disorder and is thought to be a central molecular abnormality contributing to manic symptoms and mood instability. PKC is highly expressed in regions crucial for emotional regulation, memory, and executive function, such as the prefrontal cortex, hippocampus, and amygdala (Saxena et al., 2017). The PKC family has 9 genes with its proteins grouped by cofactor dependence. PKC's role in cancer is still being studied; however, somatic mutations in PKC isoenzymes are associated with cancer (Callender & Newton, 2017). PKC has also long been implicated in the regulation of neurotransmission and synaptic plasticity by phosphorylating transporters, ion channels, and G protein-coupled receptors (Callender & Newton, 2017). Evidence indicating PKC hyperactivity in bipolar disorder shows increased membrane-bound PKC activity and PKC association with membrane anchors and greater stimulus-induced PKC translocation to the membrane during mania (Saxena et al., 2017). Animal mania models additionally show increased PKC activity in the prefrontal cortex (PFC) and hippocampus (Saxena et al., 2017).

Estrogen

Estrogen receptors play a significant role in the signaling across psychiatric disorders. There are three main estrogen receptors: ERα, ERβ, and GPER. ERα centers around reproductive, autonomic, and affective functions, while ERβ is more tied to cognitive, anxiety, and sensorimotor functions. Additionally, while ERβ tends to dominate in the hippocampus, somatosensory cortex, thalamus, and cerebellum, ERα dominates in the amygdala and the hypothalamus, exemplifying the regions repeatedly

abnormal in major psychiatric disorders (Hwang et al., 2020). Overall, estrogen improves working memory, verbal memory, and learning processing speed. Selective Estrogen Receptor Modulators (SERMs) are a group of drugs that act on estrogen receptors and can have opposite effects on these receptors depending on the receptor's location in the body. Tamoxifen is an example of a SERM. SERMs essentially act as estrogen receptor (ER) agonists in the brain/bone and antagonists in the breast/uterus. They can activate pro-cognitive and neuroprotective pathways without causing oncogenic risks, making them attractive companions in psychiatric disorders (Hwang et al., 2020). In bipolar disorder, symptoms often worsen in low estrogen states. Major Depressive Disorder (MDD) also has a high prevalence in women with estrogen withdrawal (postpartum, menopause) (Hwang et al., 2020). GPER levels elevated in MDD correlate with depression (Hwang et al., 2020).

Tamoxifen

Tamoxifen has been proven to display many effects on its users by influencing psychiatric symptoms ranging from depression to mania. Preclinical animal data in cognition displays tamoxifen's impairment on working memory, object recognition, and learning for animals with normal estradiol; however, animals that have been ovariectomized or are aged females benefit from improved working memory, spatial memory, and increased spine density, likely due to their low estradiol levels (Callender & Newton, 2017). In postmenopausal women with cancer, data shows minimal change to tamoxifen; however, in breast cancer patients, most controlled studies show worse verbal memory, working memory, and psychomotor speed (Novick et al., 2020). Additionally, patient interaction with chemotherapy and illness stress contributes to the worsening of their neurological conditions (Callender & Newton, 2017). Regarding depression and anxiety, large trials and cohorts show no clear increase in clinical depression or anxiety due to tamoxifen; however, recent small reports are raising concern (Callender & Newton, 2017). In breast cancer patients, there have been greater cognitive complaints than mood changes regarding treatment with tamoxifen.

It is not yet clear how much of the cognitive and mood changes seen in breast cancer patients on tamoxifen are caused by PKC inhibition in the brain versus by estrogen blockade or by the stress of cancer treatment itself. However, this paper will shed light on tamoxifen's role as a PKC inhibitor, specifically surrounding its potential effect on psychological disorders such as mania or psychological disorder symptoms. It is especially important to discuss these effects now, as tamoxifen therapy has been a treatment that doctors are prescribing for breast cancer. With this significance, it is important to reflect and discuss the potential neurological and psychological effects PKC inhibition may have on breast cancer patients taking tamoxifen. To address this question, the current paper will analyze existing research in humans and animals to identify the potential psychological effects of various PKC inhibitors. Then, the effects identified will be discussed in the context of what is known about tamoxifen's effects and the experiences of breast cancer patients.

METHODLOGY

Using Google Scholar and PubMed, I searched for academic journal articles on the psychological effects PKC inhibitors have on the brain. The search terms I used for each database differed; for example, for PubMed I used two search strings:

1. (behavior) AND ("protein Kinase C inhibitor" [Title/Abstract])
2. (mental disorder) AND ("protein Kinase C inhibitor" [Title/Abstract]).

For Google Scholar, I used two search strings:

1. intext: behavior intitle:"protein kinase c inhibitor"
2. intext: mental disorder titled “protein kinase c inhibitor."

All searches were conducted between dates 11/1/25 and 11/15/25. To determine which articles would be useful to my current study, I identified articles that reported research studies on the psychological effects PKC inhibitors had on the brain. Articles that specifically discussed symptoms associated with psychiatric disorders were very prevalent results of PKC inhibition. I also examined research on all PKC inhibitors and included studies conducted in both human and animal models. Using these articles, I extracted the PKC inhibitors mentioned, the article title, the effects of PKC inhibition found by the study, the behaviors measured in the article, and the psychiatric disorders/symptom(s) mentioned in the article.

I analyzed the information by first reviewing each article and extracting all reported neurological or psychological effects caused by PKC inhibition. I then grouped these findings into categories based on the psychological disorder or symptom they most closely resembled. For example, depressive behaviors would be placed under depression, increased risk-taking or mood elevation under mania, anxiety-like responses under anxiety, and increased pain sensitivity under hyperalgesia.

After forming these categories, I evaluated their relevance to breast cancer patients by comparing each PKC-related effect to known side effects and clinical challenges experienced by patients taking tamoxifen, a therapy that also interacts with PKC pathways. Ultimately, this connection allowed me to answer the underlying research question about the potential neurological and psychological effects that PKC inhibition can have on breast cancer patients taking tamoxifen.

RESULTS

Thirteen articles found in my literature research were included in my final analysis (the articles included in my final analysis are described in Table 1). The articles that were not included centered around information that was not relevant to my topic of the neurological and physiological effects of PKC inhibition on patients. For example, some papers discussed the effects of PKC inhibition in the blood. The time range that the included articles had been published varies from as early as 1992 to as late as 2023. Analyzing these articles, the PKC inhibitors studied included chelerythrine, myricitrin, endoxifen, staurosporine, Go 6976, H-7, H-8, NPC 15437, and Ro31-8220. These PKC inhibitors were evaluated across many different biological models to observe their neurological impact. Specifically, the animals that had been studied in these articles included rats, mice, and chickens, alongside clinical data involving some bipolar and borderline personality patients.

I grouped the articles into topic categories based on different psychological symptoms and disorders associated with PKC inhibitors. These categories included bipolar disorder, borderline personality disorder, schizophrenia, and specific symptoms such as nociception/hyperalgesia, substance abuse, and memory-related disorders or symptoms, including amnesia and memory disruption. Within these categories, two articles were relevant to PKC inhibition and bipolar disorder, while one article focused on borderline personality disorder. Additionally, two articles addressed schizophrenia, and two articles were relevant to substance abuse. Three articles were linked to nociception and hyperalgesia, and three articles were associated with memory-related disorders or symptoms, one on fear conditioning and two on memory formation.

Author, publication date	**PKC Inhibitor**	**Effects of PKC inhibition found by study**	**Animal Studied**	**Psychiatric disorder(s)/symptom(s) mentioned in the article**
Einat, 2014	Chelerythrine	Chelerythrine, when administered to black Swiss mice which innately show mania-like behaviors, reduced spontaneous activity and sweet solution preference.	Mice	Bipolar disorder/Mania
Pereira et al., 2011	Myricitrin	Myricitrin PKC inhibition blocked amphetamine induced hyperlocomotion which suggests antipsychotic effects.	Mice and rats	Schizophrenia

Chang et al., 2021	Go 6976	The PKC inhibition of Go 6976 interfered with the reduction of mechanical hyperalgesia induced by TLR-5 and MOR agonists in rats with chronic constriction injury.	Rats	Hyperalgesia
Ahmad et al., 2021	Endoxifen	Endoxifen reduced mania ratings and improved depression ratings in bipolar I disorder patients.	Humans	Bipolar disorder
Fang et al., 2005	Staurosporine	During methamphetamine-induced behavior sensitization to the locomotor effects of dizocilpine (a model for schizophrenia), staurosporine blocked the development of this behavior sensitization.	Rats	Schizophrenia
Serrano et al., 1995	Chelerythrine	The administration chelerythrine near training time significantly impaired memory formation by 60 mins later, however it had failed to produce amnesia in the first 45 minutes of the study.	Chicks	Memory formation
Li et al., 2002	Staurosporine	The chronic administration of staurosporine reduced the learning of conditioned freezing but failed to block the freezing behavior after it had been learned.	Rats	Fear conditioning
Ghelardini et al., 2007	Chelerythrine	PKC inhibition blocked morphine-induced thermal hyperalgesia.	Mice	Hyperalgesia
Banerjee & Ray, 2023	Endoxifen	Endoxifen administered to borderline personality patients helped improve their impulsivity domain, attention deficits, mood fluctuation, and overall functioning.	Humans	Borderline personality disorder
Tokuyama et al., 1995	H-7 and H-8	H-7 and H-8 reduced the behavioral opioid withdrawal signs.	Rats	Substance abuse
Browman et al., 1998	Ro31-8220	PKC inhibition inhibited dopamine release from the nucleus accumbens in response to	Rats	Substance abuse

		amphetamines and pretreatment of this PKC inhibitor reduced how much amphetamine increased movement.		
Mathis et al., 1992	NPC 15437	PKC inhibitor impaired memory consolidation in a Y-maze avoidance task.	Mice	Memory formation
Wu et al., 2006	Chelerythrine	Chelerythrine blocked the loss of morphine's pain-relieving effect, allowing morphine to work better in a thermal hyperalgesia model that normally responds poorly to morphine	Rats	Hyperalgesia

Table 1: Literature Analysis Results

This paper addresses the research question: what are the potential neurological and psychological effects that PKC inhibition may have on breast cancer patients taking tamoxifen? To answer this, I analyzed literature that researched the possible psychological effects associated with PKC inhibition. The results of the literature analysis revealed 6 different categories of psychological disorders and effects linked to PKC inhibition: bipolar disorder/mania, substance abuse, hyperalgesia, schizophrenia, borderline personality disorder, and memory-related disorders/symptoms.

The literature analysis identified 2 studies on bipolar disorder/mania: one demonstrating that the PKC inhibitor chelerythrine reduced manic-like behaviors in mice (Einat et al., 2014) and the other finding that the PKC inhibitor endoxifen improved mania and depressive symptoms in patients with bipolar disorder (Ahmad et al., 2021). Research suggests that tamoxifen may have similar effects on mania as those observed with other PKC inhibitors in the two studies. Tamoxifen is an effective treatment against the manic stage in bipolar patients without breast cancer. Studies show that tamoxifen inhibits increased PKC activity in patients with bipolar disorder (Holden, 2007). Considering the relationship between bipolar disorder (BD) and breast cancer, the risk of development for both is complex and has been a source of ongoing investigation. A prior Mendelian randomization study revealed that genetic predisposition to bipolar disorder increases breast cancer risk by 5.9% (Peng et al., 2021). In fact, in a case study focused on a breast cancer patient, symptoms of mania occurred 2 months after her breast cancer diagnosis and 5 days before her manic episode, when the patient had been experiencing elevated moods and insomnia (Asevedo et al., 2013), demonstrating how mania symptoms can affect breast cancer and may even be triggered by it. However, in a case study of a 58-year-old breast cancer patient taking tamoxifen, the patient had developed manic symptoms during her treatment, which only subsided after the cessation of tamoxifen, indicating that behavioral symptoms such as mania may occur as an effect of tamoxifen (Duman et al., 2020). Given that PKC inhibitors like chelerythrine and endoxifen inhibit the manic-like symptoms in bipolar disorder models, and tamoxifen decreases the PKC activity in bipolar disorder, there is strong support for the possibility that tamoxifen can reduce symptoms of bipolar disorder in breast cancer patients. Yet, a case study showing that tamoxifen may induce manic symptoms in breast cancer patients using tamoxifen as a treatment for their cancer highlights that additional research on tamoxifen use in breast cancer patients is needed to fully understand how PKC inhibition influences bipolar disorder symptoms in this population.

Additionally, the literature analysis identified 2 studies on substance abuse: one revealing that the PKC inhibitors H-7 and H-8 reduced the behavioral opioid withdrawals associated with the morphine and butorphanol administration in rats (Tokuyama et al., 1995), and the other finding that the PKC inhibitor Ro31-8220 inhibited amphetamine-induced dopamine release from the nucleus accumbens, reducing the amphetamine-induced movement in rats (Browman et al., 1998). Determining whether tamoxifen displays similar effects in substance abuse cases to the PKC inhibitors found in the literature analysis, research indicates that tamoxifen counteracts amphetamine abuse by dampening amphetamine-induced dopamine release in the brain; however, the site of action of tamoxifen inhibiting amphetamine is still unknown (Mikelman et al., 2017). Given that tamoxifen is a PKC inhibitor, inhibiting PKC can lower amphetamine-triggered dopamine overflow (which can drive euphoria and hyperactivity) without blocking normal dopamine signaling (Mikelman et al., 2017). However, a study done on breast cancer patients (prescribed opioids for pain management) comparing the treatment effects of aromatase inhibitors (AI) and tamoxifen on opioid use had results that showed that patients who had switched from AI to tamoxifen had higher opioid use probabilities than those who stayed on just one therapy (Tan et al., 2017). AI significantly lowers estrogen levels by blocking the aromatase enzyme (Depolo, 2026).

Regarding the occurrence of substance abuse in patients with breast cancer, research shows that women with drug use disorder (DUD) have worse breast cancer outcomes than women without drug use disorders (Dahlman et al., 2021). Since drug addiction increases breast cancer mortality and severity, women with DUD are slightly more likely to develop breast cancer but much more likely to die from it and to be diagnosed at a late metastatic stage (Dahlman et al., 2021). Additionally, opioid use and high-dosage use are common for breast cancer patients and may increase their risk for drug addiction (Haque, 2025). Research on PKC inhibitors such as H-7, H-8, and Ro31-8220 shows that they reduce drug-induced effects in various models of substance abuse. Additionally, tamoxifen similarly counteracts amphetamine abuse, suggesting that tamoxifen may reduce symptoms of substance abuse in breast cancer patients. However, the finding of higher probabilities of opioid use in breast cancer patients who switched from AI treatment to tamoxifen highlights the research still needed to be conducted on whether tamoxifen can reduce opioid abuse symptoms in this population. Additionally, tamoxifen's effects on substance abuse may vary with different substances, highlighting the additional need for research on tamoxifen use regarding substance abuse in breast cancer patients.

The literature analysis outlined two research studies on schizophrenia; the first study displays how PKC inhibitor staurosporine inhibited the development of methamphetamine-induced sensitization to the drug dizocilpine (Fang et al., 2005), and the other study found that PKC inhibitor myricitrin blocked amphetamine-induced hyperlocomotion, suggesting antipsychotic effects (Pereira et al., 2011). Comparing the effects of tamoxifen on schizophrenia to the effects observed in the literature analysis on PKC inhibitors, research indicates that tamoxifen may have potential as a supplement to antipsychotic treatment. In a study using ketamine-treated rats as a model for psychosis, tamoxifen reduced oxidative stress by lowering malondialdehyde levels and increasing glutathione levels. It also increased brain-derived neurotrophic factor (BDNF), which helped improve hippocampal structure, supporting the idea that tamoxifen may play a role in inhibiting psychotic effects (Sedky et al., 2022). Considering the relevance of schizophrenia to breast cancer and the correlation tamoxifen may have, research reveals that

breast cancer patients with schizophrenia experienced breast cancer care disruption and cancer recurrence during treatment (Irwin et al., 2017). In the literature analysis the PKC inhibitors were found to promote antipsychotic effects by either blocking the development of methamphetamine-induced sensitization to the drug dizocilpine or inhibiting amphetamine-induced hyperlocomotion; however, with only one study in rats suggesting the antipsychotic effects that may occur with tamoxifen, additional research on tamoxifen use in breast cancer patients is needed to fully understand how PKC inhibition influences schizophrenia symptoms in this population.

The 3 studies on memory-related disorders/symptoms outlined two research studies on memory formation and one on fear conditioning; the first study demonstrates how the PKC inhibitor chelerythrine impaired memory formation after 60 minutes in chicks (Serrano et al., 1995), and the second study reveals how the PKC inhibitor NPC 15437 impaired memory consolidation in a Y-maze avoidance task in rats (Mathis et al., 1992). Finally, the third study demonstrates how the PKC inhibitor staurosporine reduced the learning of conditioned freezing but failed to block the freezing behavior after it had been learned in rats (Li et al., 2002). Determining the effects tamoxifen may have in distinction to the literature analysis, research suggests that tamoxifen did not affect long‑term memory, working memory, and visual short‑term memory, yet it seemed to impair verbal short‑term memory in women with breast cancer (Jebahi et al., 2021). Additional research done on mice taking tamoxifen displays effects of delayed latency of finding food in well-trained mice and impaired memory consolidation and retrieval processes (Chen et al., 2002). In a study that evaluated the effects of subchronic administration of tamoxifen in female Wistar rats, the results revealed that tamoxifen reduced spatial and recognition memory performance in the female rats (Klann et al., 2023). Regarding the relevance of breast cancer to memory-related disorders, a study done on researching the effect of chemotherapy on memory in breast cancer survivors states that effects of chemotherapy may cause disruptions in the recollection network and related episodic memory impairments in the survivors. Additionally, the study noted that systemic chemotherapy treatments used in breast cancer commonly cause neurotoxicity within the hippocampus, nurturing a vulnerability to memory impairment (Bradley-Garcia et al., 2022). Given that PKC inhibitors like chelerythrine and NPC 15437 impair memory formation in the chick and rat models, and tamoxifen reduced memory performance and memory formation in rat, mice, and breast cancer patient models, there is very strong support for the possibility that tamoxifen can impair memory performance in breast cancer patients. However, whether the impairment of memory is due to the PKC inhibition or the estrogen inhibition is still unknown, which indicates that additional research on tamoxifen use in breast cancer patients is needed to fully understand how PKC inhibition influences memory-related disorders/symptoms in this population.

The literature analysis revealed 3 studies on hyperalgesia; the first study demonstrates how the PKC inhibitor Go 6976 interfered with the reduction of mechanical hyperalgesia induced by TLR-5 (toll-like receptor 5) and MOR (mu-opioid receptor) agonists in rats with chronic constriction injury (Chang et al., 2021). The second study discovered that the PKC inhibitor chelerythrine blocked morphine-induced thermal hyperalgesia (Ghelardini et al., 2007). The third study revealed how the PKC inhibitor chelerythrine blocked the loss of morphine's pain-relieving effect, allowing morphine to work better in a thermal hyperalgesia model that normally responds poorly to morphine (Wu et al., 2006). Regarding the effects found in the literature analysis of PKC inhibitors on hyperalgesia, research on tamoxifen suggests

tamoxifen helped prevent chemotherapy-induced nerve pain by suppressing cold and mechanical allodynia caused by paclitaxel, vincristine, and bortezomib in mice. Additionally, the study found that tamoxifen suppressed chemotherapy drug-induced mechanical hyperalgesia (Tsubaki et al., 2018). Hyperalgesia in breast cancer patients is prevalent due to the various complications that occur when a patient receives surgery. Specifically, in a cross-sectional study done comparing the effects of a lumpectomy and a mastectomy, results had shown that pressure pain hyperalgesia was common in women who received these breast cancer surgeries and did not differ by surgery type. There were decreased pressure pain thresholds (PPT) in the C5–C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle in both lumpectomy and mastectomy groups, suggesting that hyperalgesia is widespread (Fernández-Lao et al., 2011). The current analysis demonstrates how PKC inhibitor Go 697 inhibits the reduction of hyperalgesia in mouse models, while PKC inhibitor chelerythrine either blocked the development of hyperalgesia or allowed morphine to work better at reducing the pain. Research on tamoxifen's effect on hyperalgesia suggests similar effects with chelerythrine. In the study done on tamoxifen's effect on chemotherapy-induced pain in the mouse model, tamoxifen prevented chemotherapy-induced cold and mechanical allodynia while also decreasing the mechanical hyperalgesia that occurred due to the chemotherapy. Ultimately, due to the fact that tamoxifen has a similar effect to only two of the three studies relating to hyperalgesia in the literature analysis, additional research should be done on tamoxifen's effects on hyperalgesia in breast cancer patients.

The literature analysis outlined one research study on borderline personality disorder; the study displayed PKC inhibitor endoxifen’s effect on improving the impulsivity domain, attention deficits, mood fluctuation, and overall functioning in borderline personality disorder patients (BPD) (Banerjee & Ray, 2023). Regarding the relevance of tamoxifen's effects on BPD compared to the literature analysis, there is no published study examining the effect of tamoxifen in BPD. However, the prevalence of BPD in breast cancer patients is very likely: a study done on breast cancer patients testing their Quality of Life (QOL) suggests that lower QOL is associated with the existence of personality disorder (Brunault et al., 2015). Considering the fact that there is very little research done on tamoxifen in BPD, the evidence is very weak, indicating the need for additional research to be done regarding tamoxifen’s effect on BPD in breast cancer patients.

Disorder	**Symptom /Effect**	**Response to PKC inhibition identified by the literature review (and associated PKC inhibitors)**	**Response to tamoxifen**
Bipolar Disorder	Mania	↓(chelerythrine) ↓(endoxifen)	↓
	Depression	↓(endoxifen)	Uncertain

Substance abuse	Opioid withdrawal	↓(H-7 & H-8)	Uncertain
	Amphetamine-induced dopamine release	↓(Ro31-8220)	↓
Schizophrenia	Antipsychotic effect	↑(staurosporine & myricitrin)	↑
Hyperalgesia	Thermal hyperalgesia	↓(chelerythrine)	Uncertain
	Mechanical hyperalgesia	↑(Go 6976)	↓
Borderline personality disorder	Impulsivity domain, attention deficits, mood fluctuation	↓(endoxifen)	Uncertain
	Overall functioning	↑(endoxifen)	Uncertain
Memory - related disorders/symptoms	Memory Formation	↓(chelerythrine)	Uncertain
	Memory Consolidation	↓(NPC 15437)	↓
	Fear conditioning acquisition	↓(staurosporine)	Uncertain

Table 2: Comparison of the literature analysis results to what is currently known about tamoxifen

Altogether, these results illustrated that PKC inhibition decreased mania and depression symptoms of bipolar disorder, decreased withdrawal and dopamine release in response to substances of abuse, and had an antipsychotic effect in models of schizophrenia. The results also revealed that PKC inhibition decreased morphine-induced thermal hyperalgesia, increased morphine's pain relieving effect, and increased mechanical hyperalgesia in hyperalgesia models, decreased impulsivity, attention deficits, and mood fluctuation symptoms of borderline personality disorder, and impaired memory formation memory consolidation, and fear conditioning. Additional exploration based on these results revealed that tamoxifen may also have some of these effects, such as decreased mania symptoms in bipolar disorder, decreased dopamine release regarding substance abuse, antipsychotic effects in schizophrenia, decreased chemotherapy-induced hyperalgesia, and impaired memory consolidation.

CONCLUSION

Overall the current paper's literature analysis had many strengths regarding the psychological effects of tamoxifen PKC inhibition on breast cancer patients. First, evidence strongly supports that tamoxifen's PKC inhibition decreases the manic symptoms in bipolar disorder and that tamoxifen can impair memory performance in breast cancer patients. However, in many of these studies on tamoxifen, there was evidence contradicting the evidence supporting a statement. For example, for symptoms related to hyperalgesia, schizophrenia, and substance abuse, the evidence on tamoxifen's effects in breast cancer patients was less clear. The biggest weakness in this paper's literature analysis was that it could not definitively establish the effects of tamoxifen's PKC inhibition on the psychological disorder/symptoms in breast cancer patients. For symptoms related to borderline personality disorder, very little evidence exists related to tamoxifen. Additionally, in studies of tamoxifen's effect on memory, it was hard to establish whether the memory-related disorder/symptoms were due to the PKC inhibition or estrogen inhibition. Research has also shown that many psychological symptoms in breast cancer patients may be influenced by stress, treatment side effects, or hormonal changes that were not related to PKC (Izci et al., 2016). Stress from having cancer, side effects from treatments like chemotherapy, and changes in hormones can all cause mood swings or memory problems on their own, so it is hard to know if tamoxifen's PKC inhibition is the real cause. It is important to tell these causes apart so doctors do not stop a helpful medicine for the wrong reason or miss a side effect that needs care. For example, if a patient taking tamoxifen feels anxious and forgetful, the symptoms might be from stress or earlier treatment instead of PKC inhibition, and treating the wrong cause could affect both her mental health and cancer treatment. However, the significance of this literature analysis demonstrates the understanding of tamoxifen's effects on the brain, and how using this information, improvements can be made to improve the quality of life for cancer patients. Future research should focus on the plethora of tamoxifen's effects related to the effects of other PKC inhibitors identified in this paper's literature analysis; for example, investigating whether tamoxifen treatment can reduce borderline personality disorder symptoms in patients with BPD, determining if tamoxifen can decrease mania symptoms in breast cancer patients with bipolar disorder, or the comparison of tamoxifen to other PKC inhibitors without estrogen-related effects.

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