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Neuropsychiatric Effects of Tamoxifen: Challenges and Opportunities

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Abstract

Epidemiological, clinical, and basic research over the past thirty years have described the benefits of estrogen on cognition, mood, and brain health. Less is known about tamoxifen, a selective estrogen receptor modifier (SERM) commonly used in breast cancer that is able to cross the blood-brain barrier. In this article we review the basic pharmacology of tamoxifen, as well as its effects on cognition and mood. The literature reveals an overall impairing effect of tamoxifen on cognition in breast cancer patients, hinting at central antiestrogen activity. On the other hand, tamoxifen demonstrates promising effects in psychiatric disorders, like bipolar disorder, where its therapeutic action may be independent of interaction with estrogen receptors. Understanding the neuropsychiatric properties of SERMs like tamoxifen can guide future research to ameliorate unwanted side-effects and provide novel options for difficult to treat disorders.

Keywords

Tamoxifen; SERM; Estrogen; breast cancer

1. Introduction

Estrogen receptors (ER) are found throughout both the male and female brain, with significant density in brain regions associated with cognition and affect (Österlund et al., 2000). Through its interaction with central ERs, estrogen has neuroprotective effects (Arevalo et al., 2015), and also promotes activity of other neurotransmitters involved in mood and cognition, such as serotonin (Amin et al., 2005), dopamine (Yoest et al., 2014) and acetylcholine (Newhouse et al., 2013). One illustration of the importance of estrogen in brain function for both men and women can be found in the increased risk of Alzheimer's dementia in females, which is related to the more drastic decrease in estrogen that females experience as they age (Podcasy and Epperson, 2016). When patients experience decreases in estrogen prematurely (e.g. removal of ovaries), risk for dementia increases further (Bove

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et al., 2014; Phung et al., 2010; Rocca, 2007). Conversely, estrogen replacement in females, starting near the onset of menopause, has been found to have cognitive protective effects (Rocca, 2007). Estrogen's effects on mood are also most apparent during lifespan changes in estrogen levels. Unlike in males, whose estrogen levels remain relatively steady throughout life, changes in mood are found in females across the menstrual cycle, during pregnancy, following delivery and during menopause (Hara et al., 2015; Le et al., 2020; Schiller et al., 2015). Decreases in estrogen during the postpartum period and during menopause place certain women at higher risk for depression (Bloch et al., 2003; Cohen et al., 2006). Lastly, limited evidence suggests that estrogen can exert protective effects in both males and female in the severe mental illnesses of bipolar disorder and schizophrenia (Gogos et al., 2019).

The important role of estrogen in cognition and mood has led to investigations into how selective estrogen receptor modifiers (SERMs), specifically tamoxifen, exert their influence in these domains. Approved in 1998 for both the treatment and prevention of breast cancer, tamoxifen is a commonly used agent among the approximately 260,000 women and 2500 men who are diagnosed with breast cancer annually in the United States (Siegel et al., 2018) and is the most prescribed SERM. As tamoxifen can act as both an estrogen agonist and antagonist, it can both induce the positive actions of estrogen in the brain and periphery OR the negative actions. Evidence in both animals and humans suggest both types of action, in some cases demonstrating similar effects to estrogen in terms of neuroprotection, behavior and cognitive performance (Newhouse et al., 2013; Velázquez-Zamora et al., 2012) while in other cases blocking estrogen's effect and mimicking a state of estrogen suppression (Chen et al., 2002, 2014).

The evidence of tamoxifen's potential neuropsychiatric duality is noted in two separate clinical populations: breast cancer patients and psychiatric patients with severe mental illness. In breast cancer patients, there has been ongoing concern of tamoxifen's potential to produce cognitive deficits. As breast cancer patients often experience cognitive complaints due to a mix of age, chemotherapy and the stress of illness (Ahles et al., 2012), the possibility of additional cognitive impairment due to tamoxifen therapy is concerning. In contrast to these negative effects, tamoxifen may represent a promising adjunctive treatment in bipolar disorder, schizophrenia and possibly substance use disorders, one that lacks many of the side effects present in commonly used psychiatric agents (Khan, 2018, (S. Mikelman et al., 2017)).

The purpose of this review is to summarize the clinically relevant neuropsychiatric properties of tamoxifen as well as its potential use in severe mental illness. In addition to describing its pharmacology and effects in animals, a major focus will be examining its effects on cognition in breast cancer patients. While several reviews have focused on the effects of both tamoxifen and aromatase inhibitors on cognitive function (Bakoyiannis et al., 2016; Lee et al., 2016; Schilder and Schagen, 2007; Zwart et al., 2015), we have limited our discussion to only tamoxifen, given its unique pharmacology, independent widespread use, and greater potential application to psychiatric disorders.

2. Tamoxifen neuropharmacology and animal studies.

Tamoxifen, and its more potent metabolite, 4-hydroxy-tamoxifen, crosses the blood brain barrier (Lien et al., 1991) and competitively inhibits the binding of estradiol to both ER subtypes, ERα and ERβ (Kuhl, 2005) as well as the G-protein estrogen receptor-1 (GPER1) (Long et al., 2017; Revankar et al., 2005) From *in vitro* work on cloned human ERs, tamoxifen has about 20–25 fold less binding affinity to ERα and ERβ compared to estradiol (Kuiper et al., 1997). However, 4-hydroxy-tamoxifen has almost equal affinity for ERα and three times greater affinity for ERβ compared to estradiol (Kuiper et al., 1997), emphasizing the drug's ability to competitively inhibit estradiol binding at its receptors. ERα, ERβ, and GPER1 are found throughout the brain, but with different distributions based on region (Hadjimarkou and Vasudevan, 2018; Österlund et al., 2000; Österlund and Hurd, 2001; Shughrue et al., 1997). ERα is the dominant subtype in most of the hypothalamus and amygdala, while ERβ is the main subtype in regions of the hippocampus (Österlund and Hurd, 2001; Shughrue et al., 1997). While a simplistic conceptualization is that ERα is involved mainly in autonomic, reproductive and affective functions, while ERβ is involved in more cognitive functions (Österlund and Hurd, 2001), evidence suggests a more complicated picture in which both of the classical ERs as well as GPER1 contribute to multiple functions (Bean et al., 2014; Lund et al., 2005; Lymer et al., 2018; Sá et al., 2016; Shughrue et al., 1998). This is further complicated by the fact that ERβ may act as a negative regulator of ERα gene transcription (Hall and McDonnell, 1999; Han et al., 2013), and thus it can be difficult to parse out whether any given action within the brain is due action at a specific ER or via interactions between ERs. Whether tamoxifen acts as an antiestrogen or estrogen agonist is tissue-specific and has been found to be dependent on differential expression of both estrogen receptor subtypes and differential interactions with co-activators and co-repressors (Martinkovich et al., 2014).

Unfortunately, characterizing the molecular effects of tamoxifen at ERs has mainly been studied in peripheral tissues (Hall and McDonnell, 1999; Zwart et al., 2010), and significantly less is known about tamoxifen's interactions with ERs in the central nervous system (CNS). Limited evidence suggests that tamoxifen acts as an agonist at the GPER1 receptor in the CNS, mimicking the non-genomic rapid-acting effects of estradiol, at least with regards to hypothalamic-mediated reproductive behaviors (Long et al., 2017). However, overall, tamoxifen is more likely to act as an antiestrogen in the brain in the presence of estradiol or specific estrogen-agonists, while acting as an estrogen mimetic in the context of estradiol deprived states. For example, in estradiol-primed rats, tamoxifen inhibits ER-dependent sexual behavior (Etgen, 1979) and ERα-dependent transcription of progesterone receptors in the hypothalamus (Sá et al., 2016). Tamoxifen was also found to block reductions in exploration induced by an ERβ agonist in a rodent model of anxiety behavior (Lund et al., 2005). In the absence of estradiol in ovariectomized animals, tamoxifen increases ERα-dependent oxytocin receptor transcription in the hypothalamus (Patisaul et al., 2003) and can also improve cognitive performance similar to estradiol (Velázquez-Zamora et al., 2012). Variation of action based on endogenous hormonal tone suggests that tamoxifen is similar to classical partial agonists in which agonist vs antagonist properties are determined by the concentration of endogenous ligand. In support of this view, when

tamoxifen interacts with the ligand binding domain of ERs, it creates ER conformations that resemble something in between that created by estradiol and that created by a pure ER antagonist (Paige et al., 1999; Shiau et al., 1998).

Tamoxifen also has pharmacological properties that are at least partially separate from its interactions with ERs. Specifically, tamoxifen has been found to inhibit the dopamine transporter (DAT) even in the presence of ER antagonists (S. R. Mikelman et al., 2017). While estradiol itself decreases dopamine uptake and influences membrane trafficking of DAT (Disshon et al., 1998; Watson et al., 2006), this appears to be distinct from the direct non-competitive binding of tamoxifen to DAT (Mikelman et al., 2018). In addition, tamoxifen inhibits protein kinase C (PKC) (Horgan et al., 1986), which is found throughout the brain in neurons and helps regulate neurotransmission, neuron excitability and plasticity (Manji and Lenox, 1999). Tamoxifen's ability to inhibit PKC has been demonstrated in purified preparations of the enzyme (O'Brian et al., 1985) suggesting a non-ER mediated property. As estradiol has also been shown to decrease PKC activity in hippocampal neurons (Jung et al., 2005), tamoxifen's PKC inhibition via the ER cannot be totally ruled out. Both of these mechanisms, DAT and PKC inhibition, will be discussed further in their relevance to substance use disorders (section 4.3) and bipolar disorder (sections 2.2 and 4.1).

Tamoxifen and estradiol have both similar and distinct actions in the brains of animals in terms of neuroprotection, plasticity, and neurotransmitter systems. As above, tamoxifen's estrogen mimetic effects occur most often in the context of estradiol deprivation via ovariectomy. Similar to estradiol, tamoxifen decreases NMDA receptor binding in the pre-frontal cortex, while increasing NMDA receptor binding in the hippocampus in ovariectomized animals (Cyr et al., 2001). Given that synaptic density is correlated with NMDA receptor input (Woolley et al., 1997), this latter effect might contribute to tamoxifen's ability to increase synaptic density within the hippocampus of ovariectomized animals (Silva et al., 2000), similar to estradiol. Also like estradiol, tamoxifen has demonstrated neuroprotective effects in models of stroke, oxidative stress, excitotoxic damage, and inflammation (Arevalo et al., 2015). Again, these neuroprotective effects have mainly been studied in ovariectomized animals (Barreto et al., 2009; Ciriza et al., 2004) or in *ex-vivo* conditions without the presence of estradiol (Moreira et al., 2005).

Tamoxifen appears to act as an estrogen mimetic in its ability to enhance acetylcholine activity in ovariectomized animals via increasing expression of choline acetyltransferase (McMillan et al., 2002). However, in the presence of estradiol, tamoxifen acts more as an antiestrogen with regards to the serotonergic system, blocking estradiol's effects on increasing 5-HT2A receptors and serotonin transporters (Sumner et al., 1999). Tamoxifen's direct inhibition of the dopamine transporter is likely responsible for its ability to increase striatal extracellular dopamine levels in intact male rats (though to a lesser extent than amphetamine) (Chaurasia et al., 1998), while simultaneously preventing amphetamine from entering the transporter and inducing release (Mikelman et al., 2018). Tamoxifen is also neuroprotective in the dopamine neurons of intact male rats in animal models of Parkinson's (Obata and Kubota, 2001), which was hypothesized to be related to estrogen-like antioxidant effects.

Related to dopaminergic activity, Tamoxifen's effects in methamphetamine toxicity provide an example of how tamoxifen can demonstrate antiestrogen effects and estrogen mimetic activity that is dependent on estradiol concentration in addition to actions likely independent of estradiol. Estradiol has sexually dimorphic effects in preventing methamphetamine-induced dopaminergic toxicity, with neuroprotective action in female but not male mice (Liu and Dluzen, 2006). Tamoxifen on the other hand is protective against methamphetamine toxicity in intact male mice, preventing methamphetamine-induced decreases in striatal dopamine concentration, decreases in DAT binding, and increases in preproenkephalin (Bourque et al., 2007). However, in intact female mice, while tamoxifen was able to prevent decreases in striatal dopamine concentration following methamphetamine (D'Astous et al., 2005; Dluzen et al., 2001), it did not fully mimic the protective effects of estradiol on DAT binding and preproenkephalin expression (D'Astous et al., 2005). And furthermore, in ovariectomized animals administered estradiol, tamoxifen actually blocked estradiol's protective effects on dopamine concentrations (Gao and Dluzen, 2001). As such, tamoxifen effects on methamphetamine neurotoxicity may be due to a mix of estrogen-like activity that are dependent on background estradiol levels (such as antioxidant activity (Obata and Kubota, 2001) and anti-apoptotic effects (Sawada et al., 2000; Wang et al., 2011), as well as estrogen-independent functions to inhibit the dopamine transporter (thus preventing access to methamphetamine and dopamine toxins) (Mikelman et al., 2018).

2.1. Pre-clinical studies on tamoxifen and cognition

Estradiol's effects on various aspects of cognition have been attributed to its action at each of its major target receptors, as its effects on various types of cognitive performance generally follow an inverted-U pattern, with increasing estradiol levels improving performance up to a point with subsequent performance impairments (Duarte-Guterman et al., 2015; Foster, 2012). Decreasing estradiol in animals via ovariectomy reliably produces deficits in multiple domains of cognition including working memory (Cao et al., 2013; Gibbs and Johnson, 2008) as well as hippocampal-dependent processes such as object recognition (Fernandez et al., 2008; Fonseca et al., 2013; Wallace et al., 2006). The pre-clinical data is very consistent that tamoxifen impairs cognition in intact animals while improving it in ovariectomized animals.

In intact male and female mice, tamoxifen impaired retrieval processes in a working memory task when administered 30 minutes prior to testing in well trained mice. In the same study, it also impaired both memory consolidation and retrieval processes in a passive avoidance task (Chen et al., 2002). Similar impairing effects of tamoxifen were found on acquisition and retention of a learned response to receive reward in intact male mice (Walker et al., 2011). Tamoxifen also impaired novel object recognition performance (which depends on the hippocampal function) and induced a corresponding decrease in both brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in the hippocampus of intact female rats (Samira S. Valvassori et al., 2017). While none of the above studies took into account the reproductive phase of the rats, the fact that deficits were seen in intact males suggests that perhaps only minimal estradiol levels are needed to be present for tamoxifen to have an impairing antiestrogen effect on cognition. However, further research using dose-response testing of estradiol and tamoxifen would be needed to confirm this hypothesis.

In contrast to its effects in intact animals, tamoxifen's effect in ovariectomized animals is practically the opposite, where it appears to act as a form of estrogen replacement. When given one week after ovariectomy in rats, tamoxifen had similar effects as estradiol in terms of improving working memory performance and increasing prefrontal cortex dendritic spine density (Velázquez-Zamora et al., 2012). In aged mice, tamoxifen was able to counter the effects of amyloid-beta injection on measures of spatial and contextual memory, while also preventing amyloid-induced decreases in striatal dopamine and cortical acetylcholine (Pandey et al., 2016). Tamoxifen was found neither to impair nor improve working memory in ovariectomized rhesus macaques (Lacreuse et al., 2009)

Thus, the underlying hormonal state of an animal appears to moderate the cognitive effects of tamoxifen. In animals with low estradiol levels, tamoxifen appears to improve cognition in several measured domains. In animals whose estrogen levels are unaltered, the drug causes impairments in several cognitive domains.

2.2. Pre-clinical studies on Tamoxifen in models of depression, anxiety, mania and psychosis

Similar to its effects on cognition, tamoxifen's effects on depressive and anxiety-like behaviors may depend on the hormonal status of the animal. In ovariectomized mice who underwent chronic unpredictable stress, acute treatment with tamoxifen had similar effects to estradiol, decreasing immobility in the forced swim test and increasing time spent in the open-arms of the elevated plus maze (Calmarza-Font et al., 2012). Decreased immobility in the forced swim test may reflect enhanced active-coping in the face of stress, something that is often deficient in depressive-like states (Commons et al., 2017). Increased time in the open-arms of the elevated plus maze is indicative of decreased avoidance and increased exploration, which is often decreased in anxious states. Thus, these effects of tamoxifen are suggestive of antidepressant and anxiolytic effects, respectively. A similar effect was found in ovariectomized rats, though with some indication of increased immobility behavior in the forced swim test (Azizi-Malekabadi et al., 2015). While these results would suggest that tamoxifen acts like an estrogen agonist in ovariectomized animals to improve behaviors related to depressive and anxious-states, opposite results were found in ovariectomized rhesus monkeys, where tamoxifen resulted in increased levels of anxiety behaviors (Mook et al., 2005).

In contrast to data in ovariectomized rodents, limited evidence suggests that in *intact* rodents, tamoxifen may act as an antiestrogen to increase anxiety-like behavior. In intact male mice (Li et al., 2019) and intact female rats in the proestrous phase (high estradiol level) (Azizi-Malekabadi et al., 2015), tamoxifen-treated animals spent less time in the open arms of the elevated plus maze. Thus, with the possible exception of non-human primates, tamoxifen may possess antidepressant and anti-anxiety properties in estrogen-deficient states, while having the opposite effect when estrogen is present.

In animal models of mania, there is less evidence to suggest that tamoxifen's effects vary according to endogenous estrogen levels. This is likely due to the fact that tamoxifen's anti-manic effects are ER independent, and instead likely work through an inhibition of protein kinase C that does not include the ER (O'Brian et al., 1985). Tamoxifen has been found to

have similar effects as lithium in intact rodents in various models of manic-like behavior. Tamoxifen decreases the hyper-locomotion induced by oubain (Samira S Valvassori et al., 2017), amphetamine (Einat et al., 2007; Sabioni et al., 2008), and sleep deprivation (Abrial et al., 2014; Armani et al., 2012). Tamoxifen's efficacy in mania is also suggested by its lithium-like ability to decrease amphetamine-induced 50-kH ultrasonic vocalizations (Pereira et al., 2014), which are markers of a positive affective state in rats (Panksepp, 2007).

Decreased ability to gate information is a neurophysiological hallmark of schizophrenia and can be measured by the pre-pulse inhibition (PPI) paradigm in both humans and animals (Geyer et al., 2001). This paradigm consists of first measuring startle response to a loud noise. Subsequently, a "pre-pulse" (slightly softer noise) is presented prior to the startle noise, which, when sensorimotor gating is normal, has the effect of decreasing the startle response. Failure to inhibit startle after experiencing the pre-pulse suggests deficient information gating and is commonly found in schizophrenia. While antipsychotics have variable ability to influence PPI in schizophrenia, the ability of compounds to ameliorate pharmacologically-induced deficits in PPI in animals remains a way to test for drugs with potential antipsychotic activity(Geyer et al., 2001). Thus, it is meaningful that in ovariectomized rats with PPI deficits following dopaminergic stimulation with both methamphetamine and the direct dopamine agonist apopmorphine, tamoxifen is able to rescue PPI performance similar to estradiol (Gogos and van den Buuse, 2015; Sbisa et al., 2018). This was hypothesized to be mediated via tamoxifen's actions at the ERβ, as administering the SERM raloxifene which has significantly less affinity for ERβ was not effective at rescuing dopaminergic-induced PPI deficits (Sbisa et al., 2018). And while tamoxifen's activity at the dopamine transporter (potentially minimizing methamphetamine induced dopamine release) (Mikelman et al., 2018) might explain its action in methamphetamine-induced PPI, its role in treating PPI deficits due to direct dopamine agonism with apopmorphine remains more elusive. Neither estradiol nor tamoxifen appear to have direct dopamine receptor blocking activity, instead appearing to overall enhance dopamine tone in striatal regions (Becker, 1990; Chaurasia et al., 1998; Yoest et al., 2014). Thus, it's likely that more nuanced regulation of the dopamine system and sensory gating functions may be occurring with regards to tamoxifen's action in models of psychosis.

3. Effects of tamoxifen on cognition and affect in humans

3.1. Effects of tamoxifen on cognition in breast cancer patients and non-breast cancer Patients

Cognitive side-effects in patients taking tamoxifen is a topic of great interest, given the efficacy and wide-spread use of the drug in breast cancer treatment and the prevalence of cognitive complaints post-treatment (Epperson et al., 2015) There is now a substantial literature investigating the issue, including multiple reviews (Bakoyiannis et al., 2016; Lee et al., 2016; Schilder and Schagen, 2007; Zwart et al., 2015) as well as a recent meta-analysis (Underwood et al., 2018). While these reviews (including the meta-analysis) all suggest a possible detrimental effect of tamoxifen on cognitive function, the literature is by no means uniform, and authors are quick to point out the heterogenous methodology of the current literature and the need for further investigation. Some of the most frequently identified

issues that limit more definitive conclusions include problems with comparison groups (healthy controls vs breast cancer controls not on tamoxifen), timing of assessment in relation to treatment (acute, longitudinal, post-treatment), experience of prior chemotherapy, combined analysis of tamoxifen with aromatase inhibitors, and hormonal status/age of population. For the purposes of this review, we have limited our summary of literature primarily to studies that A) used objective neuropsychological measures as opposed to self-report and B) were able to analyze tamoxifen use on its own vs grouping tamoxifen with other endocrine treatments such as aromatase inhibitors.

There are limited studies on tamoxifen's effects on cognition in women without breast cancer. Two notable studies suggest either no effect on cognition or a potential protective effect, at least in postmenopausal women. In one study, postmenopausal women aged 65 and older were randomized to receive either tamoxifen or a separate SERM, raloxifene, and assessed on multiple cognitive domains at multiple timepoints over the course of three years. Raloxifene is currently approved for preventing osteoporosis in postmenopausal women, and can also be used to prevent breast cancer in those at high risk (Li et al., 2016). Not only were there no differences on cognitive measures between the raloxifene and tamoxifen group, there was no indication of cognitive decline in either group when compared to baseline measurements (Legault et al., 2009). A separate placebo controlled, cross-over study in postmenopausal women without breast cancer evaluated the effects of tamoxifen during anticholinergic drug challenges. Tamoxifen was able to prevent anticholinergic cognitive deficits in hippocampal-dependent cognitive domains such verbal episodic memory as well as spatial navigation (Newhouse et al., 2013). Interestingly, the study found that tamoxifen's protective effects were most apparent in individuals with the APOE ε4 genotype, which is considered a risk factor for Alzheimer's disease and may decrease cholinergic function (Poirier et al., 1995). The authors hypothesized that tamoxifen, acting similar to estrogen, enhanced cholinergic and hippocampal function.

The studies in breast cancer patients paint a somewhat different story. In one study, postmenopausal breast cancer patients were randomized to receive either tamoxifen or the aromatase inhibitor exemestane, and received neuropsychological assessments at baseline and one year after treatment initiation. Tamoxifen users were found to perform worse than healthy controls in terms of verbal memory and executive function, and worse than exemestane users on tests of information processing speed. In addition, individuals over the age of 65 seemed to be more sensitive to tamoxifen's impairing cognitive effects (Schilder et al., 2010). A separate study comparing postmenopausal breast cancer patients on either tamoxifen or the aromatase inhibitor letrozole also demonstrated that individuals assigned to the tamoxifen group performed significantly below age expected norms on domains of psychomotor function, working memory, visual learning, and verbal memory. And while there was evidence of impairments compared to those receiving letrozole, the study is limited in its ability to clearly differentiate the effects of breast cancer and other breast cancer treatments from the use of tamoxifen (Phillips et al., 2010).

Given the well-known cognitive effects of various chemotherapies, several studies have attempted to parse out the effects of chemotherapy from hormonal adjuvant treatments like tamoxifen. Premenopausal individuals receiving chemotherapy plus tamoxifen had

decreased performance on verbal learning, visual memory and visuospatial measures as well as global neurocognitive performance compared to those who only received chemotherapy (Castellon et al., 2004). Similar results were found in a longitudinal study comparing breast cancer survivors receiving chemotherapy, chemotherapy plus tamoxifen, or no chemotherapy with tamoxifen (Bender et al., 2006). Over the course of a year, the chemotherapy plus tamoxifen group had the greatest decrements in areas of visual memory and verbal working memory.

In chemotherapy naïve patients, breast cancer survivors taking tamoxifen demonstrated significantly lower hippocampal volumes as well as decreased glucose metabolism in the areas of the frontal cortex compared to postmenopausal women taking estrogen (Eberling et al., 2004). In addition, women on tamoxifen had decreased semantic memory performance compared to individuals both with and without estrogen treatment (Eberling et al., 2004), suggesting that tamoxifen may be acting as an estrogen antagonist rather than agonist in these patients. Controlling for the effects of breast cancer and breast cancer treatment, Boele et al (Boele et al., 2015) demonstrated that breast cancer survivors taking tamoxifen performed worse on measures of verbal memory than individuals who had just received surgical/radiotherapy interventions. Another study that compared chemotherapy naïve premenopausal breast cancer patients with and without tamoxifen found tamoxifen to be associated with deficits in verbal memory and executive function tasks (Chen et al., 2014). The study also demonstrated deficits in adaptive decision making on the Iowa Gambling Task and Game of Dice Task. Given the role of regions of the frontal cortex in decision making and responding to feedback, these results were consistent with that of Eberling who showed decreased glucose metabolism in the frontal cortices of tamoxifen patients (Eberling et al., 2004).

It should be noted that several studies have failed to find deficits in cognitive function in breast cancer patients taking hormonal adjuvant therapies. An early study that assessed clock drawing, box drawing and narrative writing in breast cancer patients did not find differences in performance between tamoxifen-users and never-users (Paganini-Hill and Clark, 2000). However, the tamoxifen patients were more likely to visit a medical professional for memory complaints. And given that the tasks did not have an extensive component of functions highly correlated with estrogen such as verbal memory, it may be that tamoxifen treated individuals had more cognitive deficits than were captured by objective assessment. Additional studies that found no effect of hormonal treatments in breast cancer did not differentiate between tamoxifen and aromatase inhibitors (Breckenridge et al., 2012; Dyk et al., 2019; Hermelink et al., 2008). And given that several studies have suggested that tamoxifen may have more impairing effects compared to aromatase inhibitors (Phillips et al., 2010; Schilder et al., 2010), conclusions about tamoxifen from such combined analyses should be made with caution.

While ongoing study is needed in both breast cancer patients and non-breast cancer patients, a preponderance of evidence suggests that tamoxifen has cognitive impairing properties, especially in domains known to be sensitive to estrogen levels such as verbal memory. Unlike the animal data, there is not a clear delineation of tamoxifen’s action based on hormonal status in humans. Ideally, placebo-controlled studies in non-breast cancer patients

that are clearly able to delineate effects based on endogenous hormone status would aid our understanding of how tamoxifen affects cognition. At the same time, ongoing studies in breast cancer patients are important, given that these individuals undergo specific stressors and sometimes neurotoxic treatments that might make them more sensitive to cognitive anti-estrogen effects.

3.1.5 Differences in cognitive effects between animal models and humans—

In animals, tamoxifen demonstrates mainly pro-cognitive effects when estrogen has been decreased by ovariectomy, while impairing cognition when estrogen levels remain intact. The majority of literature in humans shows that tamoxifen can result in cognitive impairment regardless of endogenous estrogen status. The reasons for a lack of concordance between the animal and human literature are likely multifold. First, while ovariectomy in rodents has similarities to surgical menopause in humans, it is different than transitional menopause in humans given the ongoing presence of low levels of gonadal hormones (Koebele and Bimonte-Nelson, 2016). Thus, giving tamoxifen to an ovariectomized rodent is modeling its effects in more of an absolute state of hypogonadism. On the other hand, in postmenopausal humans, tamoxifen may still be competing with endogenous estrogens (even though such endogenous levels are lower than the premenopausal state). As such, tamoxifen may still be antagonizing the pro-cognitive effects of endogenous estrogen in postmenopausal women. Second, methodology of determining premenopausal and postmenopausal status in most studies are often varied, and women varied in the length of time they may have been postmenopausal prior to tamoxifen initiation (Zwart et al., 2015). The issue of timing when it comes to the role of estradiol and cognition is particularly important due to what's become known as the "window of opportunity hypothesis." Although not universally supported by evidence (Henderson and Popat, 2011), data from observational studies and clinical studies suggested that estrogen replacement might be beneficial for cognition when it is initiated early in menopause, but have lesser effect when initiated later (for review see (Maki, 2013)). This hypothesis is supported by animal work demonstrating that after a certain duration of estrogen deprivation, the brain becomes insensitive to the effects of estrogen replacement on improving hippocampal morphology (Vedder et al., 2014).

3.2. Effects of tamoxifen on depression and anxiety

Given that ovariectomy in animals as well as menopause in humans can increase measures of depression and anxiety, there is rationale that tamoxifen's antiestrogen effects might result in worsening depression and anxiety. Conversely, limited animal literature discussed above suggests that in the context of women who are already postmenopausal, tamoxifen might have antidepressant and anxiolytic properties. While there has been some indication of increased depression and anxiety symptoms with tamoxifen, the majority of data has been negative.

An early review by Thompson et al (Thompson et al., 1999) raised concern for depression in tamoxifen patients, citing several studies in which there was either increased incidence of depressive symptoms compared to a patients not taking tamoxifen (Cathcart et al., 1993), or evidence of increased depression following tamoxifen initiation (Anelli et al., 1994; Shariff

et al., 1995). However, in a large randomized placebo controlled study of tamoxifen for breast cancer prevention in >11,000 women ages 35–79, tamoxifen was not found to induce or exacerbate existing depression (Day et al., 2001). A subsequent longitudinal study of breast cancer patients found that while tamoxifen was associated with increased cognitive complaints over time, there was no significant increase in depressive symptoms as measured by the Beck Depression Inventory (Bender et al., 2006). And finally, in a retrospective cohort study of 2,943 patients, researchers found that while chemotherapy and ER-positive breast cancer status were associated with increased risk of depression, use of tamoxifen was not (Lee et al., 2007).

Given findings in animal models, it might be expected that tamoxifen's effects on depression might be dependent on hormonal status. However, in the above studies that included a diverse age-range (and thus menopausal status), no differences were found when taking age into account (Day et al., 2001; Lee et al., 2007). A similar lack of association between tamoxifen treatment and worsening anxiety symptoms was found in several studies in both premenopausal and postmenopausal women (Biro et al., 2019; Boele et al., 2015; Marianne Nystedt, 2000).

4. Tamoxifen as treatment in psychiatric disorders

4.1. Bipolar Disorder

In both bipolar disorder and schizophrenia, there are links between estrogen status and symptom severity. In bipolar disorder, decreased sex steroids (including estrogen) in the early and late luteal phases of the menstrual cycle have been associated with both manic and depressive symptom exacerbation (Rasgon et al., 2003; Shivakumar et al., 2008). Similar findings of bipolar women in hypoestrogenic states (menopause and the postpartum period) have also revealed an increased risk for symptom exacerbation (Gogos et al., 2019; Marsh et al., 2015). However, it should be noted that in addition to estrogen, changes in progesterone and its associated neuroactive steroids, such as allopregnanolone, may also drive bipolar symptom severity during the menstrual cycle, the postpartum period, and menopause (George et al., 1994; Gogos et al., 2019).

As described in section 2.2., tamoxifen's role in bipolar disorder is likely less about modulation of estrogen and more to do with its activity as a PKC inhibitor, which appears to be at least partially independent of its action at ERs (O'Brian et al., 1985). PKC is expressed within both the cortical and limbic structures and is an important regulator of neurotransmitter release, receptor regulation and neuroplasticity and gene expression (Saxena et al., 2017). Importantly, PKC activity is attenuated by the mood stabilizers lithium and valproic acid (Zarate and Manji, 2009). And while these agents influence PKC activity, tamoxifen has been billed as the only commercially available direct PKC inhibitor that is active in the central nervous system (Zarate and Manji, 2009). One of the earliest studies of tamoxifen in bipolar disorder was a single-blinded trial by Bebchuk et al., in which administration of 20–80mg/day of tamoxifen resulted in a significant reduction in manic symptoms for patients hospitalized for a manic episode (Bebchuk et al., 2000). Two subsequent randomized controlled trials (RCTs) comparing tamoxifen monotherapy (20–140mg/d) to placebo yielded a significant reduction in mania symptoms in patients treated

with tamoxifen (Yildiz et al., 2016; Zarate et al., 2007). When used as adjunctive therapy, tamoxifen has also been shown to be efficacious for reducing manic symptoms in RCTs (Amrollahi et al., 2011; Kulkarni et al., 2014, 2006). When these trials were combined in a recent meta-analysis, tamoxifen was found to have a substantial treatment effect over placebo, but with similar tolerability (Palacios et al., 2019). Importantly, all of these studies used participants across the adult lifespan, and with the exception of two (Kulkarni et al., 2014, 2006) tested tamoxifen's effects in men and women suggesting that it would be a potential treatment regardless of sex and hormonal status. It should be noted that these trials were only conducted for 4–6 weeks, so long-term effects of tamoxifen are still unknown. And no studies have yet to test tamoxifen's effects in bipolar depression. Nonetheless, these studies suggest that tamoxifen is an efficacious, well tolerated agent for the treatment of acute mania.

4.2. Schizophrenia

A potential relationship between psychosis and estrogen was first mentioned in the mid 20th century, in which a protective effect of estrogen on psychosis was hypothesized (Riecher-Rössler and Häfner, 1993). This is based on both clinical observations of sex differences in which premenopausal women seem to be protected to some extent against psychosis (Gogos et al., 2015), while an increase schizophrenia onset in women has been noted to occur closer to menopause (Häfner et al., 1993). Hormone studies of women admitted for an acute psychotic episode show decreased levels of estradiol on admission compared to controls, and symptomatic improvement with increased serum estradiol (Huber et al., 2001; Riecher-Rössler et al., 1994). The addition of exogenous estradiol in female psychotic patients improved the antipsychotic activity of previously ineffectual doses of clozapine and haloperidol (Kulkarni et al., 2008). Given that estradiol may not be appropriate for all patients, research has emerged to assess whether SERMs such as raloxifene or tamoxifen are a safer adjunctive hormonal therapy for schizophrenic psychosis. Most studies to date have focused on raloxifene as adjunctive therapy for schizophrenia, while there are no current studies on the use of tamoxifen. While some studies on raloxifene have been promising, they have also yielded mixed results in their ability to address the positive and negative symptoms of schizophrenia (Kulkarni et al., 2019). It is possible that the inconsistent results across studies are due to differing doses of raloxifene, measures, and insufficient sample sizes (Weickert and Weickert, 2017). Nonetheless, there is substantial rationale and evidence for the use of estrogen agonists in schizophrenia. However, the role of SERMs, and tamoxifen in particular, in schizophrenia requires additional study.

4.3. Substance Use Disorders

Mikelman et al (S. Mikelman et al., 2017) has proposed tamoxifen and tamoxifen analogues as potential therapeutic options for amphetamine use disorder. And it's likely that its utility would apply to other psychostimulants like cocaine, as well as non-stimulants like ethanol. As described above, tamoxifen can inhibit amphetamine-induced dopamine release and hyperlocomotion likely through its actions as both dopamine transporter inhibitor (Mikelman et al., 2018) and PKC inhibitor (Einat et al., 2007). Furthermore, tamoxifen has been found to prevent the dopamine neurotoxic effects of methamphetamine (D'Astous et al., 2005). Tamoxifen's PKC inhibitory activities may be particularly useful in amphetamine

and cocaine use disorders, as PKC inhibitors can reduce the sensitization to amphetamine's effects that are associated with increased self-administration in animals (Howell et al., 2014; Vezina, 2004). PKC inhibitors also reduce amphetamine and cocaine downregulation of D2 autoreceptors and upregulate D2 postsynaptic receptors (Namkung and Sibley, 2004; Ortinski et al., 2015). Such action would be expected to decrease the reinforcing nature of amphetamine and cocaine (Ashok et al., 2017). And indeed, a tamoxifen analog has been found to reduce amphetamine self-administration in rats (Carpenter et al., 2005). Inhibition of PKC could also reduce self-administration of ethanol (Olive et al., 2000), highlighting a potential role for tamoxifen in non-stimulant use disorders. While more research is needed, especially in humans, given the current lack of available options for substance use disorders, tamoxifen (and potential analogues) remain a promising possibility for treatment.

5. Conclusions

Tamoxifen induces clinically meaningful neuropsychiatric effects as a result of its ability to cross the brain-blood-barrier and affect both ER-dependent and non-ER dependent mechanisms. Tamoxifen's mixed ability to act as both estrogen mimetic and antiestrogen are particularly relevant in its effects on cognition, where endogenous estradiol plays a key role in maintaining cognitive ability. Tamoxifen's actions as a PKC inhibitor and dopaminergic modulator also have clinical implications, specifically for the treatment severe mental illness and substance use disorders.

Much of the pre-clinical rodent literature on tamoxifen gives the impression that it is similar to a classical partial agonist, producing effects that are dependent on levels of the endogenous ligand. Thus, in ovariectomized animals, it behaves similar to estradiol, improving cognitive performance and having anti-anxiety effects. However, in animals with intact levels of estradiol, it is an estrogen antagonist producing opposite effects.

This simple dichotomy of tamoxifen action based on hormonal status breaks down when looking at its effects on cognition in humans, especially its effects on cognition in breast cancer patients. While there is some indication that tamoxifen may have a protective effect on cognition in postmenopausal women, at least when submitted to anticholinergic challenge (Newhouse et al., 2013), the majority of evidence suggests a deleterious effect on cognition regardless of menopausal status. The lack of beneficial effects of tamoxifen on cognition in postmenopausal women may be due to the intact low levels of estradiol compared to ovariectomized animals (Koebele and Bimonte-Nelson, 2016), which result in tamoxifen acting as an antiestrogen rather than estrogen mimetic. Alternatively, tamoxifen in postmenopausal women may be similar to the effects seen with hormone replacement therapy that is initiated "outside the window" of time for potential benefit, and this may be exacerbated by the fact that breast cancer therapies on their own may induce premature menopause (Durrani and Heena, 2020). In order to better clarify tamoxifen's varied effects, future studies in animals and humans could utilize a combined dose-response strategy in which various doses of tamoxifen are studied alongside various doses of estradiol. In addition, studies evaluating the effects of tamoxifen in postmenopausal women that takes into account time from menopause onset would help support or refute the "window of opportunity" hypothesis.

While it is possible that aromatase inhibitors may have less cognitive-impairing activity than tamoxifen, aromatase inhibitors cannot be used in premenopausal breast cancer patients without concurrent ovarian suppression, limiting their utility compared to tamoxifen (Pistelli et al., 2018). As such, it is important to find ways of minimizing the potential deleterious cognitive effects of tamoxifen. While little evidence exists on interventions specific to tamoxifen-induced cognitive deficits, there is a large body of preliminary data for interventions to combat cancer-relate cognitive impairment. This includes pharmacological agents like methylphenidate and modafinil (Miladi et al., 2019), physical exercise (Campbell et al., 2020), and cognitive training and rehabilitation (Zeng et al., 2020).

Concerns about tamoxifen's effects on cognition stand in sharp contrast to its potential application in bipolar disorder, schizophrenia, and substance use disorders. In schizophrenia, there appears to be a clear rationale as well as supporting data for the use of estrogen agonists. SERMS like tamoxifen and raloxifene have some evidence both in animals and humans as promising agents for schizophrenia, however additional randomized trials are needed before they would be accepted into more widespread use. With regards to bipolar disorder and substance use disorder, tamoxifen's actions as a PKC-inhibitor and dopaminergic modulator appear to mediate its efficacy, and these are at least partially independent from its action on ERs. Randomized controlled trials in bipolar mania have been particularly promising (Palacios et al., 2019), arguing for larger and more prolonged trials. And while the data on substance use disorders remains pre-clinical and hypothetical, there is an urgent need for interventions to address the worldwide methamphetamine epidemic. As such future research should focus on translating the pre-clinical studies on tamoxifen to substance use disorders in humans. One group has already been successful in designing tamoxifen-analogues that lack tamoxifen's ER affinity but retain its DAT and PKC inhibitor qualities, and these might be particularly useful as they would avoid the complications of tamoxifen's antiestrogen/estrogen mimetic effects (Carpenter et al., 2017, 2016)

The story of tamoxifen illustrates the importance of understanding the neuropsychiatric effects of drugs that were not originally intended to act on the brain. Tamoxifen use is subject to suboptimal adherence, often due to the experience of side-effects (Sawesi et al., 2014). Acknowledging tamoxifen's potential cognitive side-effects and recommending intervention (exercise, cognitive training, pharmacological agents) may be one way to improve adherence and by extension, reduce morbidity and mortality associated with breast cancer. Simultaneously, the neuropsychiatric effects of tamoxifen has opened up research into its re-purposing for some of our most difficult to treat psychiatric disorders.

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Highlights

- Tamoxifen has both estrogen antagonist and mimetic properties in the brain.
- Tamoxifen appears to impair cognition in breast cancer patients.
- Tamoxifen has therapeutic potential for bipolar mania and substance use disorders.
- Tamoxifen's central effects may differ depending on levels of endogenous estrogens

Table 1

Simplified summary of effects of tamoxifen on various behaviors and neuropsychiatric functions in both humans and animals according to hormonal status and the hypothesized mechanism.

Neuropsychiatric function/behavior	Species	Hormonal status	Tamoxifen effects	Proposed mechanism	References
Cognition	Mice, Rats	Intact adult males and females	Impaired working memory and object recognition	Antiestrogen	Chen et al., 2002; Walker et al., 2011; Valvassori et al., 2017a, 2017b
	Mice, Rats	Ovariectomized and aged intact females	Improved working memory and spatial memory	Estrogen mimetic	Velázquez-Zamora et al., 2012; Pandey et al., 2016
	Humans	Premenopausal and postmenopausal females	Impaired verbal memory	Antiestrogen	Schilder et al., 2010; Castellon et al., 2004; Bender et al., 2006; Boele et al., 2015; Chen et al., 2014.
Depressive-like behavior	Rats	Intact adult females	Increased immobility in the forced swim test	Antiestrogen	Azizi-Malekabadi et al., 2015
	Mice	Ovariectomized	Decreased immobility in forced swim test	Estrogen mimetic	Calmarza-Font et al., 2012
	Humans	Premenopausal and postmenopausal females	No increase in depressive symptoms	–	Bender et al., 2006; Day et al., 2001; Lee et al., 2007
Anxiety-like behavior	Mice, Rats	Intact adult males and females	Decreased exploration in elevated plus maze	Antiestrogen	Li et al., 2019; Azizi-Malekabadi et al., 2015
	Mice, Rats	Ovariectomized	Increased exploration in elevated plus maze	Estrogen mimetic	Azizi-Malekabadi et al., 2015; Calmarza-Font et al., 2012
	Human	Premenopausal andpostmenopausal Females	No effect	–	Biro et al., 2019; Boele et al., 2015; Marianne Nystedt et al.,2000
Mania	Mice, Rats	Intact adult males and females	Reduction in induced hyperlocomotion	Protein kinase C inhibition	Abrial et al., 2014; Armani et al., 2012; Einat et al., 2007; Sabioni et al., 2008; Valvassori et al., 2017a, 2017b
	Humans	Males and females (all ages)	Decreased mania per standardized rating scales	Protein kinase C inhibition	Amrollahi et al., 2011; Bebchuk et al., 2000; Kulkarni et al., 2014; Palacios et al., 2019; Yildiz et al., 2016; Zarate et al., 2007
Psychosis	Rats	Ovariectomized females	Restoration of deficient sensory gating (Pre-pulse inhibition) induced by dopaminergic stimulation	Estrogen mimetic	Gogos & van den Buuse, 2015; Sbisa et al., 2018
Substance use	Rats	Intact males	Decreased amphetamine-induced dopamine efflux and decreased self-administration (tamoxifen analog)	Dopamine transporter inhibition, Protein Kinase C inhibition	Carpenter et al., 2005; Mikelman et al., 2018