

## Treatment of Depression in Patients under Breast Cancer Therapy: Antidepressant-Tamoxifen Drug Interactions

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### Abstract

The hormone therapy with tamoxifen is used in patients with breast cancer. The tamoxifen mechanism of action is based on the antagonist action of selective estrogen receptors. Depression and anxiety are psychiatric disorders which frequently coexist in patients with breast cancer. In the last decades, there has been an increase in the use of antidepressants. This literature review aims to provide a general view of pharmacokinetic knowledge of drug interactions between tamoxifen and antidepressants. Since tamoxifen is metabolized by CYP2D6, the use of antidepressants that are inhibitors of this enzyme, such as paroxetine, fluoxetine and bupropion must be avoided. Based on cytochrome p450 drug interactions, it can be concluded that the use of citalopram, escitalopram, desvenlafaxine and venlafaxine are safe and effective treatment unlikely to alter tamoxifen efficacy.

**Keywords:** Breast cancer; Tamoxifen; Antidepressant; I cytochrome p450

### Introduction

Breast cancer is a neoplasm with high incidence in women. In 2016, for example, there was an estimate of 61,000 cases of carcinoma in situ and 246,660 cases of invasive disease in the United States [1]. Breast cancer is responsible for the largest number of diagnoses and deaths in Latin America [2]. Epidemiological data collected in 2002 indicated that breast cancer was responsible for approximately 33% of all the neoplasms, and for 20% of deaths caused by cancer [3].

Hormone therapy has been used for more than 30 years with the administration of tamoxifen, a selective estrogen receptor modulator. It is probably the first targeted therapy widely used in the treatment of patients with breast cancer presenting the endocrine receptors, estrogen and progesterone [4].

Hormone therapy with tamoxifen (Figure 1) is used in patients with breast cancer that has been early detected and which can be surgically removed, as well as in patients with metastatic breast cancer. The use of tamoxifen brings both risks and benefits. One example is that its use can increase the risk of endometrial cancer [5].

Tamoxifen was developed in the 1970s and is currently prescribed for estrogen receptor-positive breast cancer. The tamoxifen mechanism of action is based on the antagonist action of selective estrogen receptors in the tissues, on its interaction with estrogen receptor, and these properties encompass a certain level of molecular and functional complexity [6]. However, tamoxifen may act as an agonist in the endometrial hyperplasia and the production of polyps, possibly with a higher risk of endometrial cancer [7]. Tamoxifen should be used in patients with estrogen receptor-positive or progesterone receptor-positive tumors. In such cases, an adjuvant endocrine therapy should be used after the primary therapy. Tamoxifen and aromatase inhibitors are the drugs used in the adjuvant therapy. The treatment with tamoxifen is supposed to last for 5 years [8].

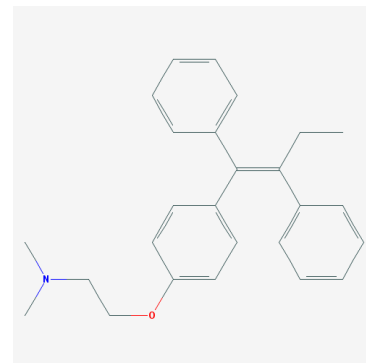


Figure 1: Tamoxifen.

### Tamoxifen Metabolism

Tamoxifen is a prodrug that needs to be metabolized to become pharmacologically active. Tamoxifen produces three main active metabolites. It is converted into N-desmethyltamoxifen by CYP 3A4 and 3A5, which is then converted into 4-hydroxy-N-desmethyltamoxifen (endoxifen) by cytochrome P450 2D6 (CYP2D6). Tamoxifen is also converted into 4-hydroxy tamoxifen by CYP2D6 and, afterwards, into endoxifen by CYP 3A4 and 3A5. The 4-hydroxy tamoxifen metabolite is 100 times stronger as an anti-estrogen agent than tamoxifen and N-desmethyltamoxifen. Endoxifen is equivalent to 4-hydroxy tamoxifen regarding its strength, but its concentrations in the stationary phase are 6 to 10 times higher than that of the latter. Endoxifen is also 30 to 100 times stronger than tamoxifen as an inhibitor of cell proliferation [9].

The CYP genes are polymorphic resulting in variable enzyme activity. Retrospective clinical data suggests that specific Single Nucleotide Polymorphisms (SNPs) of CYP2D6 can lead to null or reduced enzyme activity resulting in worse outcomes for those individuals when treated with tamoxifen for HR positive breast cancer. Antidepressant drugs have also been used to manage tamoxifen induced hot flushes. These drugs potentially inhibit the metabolism of tamoxifen by CYP2D6 and thus potentially may lessen the efficacy of tamoxifen. The genetic variations in other enzymes involved in tamoxifen metabolism (CYP3A, CYP2B6, CYP2C19) do not appear to cause any meaningful difference in the efficacy of tamoxifen [10]. Individualization of patients by genotyping them would be a fine way to improve their quality of life.

Patients diagnosed with cancer suffer from some psychiatric comorbidity, depression being one of the main complications. It may even be a condition existing prior to a cancer diagnosis. Recent studies estimate a 31.8% incidence of some kind of mental disorder in patients with cancer. Doctors often underdiagnose this pathology in patients with neoplasms. When not treated, this pathology is proved to be linked to a larger number of hospitalizations [11].

It has been estimated that 30% of patients with breast cancer suffer from depression [12]. Here are some factors that may influence the development of depression in these patients: Socioeconomic status, social support, recent losses, and the patient's perception of the disease. Besides, the psychological impact of the disease itself is already an important factor for the development of psychiatric comorbidities [3].

Nowadays, the treatment of depression has become more frequent. Studies estimate that the number of antidepressant prescriptions has tripled in the last 30 years. However, the choice of medication must be a careful one. Antidepressants will target the symptoms of depression, but besides the side effects, they may interact with several drugs; for example, selective serotonin reuptake inhibitors may reduce the efficacy of tamoxifen [11].

As previously mentioned, tamoxifen is metabolized by cytochrome P 450, primarily by the CYP2D6 enzyme. Some drugs, such as the SSRIs, are also metabolized by cytochrome P 450, with possible drug interaction and lower endoxifen serum levels, therefore changing the efficacy of tamoxifen [13]. Antidepressants such as paroxetine, fluoxetine and bupropion are strong inhibitors of CYP2D6, and their use must be avoided in patients taking tamoxifen. Both fluvoxamine and nefazodone inhibit CYP3A, which might have the potential to affect the tamoxifen metabolism [14]. Sertraline and duloxetine are moderate inhibitors of CYP2D6 [15]. Venlafaxine, escitalopram and citalopram are weak inhibitors of CYP2D6, with little effect on the metabolism of tamoxifen [15,16].

Desvenlafaxine is not metabolized by the P450 system, therefore being a safe option. Although mirtazapine has not been extensively studied, existing data suggest there is a minimum effect on CYP2D6 [16].

The strong interaction between tamoxifen and strong inhibitors of CYP2D6, including several antidepressants, has been influencing the choice and prescription of antidepressants. A recent study has shown that among women who take tamoxifen and antidepressants, 34% took strong inhibitors of CYP2D6 between 2004 and 2006, against 15% in 2010. The use of weak inhibitors increased from 32% between 2004 and 2006 to 52% in 2010[17].

A systematic review of pharmacological and psychotherapeutic clinical trials on the major depressive disorder in cases of breast cancer has shown scarce data available to guide doctors in their decisions of what treatment to adopt. Therefore, the treatment of depression in cases of breast cancer is based mainly on the clinical experience [18].

After decades of research on tamoxifen, its use together with serotonin reuptake inhibitors is still controversial. Observational studies show little evidence that the use of antidepressants is associated with adverse outcomes in women taking tamoxifen [19,20].

To conclude, the treatment of depression in women with breast cancer must avoid antidepressants that inhibit the CYP2D6, including fluoxetine, duloxetine, bupropion, and especially, paroxetine. Citalopram, escitalopram and venlafaxine are weaker inhibitors and, therefore, reasonable alternatives. Desvenlafaxine is not metabolized by the P450 system and is, consequently, a safe option.

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