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Tamoxifen and serotonin reuptake inhibitors: Risks and benefits of co-administration

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Abstract

Tamoxifen citrate is a nonsteroidal compound belonging to the triphenylethylene class, characterized by a complex spectrum of pharmacological effects, acting as an estrogen antagonist or agonist depending on the tissue. In breast cancer patients, tamoxifen predominantly exerts an anti-estrogenic action on tumor tissue by inhibiting the binding of estrogen to its receptors. Tamoxifen is metabolized in the liver by the cytochrome P450 enzymatic system, resulting in active metabolites. The CYP2D6 enzyme plays a crucial role in the metabolism of approximately 25% of exogenous drugs, including tamoxifen, being considered the primary enzyme involved in the bioactivation of this therapeutic agent. This study aims to understand the metabolism of tamoxifen mediated by the cytochrome P450 system, particularly CYP2D6, which is essential for optimizing its clinical use and allowing treatment personalization based on the patient's individual metabolic profile. This literature review was conducted through the analysis of articles published in the last five years or of significant impact in the field, focusing on drug interactions and the management of depressive symptoms during oncological treatment. Measures are essential to mitigate the risks associated with drug interactions. Some studies recommend reviewing pharmacotherapy, considering not only antineoplastic drugs but also complementary, alternative therapies and the use of over-the-counter medications to reduce the number of substances administered. Furthermore, the early identification of potential interactions is crucial, enabling appropriate and proactive clinical management. Thus, an in-depth understanding of CYP2D6 pharmacogenomics and the adoption of evidence-based clinical strategies are indispensable for optimizing tamoxifen treatment, preserving its efficacy, and minimizing the risks associated with drug interactions

Keywords: Tamoxifen; Drug interaction; Selective serotonin reuptake inhibitors; Breast cancer

1. Introduction

Tamoxifen citrate is a nonsteroidal compound belonging to the triphenylethylene class, characterized by a complex spectrum of pharmacological effects, acting as an estrogen antagonist or agonist depending on the tissue. In breast cancer patients, tamoxifen predominantly exerts an anti-estrogenic action on tumor tissue by inhibiting the binding of estrogen to its receptors (BLAU FARMACÊUTICA, 2017).

In cases of estrogen receptor-positive or unknown status breast tumors, adjuvant treatment with tamoxifen has demonstrated a significant reduction in disease recurrence, as well as a 10-year survival increase. This benefit is considerably greater when the drug is administered for 5 years compared to shorter periods, such as 1 or 2 years (BLAU FARMACÊUTICA, 2017).

Tamoxifen is a widely used anti-estrogenic agent in the management of breast cancer, indicated both for the treatment of localized tumors and for chemoprevention in women at high risk for this neoplasia. This drug is often used as systemic

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adjuvant therapy, especially after surgical procedures or conventional chemotherapy (ALVES, TAVARES & BORGES, 2020).

Its mechanism of action is based on the competitive inhibition of estrogen receptors in various target tissues. By blocking these binding sites, tamoxifen prevents the activation of estrogen-dependent intracellular pathways, such as RNA synthesis and proteins essential for cell proliferation. This effect results in tumor growth suppression and a reduced risk of metastasis development (ALVES, TAVARES & BORGES, 2020).

Tamoxifen is metabolized in the liver by the cytochrome P450 enzymatic system, resulting in active metabolites. The enzymes CYP3A4 and CYP2D6 play crucial roles in this process. CYP3A4 is responsible for the N-demethylation of tamoxifen, forming N-desmethyltamoxifen, while CYP2D6 catalyzes the hydroxylation into 4-hydroxytamoxifen and the conversion of N-desmethyltamoxifen into endoxifen. These metabolites, especially 4-hydroxytamoxifen and endoxifen, exhibit significantly higher affinity for estrogen receptors and are considered the primary contributors to tamoxifen's therapeutic efficacy in breast cancer treatment (OLIVEIRA et al., 2024).

The CYP2D6 gene stands out as the most polymorphic among cytochrome P450 enzyme genes responsible for the metabolism of exogenous compounds, with over 100 allele variants already identified. The CYP2D6 enzyme plays a crucial role in the metabolism of approximately 25% of exogenous drugs, including tamoxifen, and is considered the primary enzyme involved in the bioactivation of this therapeutic agent (BORBA, 2016).

Tamoxifen, in turn, presents an extensive drug interaction profile, with a total of 460 described interactions, 132 of which are classified as severe, potentially compromising therapeutic efficacy or increasing the risk of significant adverse events (ALVES, TAVARES & BORGES, 2020).

Antidepressants with mechanisms of action based on selective serotonin reuptake inhibition (SSRIs) exhibit a high potential to inhibit the CYP2D6 isoenzyme. This drug class includes medications such as fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, and sertraline. In clinical practice, these medications are often chosen as the first-line treatment for depressive disorders due to their efficacy and safety profile (COSTA, COSTA & BARBOSA, 2023).

A cancer diagnosis is often associated with depression, with studies indicating that approximately 12.9% of patients develop depressive symptoms after diagnosis. The prevalence of depression is higher in women compared to men, with an association of 16.4% between cancer and depression in women and 8.6% in men.

Additionally, patients undergoing treatment with tamoxifen may experience early menopause symptoms due to the anti-estrogenic effect of the medication. To mitigate these symptoms, certain antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), including paroxetine, are commonly prescribed (COSTA, COSTA & BARBOSA, 2023). Therefore, understanding the metabolism of tamoxifen mediated by the cytochrome P450 system, particularly by CYP2D6, is essential for optimizing its clinical use and enabling personalized treatment based on the patient's individual metabolic profile

2. Methodology

This literature review aims to analyze the side effects of tamoxifen, its drug interactions with selective serotonin reuptake inhibitors (SSRIs), and the relationship between breast cancer and depression. The research was conducted through the analysis of articles published in the last five years or those with significant impact in the field, focusing on drug interactions and the management of depressive symptoms during oncological treatment. Data collection was carried out from recognized academic and scientific sources.

The article search was conducted in various academic and scientific information sources, including professional drug leaflets and pharmacology books; LILACS (Latin American and Caribbean Literature in Health Sciences); PubMed; Google Scholar.

The search utilized the following descriptors, in both Portuguese and English, to ensure the comprehensiveness of the articles found: Tamoxifen; Side effect; Drug interaction with SSRIs; Selective serotonin reuptake inhibitors (SSRIs); Breast cancer; Depression. These descriptors were selected based on the main topics addressed in the study, enabling the location of articles discussing the side effects of tamoxifen, its interactions with SSRIs, and the relationship between breast cancer and depression.

Inclusion criteria were: Articles published in the last five years or with significant impact in the research field; Studies addressing drug interactions between tamoxifen and SSRIs, especially in the context of patients with breast cancer and depression; Peer-reviewed articles, academic books, and professional drug leaflets; Studies discussing tamoxifen's side effects, focusing on depressive symptoms and early menopause.

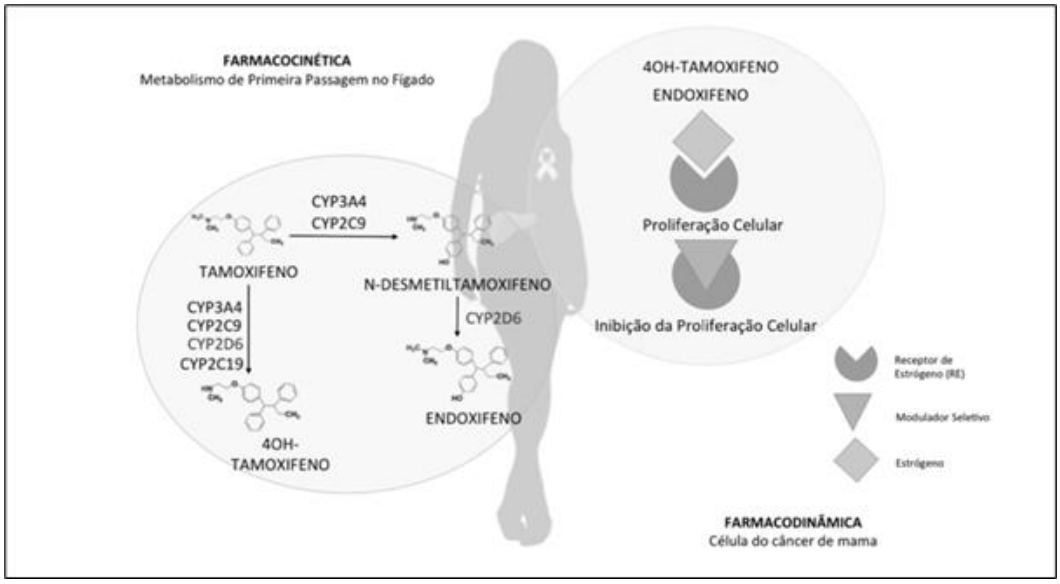
The extracted information was synthesized and presented in a structured manner, highlighting the most relevant findings for clinical practice and proposing possible strategies for managing drug interactions and treatment.

3. Literature Review

The endocrine treatment of breast cancer is the standard therapeutic approach for tumors that are positive for estrogen receptors (ER+), consisting of: (i) ovarian ablation; (ii) selective estrogen receptor modulators, which block estrogen's action on the tumor; and (iii) aromatase inhibitors, which inhibit an enzyme essential for estrogen production. However, tamoxifen, a selective estrogen receptor modulator, is widely used as the primary therapeutic option in the endocrine treatment of breast cancer (BORBA, 2016).

Tamoxifen is an antiestrogenic agent widely employed in the management of breast cancer, being indicated both for the treatment of localized tumors and for chemoprophylaxis in women at high risk for this neoplasm. This drug is frequently used as a systemic adjuvant therapy, especially after surgical procedures or conventional chemotherapy (ALVES, TAVARES & BORGES, 2020).

Tamoxifen is metabolized in the liver by the cytochrome P450 enzyme system, resulting in active metabolites. The enzymes CYP3A4 and CYP2D6 play crucial roles in this process. CYP3A4 is responsible for the N-demethylation of tamoxifen, forming N-desmethyltamoxifen, while CYP2D6 catalyzes the hydroxylation to 4-hydroxytamoxifen and the conversion of N-desmethyltamoxifen into endoxifen. These metabolites, especially 4-hydroxytamoxifen and endoxifen, have a significantly higher affinity for estrogen receptors and are considered the primary contributors to tamoxifen's therapeutic efficacy in the treatment of breast cancer (OLIVEIRA et al., 2024).



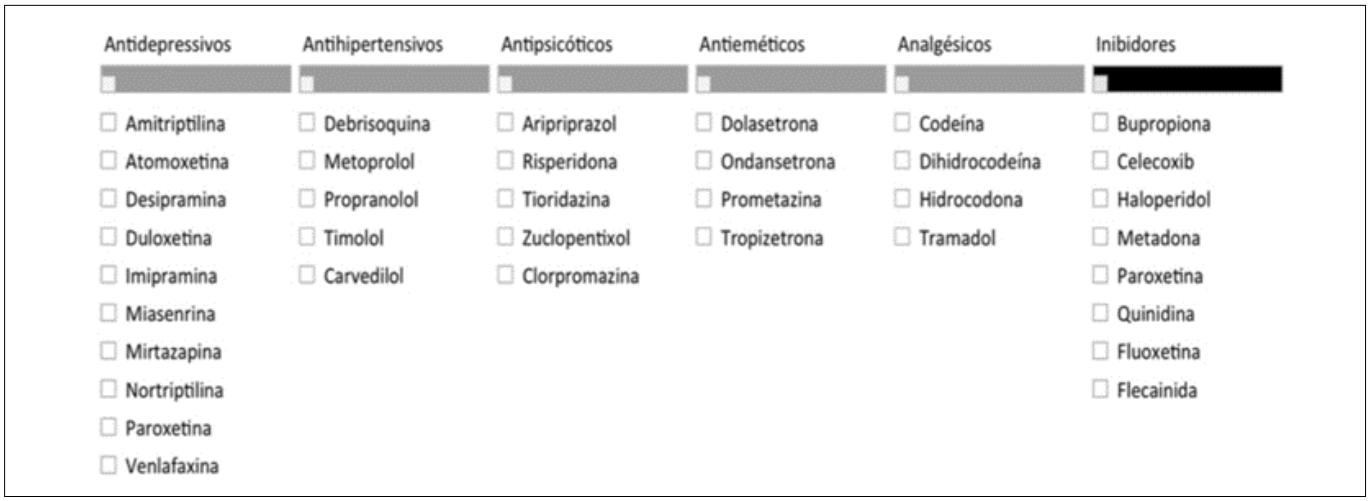
Source: BORBA, 2016.

Figure 1 Tamoxifen Metabolism

Between 30% and 50% of patients treated with tamoxifen develop some level of resistance, failing to achieve the expected response. Resistance to endocrine treatment can be caused by various mechanisms, which can be classified into three main categories: (i) alterations in the drug target, i.e., the estrogen receptor (ER); (ii) changes in the second messengers of the pathway signaled by the ER; and (iii) defects in the drug metabolism (OLIVEIRA et al., 2024).

In the pharmacogenomics of breast cancer, polymorphisms in the CYP2D6 gene have been identified as emerging biomarkers for predicting the efficacy of endocrine treatment. Although the expression of CYP2D6 is relatively low compared to other cytochrome P450 enzymes, it plays a crucial role in metabolizing up to 25% of clinically used drugs.

Among its substrates are various therapeutic classes, such as antiarrhythmics, antidepressants, antipsychotics, beta-blockers, analgesics, and antineoplastics. Therefore, polypharmacy, the concomitant use of multiple drugs, should be considered as a relevant environmental factor that can interfere with CYP2D6 activity. The phenomenon of phenoconversion, which refers to the loss of metabolism capability, may occur even without the presence of genetic polymorphisms. CYP2D6 phenoconversion usually happens due to the simultaneous administration of substrates and inhibitors of this enzyme (OLIVEIRA et al., 2024; BORBA, 2016).



Source: BORBA, 2016.

Figure 2 Substrates and inhibitors of CYP2D6

Selective serotonin reuptake inhibitors (SSRIs) were introduced to the pharmaceutical market in 1987 with the launch of fluoxetine hydrochloride, marketed under the Prozac® brand by Eli Lilly. This new class of antidepressants was quickly adopted in clinical practice due to its therapeutic efficacy and significant safety profile compared to the antidepressants available at the time. From that point on, SSRIs became the first-line therapeutic option in the treatment of depressive disorders (COSTA, COSTA & BARBOSA, 2023).

SSRIs, which have a mechanism of action based on the selective inhibition of serotonin reuptake, have a high potential to inhibit the CYP2D6 isoenzyme. This class of drugs includes medications such as fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, and sertraline. In clinical practice, these drugs are often chosen as first-line treatments for depressive disorders due to their efficacy and safety profile (COSTA, COSTA & BARBOSA, 2023).

Selective serotonin reuptake inhibitors (SSRIs) are widely used in patients diagnosed with breast cancer, both for the treatment of depressive episodes and for managing vasomotor symptoms and other menopause-like signs often observed during treatment with tamoxifen, due to its antiestrogenic effect (COSTA, COSTA & BARBOSA, 2023).

It is recommended not to combine tamoxifen with potent CYP2D6 inhibitors. When antidepressant use is necessary, medications with minimal inhibitory action on this enzyme should be preferred. According to the study by Lammers et al. (2010), the CYP2D6 phenotype is crucial for predicting therapeutic outcomes in patients treated with tamoxifen for metastatic breast carcinoma. The co-administration of CYP2D6 inhibitors may compromise tamoxifen's efficacy, requiring careful monitoring in the management of these patients (OLIVEIRA et al., 2024).

The choice of antidepressant medications in the treatment of breast cancer patients can significantly influence the survival of patients using tamoxifen. The analysis of this interaction is based on the function of the CYP2D6 enzyme, responsible for the metabolic activation of tamoxifen, and various frequent drug interactions, often overlooked, can be avoided. The use of tamoxifen is essential in the treatment of patients with hormone receptor-positive breast cancer, regardless of age or disease stage. Therefore, when co-prescribing tamoxifen with antidepressants, it is crucial to exercise caution in choosing medications, preferring those that have low or no inhibition of the CYP2D6 enzyme, so as not to compromise the treatment's efficacy (OLIVEIRA et al., 2024).

Approximately 25% of patients with breast cancer develop depressive disorders after diagnosis, and half of these patients require psychotropic medication. Selective serotonin reuptake inhibitors (SSRIs) are commonly used in the treatment of these cases. These drugs are metabolized by the CYP2D6 enzyme of the cytochrome P-450 system, and

studies indicate that the co-administration of SSRIs with tamoxifen may reduce the formation of tamoxifen's active metabolites, compromising its therapeutic action and, consequently, increasing the risk of breast cancer recurrence (COSTA, COSTA & BARBOSA, 2023).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have the ability to inhibit the CYP2D6 enzyme to varying degrees. Drugs such as paroxetine and fluoxetine are known to be potent inhibitors of CYP2D6, which can lead to a significant reduction in the production of endoxifen and, consequently, impair clinical outcomes in patients undergoing tamoxifen treatment. On the other hand, medications such as venlafaxine and escitalopram are considered safer options for these patients, as they inhibit CYP2D6 in a more moderate manner, resulting in a partial decrease in endoxifen concentrations without severely compromising tamoxifen's efficacy (OLIVEIRA et al., 2024).

Measures are essential to mitigate the risks associated with drug interactions. Some studies recommend reviewing pharmacotherapy, considering not only antineoplastic drugs but also complementary therapies, alternative treatments, and the use of over-the-counter medications, with the aim of reducing the number of substances administered. Furthermore, early identification of potential interactions is critical for appropriate and prospective clinical management. The implementation of interdisciplinary actions, involving healthcare professionals from various fields, is also crucial for optimizing patient care (LOBO et al., 2021).

4. Conclusion

The treatment of hormone receptor-positive breast cancer with tamoxifen is an essential therapeutic approach, providing significant benefits in reducing tumor recurrence and increasing long-term survival. However, the efficacy of this drug is intrinsically linked to the metabolism mediated by CYP2D6, which converts tamoxifen into its active metabolites, primarily endoxifen. Thus, drug interactions that alter CYP2D6 activity, such as those associated with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), represent a considerable clinical challenge.

Studies show that potent antidepressants that inhibit CYP2D6, such as fluoxetine and paroxetine, compromise the bioactivation of tamoxifen, reducing its therapeutic efficacy and increasing the risk of cancer recurrence. On the other hand, antidepressant agents with less impact on CYP2D6, such as venlafaxine and escitalopram, represent safer options for patients using tamoxifen, allowing proper management of depressive and vasomotor symptoms without compromising oncological outcomes.

The high prevalence of depression in breast cancer patients and the symptoms related to early menopause induced by treatment highlight the importance of an interdisciplinary approach, integrating oncologists, psychiatrists, and pharmacologists. This collaboration is essential for the careful selection of drugs and the early identification of potential drug interactions, ensuring personalized and effective therapeutic management.

Thus, a deep understanding of the pharmacogenomics of CYP2D6 and the adoption of evidence-based clinical strategies are essential for optimizing tamoxifen treatment, preserving its efficacy, and minimizing the risks associated with drug interactions. These advances underscore the need for clinical policies that prioritize pharmacological monitoring and continuous education for healthcare professionals, ensuring the quality of life and safety of patients undergoing cancer treatment.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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