Vol 7 | Issue 1 | Pages 172-174

Journal of Healthcare

ISSN: 2689-8942

Review Article

DOI: 10.36959/569/478

Pharmacogenomics of Tamoxifen: A Review

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Abstract

Tamoxifen is a first-line endocrine treatment of estrogen receptor-positive breast cancer, which is commonly used both in treatment and prevention. Although this treatment is proven to be effective, interindividual variability in treatment response is significant and can result in tumour regression, disease recurrence, or drug-related side effects. The analysis of the relationship between genetic variation, drug response, and metabolism has created a vital tool for understanding this dynamic: pharmacogenomics. Tamoxifen is a prodrug that must be metabolised to the active metabolites 4-hydroxytamoxifen and endoxifen to be therapeutically effective [1,2]. Genetic polymorphisms also influence CYP enzyme activity, altering plasma concentrations of metabolites and drug efficacy. Though CYP2D6 is a widely investigated enzyme that forms endoxifen, other enzymes, including CYP3A4, CYP3A5, and CYP1B1, may also contribute to inter-individual differences in tamoxifen metabolism and clinical outcomes [3,4]. The paper presents a summary of the pharmacogenomics of tamoxifen, CYP2D6, and CYP1B1, including their polymorphisms, clinical significance, and implications for individualised treatment of breast cancer patients.

Introduction

Breast cancer is the most frequently diagnosed malignancy among women globally and is a significant cause of death due to cancer that claims more than 370,000 lives around the globe annually [5]. Out of all breast cancer cases, it is observed that the estrogen receptor positive tumours are about 70 per cent of the total cases, thus the significance of endocrine therapy in the treatment. Tamoxifen is an adjuvant, neoadjuvant, and preventive treatment that is a selective estrogen receptor modulator (SERM) and has been used for decades [6,7]. Research studies have shown that tamoxifen is an effective anti-recurrence drug and increases the overall survival of women with estrogen receptor-positive cancer by almost 40 per cent [8].

The efficacy of tamoxifen therapy varies widely among patients. Some develop long-term remission and complete tumour regression, and those that become recurrent with the disease or unresponsive. Additionally, adverse effects such as hot flushes, endometrial alterations, and thromboembolic events may hinder adherence and thereby affect treatment outcomes [9]. Traditional clinical factors, such as tumour stage, grade, and hormone receptor status, could not entirely explain the variability. This observation has led to the study of host genetic factors, particularly pharmacogenomics, as potential contributors to tamoxifen's efficacy and toxicity [10].

Pharmacogenomics is the study of the effect of genetic polymorphism on drug-metabolising enzymes, transporters, and targets on the pharmacokinetics and pharmacodynamics of therapeutic agents. Pharmacogenomic studies of tamoxifen therapy have mainly focused on cytochrome P450 (CYP) enzymes involved in the metabolism of tamoxifen into active metabolites, which are key to its anti-estrogenic effect [11]. Knowledge of the impact of genetic variation on tamoxifen metabolism can be used to identify patients at higher risk of treatment failure or adverse events and to guide individualised treatment approaches.

Tamoxifen Pharmacogenomics

Tamoxifen as a prodrug

Tamoxifen is given in the form of a prodrug, which has

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Accepted: September 18, 2026

Published online: September 24, 2026

Citation: Naji ZH, Sahib AS, Mousa HM, et al. (2026) Pharmacogenomics of Tamoxifen: A Review. J Healthcare 7(1):172-174

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to be metabolically activated to form estrogen receptor high-affinity compounds. The anti-estrogenic activity of tamoxifen is 30-100 times less potent than the anti-estrogenic effect of the two primary active metabolites, 4-hydroxytamoxifen and endoxifen [12,13]. The synthesis of these metabolites is strongly dependent on liver cytochrome P450 enzymes, which catalyse several oxidation reactions. The variability of these enzymatic pathways can thus directly affect systemic exposure to active metabolites, thereby impacting therapeutic efficacy.

Endoxiben and CYP2D6 In vivo formation

The primary enzyme involved in the transformation of N-desmethyltamoxifen to endoxifen, the most potent metabolite of anti-estrogenic activity. CYP2D6 forms four main metabolizer phenotypes, including poor, intermediate, extensive, and ultra-rapid metabolizers, which result from polymorphisms [14,15]. Persons with poor metabolizer status have much lower endoxifen concentrations, which can decrease the effectiveness of tamoxifen. Research has indicated that poor metabolizers are at greater risk of relapse, but results have been inconsistent across groups.

The poor metabolizers of CYP2D6 depend on ethnicity, with a range of 5-10 per cent of Caucasians to 30 per cent in certain people of Asia. These disparities underscore the importance of population genetics in pharmacogenomic-based therapy [16]. Moreover, the poor metabolizer phenotype may also be replicated through concomitant use of potent CYP2D6 inhibitors, including some selective serotonin reuptake inhibitors (SSRIs), which exacerbates therapy [17].

Other phase I and phase II enzymes

Although CYP2D6 is the key enzyme, other Phase I enzymes also contribute to tamoxifen metabolism. CYP3A4 and CYP3A5 first metabolise tamoxifen to N-desmethyltamoxifen, and CYP2C9 and CYP2C19 then further metabolise it. The genetic differences in these enzymes may also alter metabolite ratios, affecting pharmacokinetics and potentially the clinical outcome.

Conjugation reactions catalysed by phase II metabolising enzymes, such as UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs), mediate the removal of tamoxifen metabolites. They are polymorphic genes that can alter the drug clearance, systemic exposure, and toxicity. The combination of these results indicates that tamoxifen pharmacokinetics is a complex interaction of several genes.

Clinical evidence and controversy

Although there is strong evidence of a genotype-outcome association between CYP2D6 genotype and endoxifen plasma concentration, inconsistencies have been noted in clinical studies examining genotype-outcome relationships. In some trials, recurrence rates were much higher in poor metabolizers, whereas others have not shown a clear correlation with either disease-free or overall survival. Some of the causes of these differences include small sample sizes, differences in study populations, ethnic differences, and inconsistent definitions of clinical endpoints.

Given these discrepancies, CYP2D6 genotyping should not be performed routinely. Nevertheless, multi-gene models that include other enzymes involved in metabolism are under consideration as more predictive of tamoxifen response [18]. These models have the potential to support personalised medicine practices, enabling individualised dosage regimens and improved prognostication.

CYP1B1 and Tamoxifen Pharmacogenomics Role

Introduction to CYP1B1

Cytochrome P450 1B1 (CYP1B1) is a Phase I enzyme found in extrahepatic tissues, such as breast epithelium and tumours, suggesting it may play a role in local drug clearance. In contrast to CYP2D6, which is largely hepatically active, CYP1B1 could regulate tamoxifen action at the tissue level, thereby influencing intratumoral levels of active metabolites.

CYP1B1 and estrogen metabolism

CYP1B1 is an enzyme which hydroxylates estradiol in order to produce 4-hydroxyestradiol, an estrogenic and highly toxic metabolite. These metabolites may cause DNase damage and facilitate signalling via the estrogen receptor, thereby affecting tumour progression. The altered activity of CYP1B1 could thus affect tumour biology and the efficacy of tamoxifen, thereby making the enzyme relevant to pharmacogenomic research.

CYP1B1 Polymorphisms

CYP1B1 has several functional polymorphisms, including rs1056827 (Leu432Val), Rs10012 (Arg48Gly), and rs1800440 (Asn453Ser). These forms affect enzyme activity and substrate specificity, estrogen metabolism, and, potentially, tamoxifen metabolism locally. Allele frequencies are diverse among populations, and this is one of the causes of ethnic disparities in breast cancer susceptibility and response to treatment.

Tamoxifen metabolism and CYP1B1.3.4 CYP1B1

Although CYP1B1 is not the major hepatic enzyme involved in tamoxifen activation, there is some evidence that it may be a local contributor to drug metabolism in tumours. Intratumoral CYP1B1 activity may affect the levels of active and inactive tamoxifen metabolites at the field of action, which may alter the estrogen receptor signalling and response to therapy.

Clinical evidence

There have been conflicting findings on clinical studies investigating the CYP1B1 polymorphisms in patients treated with tamoxifen. At the same time, others showed no significant effects. Some have been linked to disease recurrence or differences in survival. These differences may be attributable to variation in the study design, sample size, ethnic background, and interplay with other metabolism-related genes.

CYP 1B1 and tamoxifen resistance

CYP1B1 can increase tamoxifen resistance in several ways,

including increasing the production of estrogen-derived carcinogens and altering drug metabolism in the tumour [19]. High CYP1B1 levels have been associated with a poor prognosis and low response to endocrine therapy, which highlights its possible role in resistance mechanisms.

Clinical implications and future directions 3.7

Though CYP1B1 genotyping is not currently recommended, its inclusion in pharmacogenomic multi-gene models can enhance the prediction of tamoxifen response [20]. Large, ethnically diverse populations and standardised clinical endpoints should also be considered in future research to elucidate the clinical relevance of CYP1B1 polymorphisms better. The use of CYP1B1 data, in combination with other metabolic pathways, can enhance personalised medicine in tamoxifen therapy.

Conclusion

The pharmacogenomics of tamoxifen is a complex domain that involves several genes that affect its metabolism and response. The most investigated enzyme is CYP2D6, which appears to affect endoxifen plasma concentrations, but there are no consistent clinical findings regarding outcomes. CYP1B1 is a biologically relevant factor that can account for interindividual variation because it affects intratumoral estrogen and tamoxifen metabolism.

Knowledge of genetic differences in these and other enzymes has the potential to guide personalised treatment, optimise tamoxifen dosing, reduce adverse effects, and improve clinical outcomes. To translate these findings into clinical practice, multi-gene pharmacogenomic models, prospective studies, and integration with clinical and tumour-specific data will be mandatory and will eventually enhance the accuracy of breast cancer treatment.

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DOI: 10.36959/569/478

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