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Tamoxifen Therapy and *CYP2D6* Genotype

Laura Dean, MD
NCBI
dean@ncbi.nlm.nih.gov

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Tamoxifen is a selective estrogen receptor modulator (SERM) which is used in the treatment and prevention of breast cancer ([1]).

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, and is one of the main enzymes responsible for converting tamoxifen into its active metabolites. Individuals who carry two nonfunctioning copies of *CYP2D6* are known as poor metabolizers. Individuals who carry one or two decreased activity alleles are referred to as intermediate metabolizers. Importantly, there are also heterozygous individuals who carry one inactive or decreased function allele in combination with a functional allele. These individuals have decreased CYP2D6 activity and for simplicity are frequently included in the "intermediate metabolizer group". Individuals with decreased capacity to metabolize tamoxifen may benefit less from tamoxifen therapy.

At this time, the FDA-approved drug label for tamoxifen does not discuss genetic testing for CYP2D6. The National Comprehensive Cancer Network (NCCN) does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy, and this recommendation is consistent with the guidelines from the American Society of Clinical Oncology (ASCO) ([2, 3]). In contrast, the Dutch Pharmacogenetics Working Group has made recommendations for tamoxifen therapy based on *CYP2D6* genotypes (Table 1) ([4]).

Table 1.

CYP2D6 phenotypes and the therapeutic recommendations for tamoxifen therapy

Phenotype	Genotype	Therapeutic recommendation for tamoxifen
Ultrarapid metabolizer	More than two copies of functional alleles	None
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or one decreased activity allele and one inactive allele	Increased risk for relapse of breast cancer. Avoid concomitant use of CYP2D6 inhibitors. Consider aromatase inhibitor for postmenopausal women
Poor metabolizer	Two inactive alleles	Increased risk for relapse of breast cancer. Consider aromatase inhibitor for postmenopausal women

The strength of the tamoxifen therapeutic recommendations scored a maximum of 4/4 (the highest quality of evidence). Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89([5]):662–73 ([4]).

Table 2.

Activity status of *CYP2D6* alleles

Allele type	Alleles
Active	**1, *2, *33, *35*
Decreased activity	****9, *10, *17***, **29, *36,* ****41***
Inactive	****3, *4, *5, *6, *7***, **8, *11-*16, *19-*21, *38, *40, *42*

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Note: The most clinically significant variants are highlighted in bold.

Drug: Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) that is used in the treatment and prevention of breast cancer. In both men and women, tamoxifen is used to treat metastatic breast cancer—patients with tumors that are estrogen receptor positive (ER+) are more likely to benefit. In post-menopausal women with breast cancer, tamoxifen is used as an adjuvant treatment following surgery and radiation—patients with four or more positive axillary nodes may benefit the most. And tamoxifen is also used to prevent breast cancer in women who have an increased risk, and to reduce the risk of invasive breast cancer in women with ductal carcinoma in situ (DCIS) ([1]).

Tamoxifen acts on the estrogen receptor (ER) and has both estrogenic and anti-estrogenic actions, depending on the target tissue. In the breast tissue, it acts as an anti-estrogen (inhibitory effect) and competitively inhibits cancerous ER+ cells from receiving the estrogen they need to grow ([5, 6]).

In other tissues, such as the endometrium, tamoxifen acts as an estrogen agonist (stimulatory effect) leading to some of the adverse effects associated with tamoxifen therapy. These include endometrial hyperplasia, endometrial polyps, and about a 2.5 times higher risk of developing endometrial cancer. Hot flashes are the most common side effect associated with tamoxifen use, which affect up to 80% of women, and there is also an increased risk of depression and thromboembolism ([5, 7]).

Tamoxifen is a pro-drug that is metabolized in the liver to active metabolites. Tamoxifen is metabolized by numerous cytochrome P450 (CYP) drug metabolizing enzymes including CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP3A4, and CYP3A5. The metabolites 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen) are thought to be mainly responsible for the clinical effects of tamoxifen. Both of these metabolites have about a 100-fold higher affinity for the ER compared to tamoxifen, but endoxifen is thought to be the major metabolite because plasma levels of endoxifen tend to be several-fold higher than that of 4-hydroxytamoxifen ([5, 8]). Endoxifen formation mainly occurs via the conversion of the inactive primary metabolite N-desmethyltamoxifen by CYP2D6.

The mechanism of action of tamoxifen is complex and involves tamoxifen metabolites binding to the ER and inducing a conformational change that blocks or changes the expression of estrogen-dependent genes. It is also likely that tamoxifen interacts with other protein cofactors (both activators and repressors), and binds with different estrogen receptors (ER-alpha or ER-beta), to produce estrogenic and anti-estrogenic effects in different tissues. Certain tamoxifen metabolites such as norendoxifen have also been found to act as aromatase inhibitors in vitro (albeit at high concentrations)—decreasing the amount of estrogen available by inhibiting the conversion of steroids to estradiol ([9]).

The response to tamoxifen (i.e., clinical efficacy and side effects) varies widely between individuals; this may be partly caused by differences in metabolism because of variations in genes such as *CYP2D6* ([10]).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The *CYP* genes are often polymorphic and can result in reduced, absent, or increased drug metabolism.

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CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. The *CYP2D6* gene is highly polymorphic—more than 100 alleles have been described ([11]).

*CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the normal "extensive metabolizer" phenotype. The *CYP2D6* alleles **2*, **33*, and **35* are also considered to have near-normal activity. Other alleles include variants that produce a non-functioning enzyme (e.g., **3*, **4*, **5,* and **6*) ([12-15]) or an enzyme with reduced activity (e.g., **10*, **17*, and **41*) ([16-18]) (see Table 2). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6,* and **41* being more common in the Caucasian population, **17* more common in Africans, and **10* more common in Asians ([19]).

Individuals who are intermediate or poor metabolizers carry copies of reduced-activity or non-functioning *CYP2D6* alleles (Table 1). Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. In these populations, only half of *CYPD6* alleles are fully functional, with the reduced function **10* variant being very common (~40%, compared to ~2% in Caucasians) ([20]). As a result, Asians are more likely to be intermediate metabolizers than Caucasians ([19]). Similarly, in Africans and African Americans, only half of *CYPD6* alleles are functional. However, a wider range of variants account for the remaining alleles ([19, 21, 22]).

There is substantial variation in *CYP2D6* genotypes among different ethnic groups. The clinical consequences of such variation are not well characterized, and most studies that have attempted to measure the impact of genotype on clinical outcomes have been based on rather homogenous ethnic populations.

Approximately 6-10% of European Caucasians and their descendants are poor metabolizers, mainly due to the more prevalent nonfunctional **4* and **5* alleles ([19]). Notably, less than 40% are homozygous extensive metabolizers (carrying two copies of **1* allele), and more than 50% belong to a mixed group of intermediate metabolizers and heterozygote carriers of one functional allele in combination with either a deficient or non-functional allele ([15, 23-25]).

Poor metabolizers may be exposed to higher drug levels and be at an increased risk of side effects if CYP2D6 plays an important part in metabolizing and deactivating the drug. In contrast, if CYP2D6 is needed to metabolize a pro-drug in to active metabolites, these individuals may receive sub-therapeutic levels of the active form drug and benefit less from treatment.

CYP2D6 is the main enzyme involved in converting tamoxifen into its most potent anti-estrogenic metabolites, endoxifen and 4-hydroxytamoxifen. High plasma levels of endoxifen require the presence of fully functional *CYP2D6* alleles ([8, 26]). In poor metabolizers, endoxifen levels are decreased.

Some studies suggest that genetic polymorphisms of *CYP2D6* may be important predictors of the clinical outcomes of tamoxifen treatment for patients with metastatic breast cancer ([27]) and for patients with early breast cancer who receive tamoxifen as an adjuvant treatment following surgery ([28, 29]). A recent review addresses the conflicting evidence concerning *CYP2D6* status and tamoxifen treatment outcomes, and summarizes the current recommendations with regard to *CYP2D6* genotyping prior to tamoxifen treatment in the USA, UK, and Germany ([30]).

The inter-individual variability of tamoxifen metabolism and treatment outcomes is not fully accounted for by *CYP2D6* variation. Additional contributors may include genetic variation

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in other metabolic pathways and the sequestration of lipophilic tamoxifen metabolites into fat tissues ([8, 26]).

Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually a patient's result is reported as a diplotype, such as *CYP2D6 *1/*1* . A result for copy number is also important when interpreting results for this gene.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores (e.g., poor metabolizers have an activity score of 0) ([31]).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): "Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein."

Please review the complete therapeutic recommendations that are located here: ([1]).

Statement from the National Comprehensive Cancer Network (NCCN): "The cytochrome P-450 (CYP450) enzyme, CYP2D6, is involved in the conversion of tamoxifen to endoxifen. Over 100 allelic variants of *CYP2D6* have been reported in the literature. Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with one or two variant alleles with either reduced or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. A large retrospective study of 1325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen. However, the BIG 1-98 trial reported on the outcome based on *CYP2D6* genotype in a subset of postmenopausal patients with endocrine-responsive, early invasive breast cancer. The study found no correlation between *CYP2D6* allelic status and disease outcome or between *CYP2D6* allelic status and tamoxifen-related adverse effects. A genetic analysis of the ATAC trial found no association between *CYP2D6* genotype and clinical outcomes. Given the limited and conflicting evidence at this time, the NCCN Breast Cancer Panel does not recommend *CYP2D6* testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines."

Please review the complete therapeutic recommendations that are located here: ([2])

Excerpt from the American Society of Clinical Oncology (ASCO) 2010 guideline:

"Are There Specific Patient Populations That Derive Differing Degrees of Benefit From an AI Compared With Tamoxifen?

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Recommendation: Direct evidence from randomized trials does not identify a specific marker or clinical subset that predicted which adjuvant treatment strategy—tamoxifen, AI monotherapy, or sequential therapy—would maximally improve outcomes for a given patient. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment. The Update Committee recommends against using *CYP2D6* genotype to select adjuvant endocrine therapy. The Committee encouraged caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, fluoxetine; see Table 11 in the full guideline for a complete list of inhibitors) and tamoxifen because of the known drug-drug interactions.

Comment: The adjuvant endocrine therapy recommendations in this update are for all women, irrespective of any specific clinical subset or prognostic marker. AI therapy has not been evaluated in men, thus the continued recommendation that men with breast cancer receive adjuvant tamoxifen.

Data suggest that variability in tamoxifen metabolism affects the likelihood of cancer recurrence in patients treated with tamoxifen. Factors that contribute to this variability include concurrent use of other drugs that inhibit the CYP2D6 isoenzyme and pharmacogenetic variation (polymorphisms) in *CYP2D6* alleles. It is not yet known whether these variations account for differences in outcomes among patients treated with tamoxifen.

Available data on CYP2D6 pharmacogenetics are insufficient to recommend testing as a tool to determine an adjuvant endocrine strategy. Patients who clearly benefit from known CYP2D6 inhibitors might consider avoiding tamoxifen because of potential pharmacologic interactions. Conversely, patients who receive tamoxifen may prefer to avoid concurrent use of known CYP2D6 inhibitors if suitable alternatives are available."

Please review the complete therapeutic recommendations that are located here: ([3])

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): "For CYP2D6 poor metabolizers (PMs), defined as patients carrying two defective alleles […] With respect to tamoxifen, an increased risk for breast cancer relapse is present, and it is advised that an aromatase inhibitor be considered for treating postmenopausal women with breast cancer. Other recommendations included the selection of an alternative drug, therapeutic drug monitoring, increased alertness to adverse drug events and to reduced efficacy, and the recording of an electrocardiogram.

For CYP2D6 intermediate metabolizers (IMs), defined as patients carrying two decreased-activity alleles or one active/decreased-activity allele and one inactive allele […] For tamoxifen, the use of an aromatase inhibitor for treating postmenopausal women with breast cancer and the avoidance of concomitant use of a CYP2D6 inhibitor are advised. Other recommendations are comparable to the recommendations for PMs."

Please review the complete therapeutic recommendations that are located here: ([4]).

The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

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Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.4:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.4:c.320C>T NM_000106.4:c.886T>C	NP_000097.2:p.Thr107Ile NP_000097.2:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.4:c.985+39G>	Not applicable – variant occurs in a non-coding region	rs28371725

*In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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Tests in GTR by Condition

Tamoxifen response

Tests in GTR by Gene

CYP2D6 gene

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