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NLM Citation: Dean L. Tamoxifen Therapy and *CYP2D6* Genotype. 2014 Oct 7 [Updated 2019 May 1]. In: Pratt VM, McLeod HL, Rubinstein WS, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Tamoxifen Therapy and *CYP2D6* Genotype

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Created: October 7, 2014; Updated: May 1, 2019.

Introduction

Tamoxifen (brand name Nolvadex) is a selective estrogen receptor modulator (SERM) that is commonly used in both the treatment and prevention of breast cancer. When taken for 5 years, tamoxifen almost halves the rate of breast cancer recurrence in individuals who have had surgery for estrogen-receptor–positive (ER+) breast cancer.

Tamoxifen is the endocrine therapy of choice for treatment of premenopausal women with ER+ breast cancer, and an important alternative, or sequential treatment for postmenopausal women with ER+ breast cancer. In addition, tamoxifen is the only hormonal agent approved by the FDA for the prevention of premenopausal breast cancer in women who are at high risk, and the treatment of premenopausal invasive breast cancer and ductal carcinoma *in situ* (DCIS).

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs and is one of the main enzymes involved in converting tamoxifen into its major active metabolite, endoxifen. Genetic variation in the *CYP2D6* gene may lead to increased ("ultrarapid metabolizer"), decreased ("intermediate metabolizer"), or absent ("poor metabolizer") enzyme activity. Individuals who are intermediate or poor metabolizers may have reduced plasma concentrations of endoxifen and benefit less from tamoxifen therapy.

At this time, the FDA-approved drug label for tamoxifen does not discuss genetic testing for *CYP2D6* (Table 1) (1). The National Comprehensive Cancer Network (NCCN) Breast Cancer Panel does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy (Table 2), and this recommendation is consistent with the 2010 update of the American Society of Clinical Oncology (ASCO) Guidelines (the most recent update, 2014, does not discuss pharmacogenetic testing) (2, 3).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recently published updated guidelines for the dosing of tamoxifen based on CYP2D6 phenotype, with therapeutic recommendations for each metabolizer phenotype (Table 3). For CYP2D6 poor metabolizers, CPIC recommends using an alternative hormonal therapy, such as an aromatase inhibitor for postmenopausal women; or an aromatase inhibitor along with ovarian function suppression in premenopausal women. This recommendation is based on these approaches being superior to tamoxifen regardless of *CYP2D6* genotype, and the knowledge that CYP2D6 poor metabolizers who switched from tamoxifen to anastrozole do not have an increased risk of recurrence. The CPIC recommendation also states that higher dose tamoxifen (40 mg/day) can be considered if there are contraindications to aromatase inhibitor therapy; however, the increased endoxifen concentration among CYP2D6 poor metabolizers treated with a higher tamoxifen dose does not typically reach the level as in normal metabolizers (4).

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Recommendations from the Dutch Pharmacogenetics Working Group (DWPG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) also discuss using an alternative drug to tamoxifen in CYP2D6 poor metabolizers (Table 4) (5).

Table 1. The FDA (2018) Drug Label for Tamoxifen: Metabolism

Recommendations
Tamoxifen is a substrate of CYP3A, CYP2C9 and CYP2D6, and an inhibitor of P-glycoprotein.

This FDA table is adapted from (1)

Table 2. NCCN (2018). *CYP2D6* Phenotypes and Therapeutic Recommendations for Tamoxifen

Genetic test	Recommendation
CYP2D6	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. When prescribing a selective serotonin reuptake inhibitor (SSRI), it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

This National Comprehensive Cancer Network (NCCN) table is adapted from (2). ASCO - American Society of Clinical Oncology

Table 3. CPIC (2018). Dosing Recommendations for Tamoxifen based on CYP2D6 Phenotype

Phenotype		Implications	Therapeutic recommendation[b]	Classification of recommendation[a]
Metabolizer status	Activity score			
CYP2D6 ultrarapid metabolizer	>2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 normal metabolizer	1.5–2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (no *10 allele present)[b]	Lower endoxifen concentrations compared with normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared with normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for post-menopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Avoid CYP2D6 strong to weak inhibitors.	Optional[b]

Table 3. continued from previous page.

Phenotype		Implications	Therapeutic recommendation[b]	Classification of recommendation[a]
Metabolizer status	Activity score			
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (*10 allele present)[b]	Lower endoxifen concentrations compared with normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared with normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for post-menopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Avoid CYP2D6 strong to weak inhibitors.	Moderate[b]
CYP2D6 intermediate metabolizer	0.5	Lower endoxifen concentrations compared with normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared with normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for post-menopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Avoid CYP2D6 strong to weak inhibitors.	Moderate

Table 3. continued from previous page.

Phenotype		Implications	Therapeutic recommendation[b]	Classification of recommendation[a]
Metabolizer status	Activity score			
CYP2D6 poor metabolizer	0	Lower endoxifen concentrations compared with normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared with normal metabolizers.	Recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype and based on knowledge that CYP2D6 poor metabolizers switched from tamoxifen to anastrozole do not have an increased risk of recurrence. Note, higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy.	Strong

Activity score – for a description of how scores are calculated, please see the "Genetic Testing" section below.
[a]Rating scheme described in the CPIC Supplement (4).
[b] CPIC has generally classified individuals with an activity score of 1 as a "normal metabolizer." However, in the case of tamoxifen, prescribing recommendations for those with an activity score (AS) of 1.0 are allele dependent, based on the presence of the *10 allele. Those individuals with an AS of 1.0 on the basis of a *10 allele are provided a "moderate" recommendation. In contrast, prescribing recommendations for those with an activity score of one based on the presence of CYP2D6 alleles other than *10 are graded as "optional" because the recommendations are primarily extrapolated from evidence generated from *10 individuals (i.e., limited data for clinical outcomes and pharmacokinetics for this group).
This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (4)

Table 4. DPWG (2015). *CYP2D6* Phenotypes and Therapeutic Recommendations for Tamoxifen

CYP2D6 phenotype	Recommendation
Ultrarapid metabolizer	No action is needed for this gene-drug interaction.
Intermediate metabolizer	1 Select an alternative or measure the endoxifen concentration and increase the dose if necessary by a factor of 1.5–2. Aromatase inhibitors are a possible alternative for post-menopausal women. 2. If tamoxifen is selected: avoid co-medication with CYP2D6 inhibitors such as paroxetine and fluoxetine.
Poor metabolizer	Select an alternative or increase the dose to 40 mg/day and monitor the endoxifen concentration. Studies have demonstrated that poor metabolizers can achieve an adequate endoxifen concentration when the dose is increased to 40-60 mg/day. Aromatase inhibitors are a possible alternative for post-menopausal women.

This Dutch Pharmacogenetics Working Group (DWPG) table is adapted from (5).

Drug: Tamoxifen

Tamoxifen is a SERM that is used in both the treatment and prevention of breast cancer.

For treatment, tamoxifen is used in both men and women with metastatic breast cancer, particularly among individuals with ER+ tumors. Tamoxifen is also used as adjuvant treatment among women who have undergone surgery and radiation, as this almost halves the rate of reoccurrence of breast cancer in woman with ER+ tumors. Tamoxifen reduces the risk of progression to invasive breast cancer in women with DCIS.

For prevention, tamoxifen has been shown to reduce the occurrence of contralateral breast cancer. And in women who do not have breast cancer, tamoxifen has been shown to reduce the incidence of breast cancer in women at high risk. Risk factors for breast cancer include increasing age, Caucasian race, the number of first-degree relatives with breast cancer, obesity (for postmenopausal women), and an increased exposure to estrogen (e.g., early menarche, later age of first pregnancy or no children, absence of breastfeeding, later menopause) (1, 4).

Tamoxifen acts on the estrogen receptor 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 proliferate.

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 around 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 (6-8).

The antiestrogenic properties of tamoxifen are expected to affect fetal reproductive functions and increase the risk of fetal harm. Therefore, women may be advised not to become pregnant while taking tamoxifen or within 2 months of discontinuing tamoxifen, and to use barrier or nonhormonal contraception (1).

Tamoxifen also increases the risk of thromboembolic events, such as deep vein thrombosis and pulmonary embolism. The risk of tamoxifen-associated thromboembolic events is further increased when tamoxifen is coadministered with chemotherapy. The drug label for tamoxifen states that the risks and benefits of tamoxifen therapy should be carefully considered in women with a history of thromboembolic events (1).

Some studies suggest that clinicians should consider screening breast cancer individuals before prescribing adjuvant tamoxifen to identify women who are at risk of thrombotic embolic disease as a result of having the Factor V Leiden (p.R506Q) variant, or a variant in the estrogen receptor gene (*ESR1*) (9-12). However, a small substudy (N=81) of the national surgical adjuvant breast and bowel project breast cancer prevention (NSABP P-1) trial found no benefit in screening women for Factor V Leiden or *F2* prothrombin (c.*97G>A) thrombophilia to identify women who may not be appropriate for tamoxifen therapy due to an increased risk for thromboembolic side effects (13).

Tamoxifen is inactive, and its active metabolite endoxifen (4-hydroxy-N-desmethyl tamoxifen) is thought to mediate most of its therapeutic effects. Both endoxifen and another metabolite, 4-hydroxytamoxifen, have around a 100-fold higher affinity for the ER compared with tamoxifen, but endoxifen is thought to be the major metabolite because plasma levels of endoxifen tend to be several-fold higher.

The mechanism of action of tamoxifen involves 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 (14).

The tamoxifen metabolite, norendoxifen, has also been found to act as an aromatase inhibitor *in vitro* (albeit at high concentrations). Aromatase inhibitors are a class of drug used to treat breast cancer and gynecomastia. They decrease the amount of estrogen available by inhibiting the conversion of steroids such as androgen into estradiol (15).

The pharmacokinetics of tamoxifen are complex, involving many enzymes (including several cytochrome P450 enzymes) and transporter proteins (including ATP-binding cassette transporters (ABC) transporters). However, CYP2D6 is thought to be important because it mediates the formation of endoxifen via the conversion of the inactive primary metabolite N-desmethyl tamoxifen.

The response to tamoxifen therapy (i.e., clinical efficacy and side effects) varies widely between individuals. This is due to a number of variables, including drug interactions (e.g., coadministration of a drug that inhibits or induces *CYP2D6*) and interindividual differences in drug metabolism driven by polymorphic germline *CYP2D6* variant alleles (16-18).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse superfamily of enzymes that form the major system for metabolizing or detoxifying lipids, hormones, toxins, and drugs. The *CYP450* genes are often very polymorphic and can result in reduced, absent, or increased enzyme activity.

The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. And, CYP2D6 is the main enzyme that catalyzes the rate-limiting step in the metabolism of tamoxifen to its potent metabolite, endoxifen. Other CYP enzymes involved in tamoxifen metabolism include CYP2C9, CYP2C19, CYP2B6, CYP3A4, and CYP3A5.

CYP2D6 Alleles

The CYP2D6 enzyme catalyzes the main pathway for converting tamoxifen into its most potent metabolite, endoxifen, and together with other CYP enzymes, catalyzes the formation of 4-hydroxytamoxifen. Therefore, genetic variations in the *CYP2D6* gene can influence tamoxifen metabolism (19).

The *CYP2D6* gene is highly polymorphic, as over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 5).

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (e.g., CYP2D6 *4/*4). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (e.g., CYP2D6 poor metabolizer). However, the activity score system is not standardized across clinical laboratories or *CYP2D6* genotyping platforms.

Table 5. Activity Status of Selected *CYP2D6* Alleles

Allele type	*CYP2D6* alleles
Normal function	**1, *2, *33, *35*
Decreased function	**9, *10, *14B, *17, *29, *41*
No function	**3, *4, *5, *6, *7, *8, *11, *12, *13, *15, *19, *20, *21, *36, *38, *40, *42*

For a comprehensive list of *CYP2D6* alleles, please see PharmVar.

*CYP2D6*1* is assigned when no variant is detected and is assumed to have normal enzyme activity (CYP2D6 normal metabolizer phenotype). The *CYP2D6 *2*, **33*, and **35* alleles are also considered to have near-normal activity.

Alleles that encode an enzyme with decreased activity include **10*, **17*, and **41*, and alleles that encode a nonfunctioning enzyme include **3*, **4*, **5*, and **6*. There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **6*, and **41* being more common in Caucasians, **10* more common in Asians, and **17* more common in Africans (20).

Additional variant alleles and their multi-ethnic population frequencies have previously been reported (21). Moreover, given the structural variability of the *CYP2D6* region at chromosome 22q13.2, full gene deletion and duplication alleles, as well as complex tandem alleles with *CYP2D6*'s pseudogene, *CYP2D7*, also occur in some individuals and populations (22).

CYP2D6 Phenotypes

In the US and globally, most individuals, around 70-80%, are classified as "normal metabolizers" (also referred to as "extensive metabolizers"). They either have 2 normal function alleles (e.g., *1/*1) or one normal and one decreased function allele (e.g., *1/*41).

Individuals who have one normal function and one no function allele (e.g., *1/*4) or 2 decreased function alleles (e.g., *41/*41) are also categorized as "normal metabolizers" by recent nomenclature guidelines (23), but have also been categorized as "intermediate metabolizers" (24).

Individuals who have more than 2 normal function copies of the *CYP2D6* gene are classified as "ultrarapid metabolizers," which accounts for 1–10% of Caucasian individuals. For individuals of North African, Ethiopian and Saudi ancestry, the frequency is 16–28% (Table 6) (4).

Individuals who do not have any fully functional alleles are either intermediate metabolizers (one decreased function and one no function allele, e.g., *4/*41) or poor metabolizers (2 no function alleles e.g., *4/*4).

Approximately 6–10% of European Caucasians are poor metabolizers, mainly due to the prevalent nonfunctional **3*, **4* and **5* alleles. Compared with Europeans, individuals of Asian descent are likelier to be intermediate metabolizers due to high population frequencies of the *CYP2D6*10* decreased function allele. Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. Similarly, Africans and African Americans are likelier than Europeans to be intermediate metabolizers because of the prevalence of a wide range of decreased function variants. (20, 25-27)

Table 6. CPIC (2018). Assignment of likely CYP2D6 Phenotype based on Genotype

Phenotype[a]		Genotype	Examples of *CYP2D6* diplotypes[b]
Metabolizer status	Activity score		
CYP2D6 ultrarapid metabolizer	>2.0	An individual with duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN[c]
CYP2D6 normal metabolizer	1.5–2.0	An individual with 2 normal function alleles or one normal function and one decreased function allele	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0	An individual with 2 decreased function alleles or one normal function and one no function allele. *An activity score (AS) of 1.0 is associated with decreased tamoxifen metabolism to endoxifen compared with an AS of 1.5 or 2.*	*1/*4, *1/*5, *41/*41
CYP2D6 intermediate metabolizer	0.5	An individual with one decreased function and one no function allele	*4/*10, *4/*41, *5/*9
CYP2D6 poor metabolizer	0	An individual with only no functional alleles	*3/*4, *4/*4, *5/*5, *5/*6

[a] See the CYP2D6 frequency table 1 in (4) for race-specific allele and phenotype frequencies.
[b]For a complete list of CYP2D6 diplotypes and resulting phenotypes, see the CYP2D6 genotype to phenotype table in (4). Note that genotypes with an activity score of 1 are classified as normal metabolizers in the online CPIC CYP2D6 genotype to phenotype table (4).
[c]Where xN represents the number of CYP2D6 gene copies. For individuals with CYP2D6 duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes.
[d]Individuals with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. A group of CYP2D6 experts are currently working to standardize the CYP2D6 genotype to phenotype translation system. CPIC will update the CPIC website accordingly (CYP2D6 genotype to phenotype table).
This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (4).

Linking Gene Variation with Treatment Response

Genetic variation in the *CYP2D6* gene is associated with variation in plasma concentrations of endoxifen and is thought to account for up to approximately 50% of the variability in endoxifen concentrations (28).

- Individuals who are CYP2D6 poor metabolizers (activity score 0) have lower plasma endoxifen concentrations compared with normal metabolizers (with an activity score of 1.5-2.0).
- Individuals with reduced CYP2D6 activity (activity score 0.5-1) have lower plasma endoxifen concentrations compared with normal metabolizers (with an activity score of 1.5-2.0) (4).

However, while it is clear that tamoxifen biotransformation to endoxifen is highly dependent on CYP2D6 activity, the association between tamoxifen efficacy and *CYP2D6* genotype or endoxifen concentration is less clear. Because the role of *CYP2D6* in tamoxifen response has yet to be fully determined, *CYP2D6* testing remains controversial (29-40).

Some studies conclude that the *CYP2D6* genotype has minimal or no effect on tamoxifen therapy outcomes (41-45). A 2019 prospective clinical study (n=667) found no association between *CYP2D6* genotype or endoxifen concentration and clinical outcome in individuals with early-stage breast cancer receiving adjuvant tamoxifen (46).

In contrast, other studies suggest that *CYP2D6* variant alleles may be important predictors of tamoxifen clinical outcomes (28, 40, 47-52). In particular, in Asians, studies of populations with a high frequency of the decreased function *CYP2D6*10* allele (e.g., Han Chinese), found that individuals with *CYP2D6**10/*10 received less benefit from tamoxifen and poorer disease-free survival (53-55).

However, the high degree of inter-individual variability of tamoxifen metabolism and treatment outcomes is not fully accounted for by *CYP2D6* variation. Additional contributors may include genetic variation in other metabolic pathways and the sequestration of lipophilic tamoxifen metabolites into fat tissues (17, 30, 48, 56).

Genetic Testing

The NIH Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for tamoxifen response and for the *CYP2D6* gene.

The *CYP2D6* gene is a particularly complex gene that is difficult to genotype because of the large number of variants and the presence of gene deletions, duplications, multiplications, pseudogenes, and tandem alleles. The complexity of genetic variation complicates the correct determination of *CYP2D6* diplotype.

Genetic testing is currently available for approximately 30 variant *CYP2D6* alleles (over 100 alleles have been identified so far). Test results are typically reported as a diplotype, such as *CYP2D6 *1/*1*. However, it is important to note that the number of variants tested can vary among laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories (4).

A result for copy number, if available, is also important when interpreting CYP2D6 genotyping results. Gene duplications and multiplications are denoted by "xN" e.g., *CYP2D6**1xN with xN representing the number of *CYP2D6* gene copies.

If the test results include an interpretation of the individual's predicted metabolizer phenotype, such as "*CYP2D6* *1/*1, normal metabolizer", this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for no function, 0.5 for decreased function, and 1.0 for each copy of a normal function allele, Table 6).

The CYP2D6 phenotype can be defined by the sum of the 2 activity scores, which is usually in the range of 0–3.0:

- An ultrarapid metabolizer has an activity score greater than 2
- A normal metabolizer phenotype has an activity score of 1.5–2.0
- A normal metabolizer or intermediate metabolizer has a score of 1.0
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0 (4)

A standardized *CYP2D6* genotype to phenotype assignment logic is currently being developed by an international working group of CYP2D6 experts and both the CPIC and DPWG.

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.

2018 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).

2018 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 Breast International Group (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. When prescribing a selective serotonin reuptake inhibitor (SSRI), it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

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

[1] 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. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations where necessary, other author insertions are shown in square brackets.

2018 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Table 3 summarizes the therapeutic recommendations for tamoxifen prescribing based on the CYP2D6 phenotype. Based on current evidence, CYP2D6 UMs and NMs are expected to achieve therapeutic endoxifen concentrations after administration of tamoxifen and should receive the recommended standard of care doses of tamoxifen. CYP2D6 PMs and IMs (including patients with an AS of 1.0, see Supplement) are expected to have lower endoxifen concentrations compared to NMs and have a higher risk of breast cancer recurrence, and worse event-free survival compared to NMs. For CYP2D6 PMs, a "strong" therapeutic recommendation was provided to recommend alternative hormonal therapy such as an aromatase inhibitor (AI) for postmenopausal women or AI along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype and based on knowledge that CYP2D6 PMs patients who switch from tamoxifen to anastrozole do not exhibit an increased risk of recurrence. Given that escalation of tamoxifen dose from 20–40 mg/day in CYP2D6 PM significantly increases endoxifen concentrations (but not to concentrations achieved in CYP2D6 NMs), the use of an AI (± ovarian function suppression) is recommended in this setting. Tamoxifen 40 mg/day can be considered for CYP2D6 PM if there are contraindications to AI use. There are no clinical data that toremifene, another selective estrogen receptor modulator that also undergoes bioactivation, should be substituted for tamoxifen based on *CYP2D6* genotype.

For CYP2D6 IMs and *CYP2D6*10/*10* or *CYP2D6*10*/decreased function allele, a "moderate" recommendation was made to consider use of an alternative hormonal therapy (i.e., aromatase inhibitor) for postmenopausal women or AI plus ovarian function suppression in premenopausal women is recommended. In CYP2D6 IMs, if AIs are contraindicated, consideration can be given to the use of a higher FDA-approved dose of tamoxifen (40 mg/day), which is known to result in significantly higher endoxifen concentrations without an increase in toxicity. Based on extrapolation from evidence in *10 individuals, a similar recommendation applies to individuals who carry other decreased function alleles resulting in an AS of 1.0 but with an "optional" recommendation, given the paucity of data for this group.

In general, prolonged overlap of tamoxifen with strong and moderate CYP2D6 inhibitors should be avoided in tamoxifen-treated patients, whereas weak inhibitors are also contraindicated in CYP2D6 IMs.

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

2015 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 IM: TAMOXIFEN

This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness.

Recommendation:

1 select an alternative or measure the endoxifen concentration and increase the dose if

necessary by a factor of 1.5-2

Aromatase inhibitors are a possible alternative for post-menopausal women.

2. if TAMOXIFEN is selected: avoid co-medication with CYP2D6 inhibitors such as paroxetine

and fluoxetine

CYP2D6 PM: TAMOXIFEN

This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness.

Recommendation:

1 select an alternative or increase the dose to 40 mg/day and monitor the endoxifen

concentration

Studies have demonstrated that PM can achieve an adequate endoxifen concentration when the dose is increased to 40-60 mg/day.

Aromatase inhibitors are a possible alternative for post-menopausal women.

CYP2D6 UM: TAMOXIFEN

No action is needed for this gene-drug interaction.

As a result of the genetic variation, the plasma concentration of the active metabolites 4- hydroxytamoxifen and endoxifen can increase. However, there is no evidence that this results in an increase in the side effects.

Background information

Mechanism: The main conversion route of tamoxifen is by CYP3A4/5 to the relatively inactive N-desmethyltamoxifen. This is converted by CYP2D6 to endoxifen (4-hydroxy-N-desmethyltamoxifen), which has an anti-oestrogenic effect that is 30-100x stronger than tamoxifen. Tamoxifen is further converted by CYP2D6 to the active metabolite 4-hydroxytamoxifen. This metabolite is as potent as endoxifen, but occurs at much lower concentrations. CYP3A4/5 converts 4-hydroxytamoxifen further to endoxifen.

Please review the complete therapeutic recommendations that are located here: (5).

2010 Excerpt from the American Society of Clinical Oncology (ASCO) guideline[2]

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

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

[2] The 2014 ASCO practice guideline focused update does not address pharmacogenetic testing (JCO July 20, 2014 vol. 32 no. 212255-2269).

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).

Nomenclature

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names / major SNP	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Not applicable - variant occurs in a non-coding region and results in a splicing defect	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707delT Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.5:c.320C>T NM_000106.6:c.886C>T	NP_000097.3:p.Thr107Ile NP_000097.3:p.Arg296Cys	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.5:c.985+39 G>A	Not applicable – variant occurs in a non-coding region and is linked to aberrant splicing	rs28371725

SNP= Single Nucleotide Polymorphism
Note: In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.
Note: The variant 1846G>A often occurs with both 4180G>C and 100C>T; and 2988G>A occurs with 2850C>T.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (57).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

Acknowledgments

The author would like to thank Deirdre Cronin-Fenton, PhD, Associate Professor, Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; Inge Holsappel, Pharmacist at the Royal Dutch Pharmacists Association (KNMP), The Hague, Netherlands, for reviewing the information regarding the guidelines of the Dutch Pharmacogenetics Working Group (DPWG); Stuart Scott, Assistant Professor of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; and Werner Schroth, PhD, Institute of Clinical Pharmacology, Stuttgart, Germany, for reviewing this summary.

First edition:

The author would like to thank Harold Burstein, Associate Professor of Medicine, Harvard Medical School, Boston, MA, USA; and Hiltrud Brauch, Deputy Head of the Fischer-Bosch-Institute of Clinical Pharmacology (IKP) and Head of the Breast Cancer Susceptibility and Pharmacogenomics IKP Department, Stuttgart, Germany for reviewing this summary.

Version History

To view an earlier version of this summary, please see 2014 and 2016 editions.

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