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NLM Citation: Dean L. Atomoxetine Therapy and *CYP2D6* Genotype. 2015 Sep 10. In: Pratt V, McLeod H, Rubinstein W, 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/

Atomoxetine Therapy and *CYP2D6* Genotype

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Created: September 10, 2015.

Introduction

Atomoxetine was the first non-stimulant drug to be used in the treatment of attention-deficit hyperactivity disorder (ADHD). Atomoxetine is a selective noradrenaline reuptake inhibitor, and is part of a treatment plan for ADHD that may include other measures such as psychological, educational, and social support.

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including atomoxetine. Individuals who carry two nonfunctional copies of the *CYP2D6* gene are known as poor metabolizers and have higher plasma concentrations of atomoxetine compared with individuals who have two copies of normal activity alleles.

The FDA states that the dose of atomoxetine may need to be adjusted in patients known to be *CYP2D6* poor metabolizers (1). A guideline from The Dutch Pharmacogenetics Working Group includes the recommendation that poor metabolizers can be given the standard dose of atomoxetine, but physicians should be aware of adverse drug events. They also state that for individuals who have more than two functional gene copies of *CYP2D6*, i.e., individuals with so-called ultrarapid metabolizer status, physicians should either be alert to reduced efficacy with the standard dose of atomoxetine, or they should prescribe an alternative drug, such as methylphenidate or clonidine (Table 1) (2).

Table 1. *CYP2D6* phenotypes and the therapeutic recommendations for atomoxetine therapy

Phenotype	Genotype	Recommendations for atomoxetine therapy
Ultrarapid metabolizer	Three or more functional gene copies	Insufficient data to allow calculation of dose adjustment. Be alert to reduced efficacy or select alternative drug (e.g., methylphenidate, clonidine).
Extensive metabolizer	Two functional gene copies	No recommendations.
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or one decreased activity allele and one inactive allele	No recommendations.
Poor metabolizer	Two inactive alleles	Standard dose. Dose increase probably not necessary; be alert to adverse drug events.

The level of evidence for the therapeutic (dose) recommendations is 3/4 (“moderate quality”) for poor metabolizers, and 4/4 (“good quality”) for intermediate metabolizers. There are no data for ultrarapid metabolizers. The 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 (2).

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Table 2. Activity status of selected *CYP2D6* alleles

Allele type	Alleles
Normal function	**1, *2, *33, *35*
Decreased function	**9, *10, *17, *29, *41*
No function	**3, *4, *5, *6, *7, *8*

For a more detailed list of CYP2D6 alleles, please see (3).

Drug: Atomoxetine

Atomoxetine is used in the treatment of attention-deficit hyperactivity disorder (ADHD), which is one of the most common childhood disorders. Symptoms include difficulty focusing and paying attention, difficulty controlling behavior, and hyperactivity. Symptoms may continue in to adulthood. Atomoxetine may be used alone or in combination with behavioral treatment, as an adjunct to psychological, educational, social, and other remedial measures.

Atomoxetine was the first non-stimulant drug to be approved for use in ADHD. Atomoxetine is a selective norepinephrine reuptake inhibitor and it is thought to exert its therapeutic effect by increasing the concentration of synaptic norepinephrine. Because it is a non-stimulant, atomoxetine has the advantages of having less potential for abuse, and it is not scheduled as a controlled substance (4).

Atomoxetine is primarily metabolized through the CYP2D6 enzymatic pathway. The main metabolite, 4-hydroxyatomoxetine, is equipotent to atomoxetine as an inhibitor of the norepinephrine transport, but is found at much lower levels in the plasma (5). In individuals who lack CYP2D6 activity (poor metabolizers), 4-hydroxyatomoxetine is formed by other CYP enzymes, but at a much slower rate (1).

CYP2C19, along other CYP enzymes, forms the metabolite N-Desmethylatomoxetine. Although this metabolite has substantially less pharmacological activity compared to atomoxetine, and is present at much lower plasma concentrations, one study found that genetic polymorphisms of the *CYP2C*19 gene also influenced the pharmacokinetics of atomoxetine (6).

Atomoxetine has a wide therapeutic window, but the risk of adverse effects may be increased by the presence of *CYP2D6* genetic variants (7-9). Common adverse effects of atomoxetine therapy include weight loss, headache, and irritability. Psychiatric side effects may also occur; these include anxiety, depression, and the development of suicidal thoughts.

The FDA-approved drug label for atomoxetine includes a boxed warning and additional warning statements regarding the increased risk of suicidal thinking in children and adolescents treated with atomoxetine. The warning includes: “Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Results from atomoxetine clinical studies with over 2200 child or teenage ADHD patients suggest that some children and teenagers may have a higher chance of having suicidal thoughts or actions. Although no suicides occurred in these studies, 4 out of every 1000 patients developed suicidal thoughts.”(1)

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 no decreased or increased activity impacting drug metabolism.

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 (10).

*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*, among others, are also considered to have normal activity (11, 12).

Individuals who have multiple functional copies of the *CYP2D6* gene are known as "ultrarapid metabolizers" (UM) (Table 1). Because each *CYP2D6* allele contributes to the metabolism and inactivation of atomoxetine, atomoxetine may have decreased efficacy in UM individuals (2). The UM phenotype is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese (13).

The Dutch Pharmacogenetics Working Group recommendations state that for ultrarapid metabolizers, there are insufficient data to allow for an adjusted dose to be calculated, and therefore, the physician should be alert to reduced efficacy of a standard dose of atomoxetine, or prescribe an alternative drug, such as methylphenidate or clonidine.

The most common non-functional and reduced function *CYP2D6* alleles include *CYP2D6*3*, **4*, **5,* and **6* (2, 10, 11, 13-16) and *CYP2D6*10*, **17* and **41*) (4, 12, 17-19) (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 Caucasians, **17* more common in Africans, and **10* more common in Asians (20).

Individuals who are intermediate or poor metabolizers carry copies of reduced-activity or non-functioning *CYP2D6* alleles (see Table 1 and 2). In these individuals, the metabolic capacity of CYP2D6 is decreased which may result in higher levels of atomoxetine. The FDA-approved drug label for atomoxetine states that poor metabolizers of CYP2D6 have a higher exposure to atomoxetine (10-fold higher area under the cover and a 5 fold-higher peak concentration) compared to extensive metabolizers who received the same dose. The label also states that in individuals who are known to be poor metabolizers, the dose of atomoxetine should be adjusted—treatment should be initiated at 0.5mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated (see Therapeutic Recommendations) (1). However, the Dutch Pharmacogenetics Working Group recommendations state that for poor metabolizers, "a standard dose of atomoxetine is recommended. An increase in dose is probably not necessary, but the physician should be alert to adverse drug events. (2)"

One small study of 100 children with ADHD receiving atomoxetine therapy found that the presence of at least one nonfunctional or reduced function *CYP2D6* allele led to an increase in adverse effects, such as gastrointestinal problems and sleep disorders, and a late response to treatment (longer than 9 weeks). The study concluded that *CYP2D6* genotyping before atomoxetine treatment may be beneficial in preventing overdosing or early cessation of treatment because of initial adverse effects (21). However, another study found genotyping to be unnecessary, because during the routine clinical management of ADHD, investigators were able to adjust the dose of atomoxetine in children and adolescents who had normal or reduced CYP2D6 activity—so that their treatment was comparable in safety and efficacy—without knowing what their *CYP2D6* genotype was (22).

Poor metabolizers are commonly found in European Caucasians and their descendants (6-10%). The most common alleles in this population are the functional *CYP2D6*1* and **2* alleles (70%); the remaining alleles include *CYP2D6*10* and **41* conveying decreased function and the nonfunctional *CYP2D6*3, *4, *5* and **6* variants that largely account for the poor metabolizer phenotype in these populations (12). About 2-5% of African Americans are poor metabolizers, due to the presence of *CYP2D6*4 and *5* and a number of other nonfunctional alleles (1, 11, 15, 18, 20).

Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. In these populations, 40-60% of individuals carry *CYP2D6*10, a* decreased function variant (only ~2-3% of Caucasians have this allele) (23, 24). As a result, Asians are more likely to have decreased CYP2D6 activity compared to Caucasians (12). Neither the FDA-approved drug label of the Dutch Pharmacogenetic Working Group gives dosing recommendations for subjects with decreased function alleles, often classified as intermediate metabolizers.

Genetic Testing

CYP2D6 genetic testing is available. Usually a patient's result is reported as a diplotype, such as *CYP2D6*1/*1* or **2/*4*. A result for copy number is also important when interpreting results for this gene. However, it needs to be noted that the number of variants tested varies substantially among laboratories and there is no standardized way to report results (25).

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:

- An extensive (normal) metabolizer phenotype has an activity score of 1 to 2
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0
- An ultrarapid metabolizer has an activity score greater than 2 (3, 19, 26).

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):

Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs[2] — In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, atomoxetine should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, atomoxetine should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. **Please review the complete therapeutic recommendations that are located here:** (1)

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): For individuals who are poor metabolizers, a standard dose of atomoxetine is recommended. An increase in dose is probably not necessary, but the physician should be alert to adverse drug events. For individuals who are ultrarapid metabolizers, there are insufficient data to allow for an adjusted dose to be calculated. The physician should be alert to reduced efficacy of a standard dose of atomoxetine, or prescribe an alternative drug, such as methylphenidate or clonidine.

[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 labelled all formulations containing the generic drug.

[2] PMs: Poor metabolizers

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

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*	CYP2D6,DEL	NC_000022.10:g.(42534124_42531353)_(42521970_42519196)del	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>A	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

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

Acknowledgments

The author would like to thank Andrea Gaedigk, MS, PhD, Children's Mercy Kansas City, Director, Pharmacogenetics Core Laboratory, Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Kansas City, Professor, School of Medicine, University of Missouri-Kansas City; and Mia Wadelius, Senior Lecturer, Uppsala University; for reviewing this summary

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