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Atomoxetine Therapy and *CYP2D6* Genotype

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Introduction

Atomoxetine (brand name Strattera) is a non-stimulant drug used in the treatment of attention-deficit hyperactivity disorder (ADHD). It is a selective noradrenaline reuptake inhibitor (SNRI) and is approved for children aged 6 and older, adolescents, and adults.

Atomoxetine is part of a treatment plan for ADHD that may include other measures such as psychological, educational, and social support.

Because atomoxetine is not a stimulant or a controlled substance it may be used in individuals with tics or other side effects associated with stimulants, and in individuals who have a substance abuse problem (or have a family member with a substance abuse problem).

The most common side effects associated with atomoxetine therapy include weight loss, abdominal pain, headache, dizziness, fatigue, and irritability. In addition, atomoxetine has a boxed warning on the increased risk of suicidal ideation in children and adolescents treated with atomoxetine.

The CYP2D6 enzyme is involved in the metabolism of atomoxetine (and a quarter of all prescribed drugs). Individuals who lack CYP2D6 activity ("poor metabolizers") will have increased levels of atomoxetine and an increased risk of side effects compared with CYP2D6 normal metabolizers. Approximately 7% of Caucasians are CYP2D6 poor metabolizers.

The drug label states that for known CYP2D6 poor metabolizers, the initial dose should only be increased to the usual target dose if symptoms fail to improve after 4 weeks and the initial dose is well tolerated (1). Atomoxetine dosing should be adjusted for individuals who are CYP2D6 poor metabolizers, individuals who are taking a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, and quinidine), and individuals with moderate or severe hepatic impairment. However, different authorities have different dosing recommendations.

The Royal Dutch Association for the Advancement of Pharmacy (KNMP) Dutch Pharmacogenetics Working Group (DPWG) provides dosing recommendations for poor, intermediate and ultrarapid metabolizers. For poor metabolizers, DPWG recommends starting with the standard initial dose and to consult a care provider if side effects occur. If the medicine is effective, but side effects occur, DPWG recommends reducing the dose and monitoring efficacy (2).

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The Clinical Pharmacogenetics Implementation Consortium (CPIC) also provide recommendations for different CYP2D6 metabolizer phenotypes. For CYP2D6 poor metabolizers, CPIC recommends that if no clinical response is observed after 2 weeks of atomoxetine therapy, then a plasma concentration exposure check be used with an individual's *CYP2D6* genotype to help clinicians guide dose selection and titration (3).

Table 1. FDA Atomoxetine Dosing in Specific Populations: CYP2D6 Poor Metabolizers (2020)

Individual	Initial daily dose	Target total daily dose	Maximum total daily dose
Child or adolescent, up to 70 kg	0.5 mg/kg	1.2 mg/kg	1.4 mg/kg
Child or adolescent, up to 70 kg, known to be CYP2D6 PM	0.5 mg/kg	Only increase 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	Not provided
Child or adolescent over 70 kg, or adults	40 mg	80 mg	100 mg
Child or adolescent over 70 kg, or adults, known to be CYP2D6 poor metabolizer	40 mg	Only increase to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated	Not provided

This FDA table is adapted from (1).

Table 2. DPWG Atomoxetine Dosing based on *CYP2D6* Phenotype (2016)

CYP2D6 metabolizer phenotype	Dosing recommendations
Ultrarapid	Be extra alert to reduced efficacy of the treatment Advise the individual to contact their doctor in the event of inadequate effect An alternative can be selected as a precaution. Clonidine is not metabolized by CYP2D6
Intermediate	In the event of side effects occurring and/or a response later than 9 weeks: reduce the dose and check whether the effect is conserved The plasma concentration of atomoxetine is a factor of 2-3 times higher for intermediate metabolizer than for normal metabolizer at the same dose
Poor	Start with the normal initial dose, bearing in mind that an increase in this dose probably will not be required Advise the individual to seek contact if side effects occur (such as decreased appetite, vomiting, abdominal pain, constipation, insomnia, early waking, drowsiness, irritability, pupil dilation and itching) If the medicine is effective, but side effects occur reduce the dose and check whether the effect is conserved The plasma concentration of atomoxetine is a factor of 8–11 times higher for poor metabolizer than for normal metabolizer at the same dose

This DPWG table is adapted from (2).

Table 3. CPIC Dosing Recommendations for Atomoxetine based on *CYP2D6* Genotype for Children (2019)

CYP2D6 metabolizer phenotype	Activity score	Implication	Therapeutic recommendation	Classification of Recommendation[a]
Ultrarapid	>2.25	Based on very limited data available for CYP2D6 ultrarapid metabolizers taking atomoxetine, it is unlikely ultrarapid metabolizers would achieve adequate serum concentrations for the intended effect at standard dosing	Initiate with a dose of 0.5 mg/kg/day and increase to 1.2 mg/kg/day after 3 days If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered) If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml[b,c]	Moderate
Normal	1.25–2.25	Normal metabolizers of atomoxetine have a lower likelihood of response as compared with poor metabolizers. This is associated with increased discontinuation due to lack of efficacy as compared with poor metabolizers	Initiate with a dose of 0.5 mg/kg and increase to 1.2 mg/kg/day after 3 days If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered) If <200 ng/ml, consider a proportional [b,c] increase in dose to approach 400 ng/ml	Moderate
Intermediate	>0–<1.25	Decreased metabolism of atomoxetine and higher atomoxetine concentrations as compared with normal metabolizers. Intermediate metabolizers may be at an increased risk of discontinuation as compared with poor metabolizers	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2-4 h after dosing. If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml.[b,c] If unacceptable side effects are present at any time, consider a reduction in dose	Moderate

Table 3. continued from previous page.

CYP2D6 metabolizer phenotype	Activity score	Implication	Therapeutic recommendation	Classification of Recommendation[a]
Poor	0	Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared with non-poor metabolizers. This may increase the occurrence of side effects, but also a greater improvement of ADHD symptoms as compared with non-poor metabolizers in those who tolerate treatment Poor metabolizer status is associated with lower final dose requirements as compared with non-poor metabolizers	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 4 hours after dosing If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml[b,c] If unacceptable side effects are present at any time, consider a reduction in dose	Strong

AS: Activity Score
[a]Rating scheme described in the Supplement.
[b]Therapeutic range of 200 to 1000 ng/ml has been proposed.
[c]Limited data are available regarding the relationship between atomoxetine plasma concentrations and clinical response. Available information suggests that clinical response is greater in poor metabolizers (PMs) compared with non-PMs and may be related to the higher plasma concentrations 1 to 1.5 hours after dosing in PMs compared with non-PMs administered a similar dose. Furthermore, modest improvement in response, defined as reduction in ADHD rating scale (ADHD-RS), is observed at peak concentrations greater than 400 ng/ml.
This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (3).

Table 4. CPIC Dosing Recommendations for Atomoxetine based on *CYP2D6* Genotype for Adults (2019)

CYP2D6 metabolizer phenotype	Activity score	Implication	Therapeutic recommendation	Classification of Recommendation[a]
Ultrarapid	>2.25	Based on very limited data available for CYP2D6 ultrarapid metabolizers taking atomoxetine, it is unlikely ultrarapid metabolizers would achieve adequate serum concentrations for the intended effect at standard dosing	Initiate with a dose of 40 mg/day and increase to 80 mg/day after 3 days If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered) If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml[b,c] Dosages greater than 100 mg/day may be needed to achieve target concentrations[d]	Moderate

Table 4. continued from previous page.

CYP2D6 metabolizer phenotype	Activity score	Implication	Therapeutic recommendation	Classification of Recommendation[a]
Normal	1.25–2.25	Normal metabolizers of atomoxetine have a lower likelihood of response as compared with poor metabolizers. This is associated with increased discontinuation due to lack of efficacy as compared with poor metabolizers	Initiate with a dose of 40 mg/day and increase to 80 mg/day after 3 days If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered) If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml[b,c] Dosages greater than 100 mg/day may be needed to achieve target concentrations[d]	Moderate
Intermediate	>0–<1.25	Decreased metabolism of atomoxetine higher atomoxetine concentrations as compared with normal metabolizers. Intermediate metabolizers may be at an increased risk of discontinuation as compared with poor metabolizers	Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day If response is inadequate after 2 weeks consider obtaining a plasma concentration 2–4 h after dosing If concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml[b,c] If unacceptable side effects are present at any time, consider a reduction in dose	Moderate

Table 4. continued from previous page.

CYP2D6 metabolizer phenotype	Activity score	Implication	Therapeutic recommendation	Classification of Recommendation[a]
Poor	0	Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared with non-poor metabolizers. This may increase the occurrence of treatment-emergent side effects, but also a greater improvement of ADHD symptoms as compared with non-poor metabolizers in those who tolerate treatment. Poor metabolizer status is associated with lower final dose requirements as compared with non-poor metabolizers	Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day If response is inadequate after 2 weeks consider obtaining a plasma concentration 2–4 h after dosing. If concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml[b,c] If unacceptable side effects are present at any time, consider a reduction in dose	Moderate

AS: Activity score.
[a] Rating scheme described in the Supplement.
[b]Therapeutic range of 200 to 1000 ng/ml has been proposed (27).
[c]Limited data are available regarding the relationship between atomoxetine plasma concentrations and clinical response. Available information suggests that clinical response is greater in poor metabolizers (PMs) compared with non-PMs and may be related to the higher plasma concentrations 1 to 1.5 hours after dosing in PMs compared with non-PMs administered a similar dose. Furthermore, modest improvement in response, defined as reduction in ADHD rating scale (ADHD-RS), is observed at peak concentrations greater than 400 ng/ml.
[d]Doses above 120 mg/day have not been evaluated.
This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (3).

Drug: Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) that is used to treat ADHD. Atomoxetine is thought to exert its therapeutic effect by increasing the concentration of synaptic norepinephrine. Unlike several other ADHD medications, atomoxetine is not a stimulant and is not a controlled substance. Therefore, atomoxetine may be used as an alternative to stimulants for individuals who have a substance abuse problem (or have a family member with a substance abuse problem), tics, or other side effects with stimulants (4).

ADHD is one of the most common neurodevelopmental childhood disorders. In the US, approximately 9.4% of children (6.1 million) have been diagnosed with ADHD, according to a 2016 parental survey (5).

The symptoms of ADHD include difficulty focusing and paying attention, difficulty controlling behavior, and hyperactivity. Symptoms may continue into adulthood. Atomoxetine may be used alone or in combination with behavioral treatment, as an adjunct to psychological, educational, social, and other remedial measures (6).

Atomoxetine is primarily metabolized via the CYP2D6 enzyme. The main metabolite, 4-hydroxyatomoxetine, is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter; however, this metabolite is rapidly glucuronidated and is found at much lower concentrations in the plasma (7). In individuals who lack CYP2D6 activity, 4-hydroxyatomoxetine is formed by other CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4), but at a much slower rate (1).

CYP2C19, along with other CYP enzymes, forms the metabolite N-desmethylatomoxetine. Although this metabolite has substantially less pharmacological activity compared with atomoxetine, and is present at much lower plasma concentrations, one study found that genetic variants in the *CYP2C19* gene also influenced the pharmacokinetics of atomoxetine (7, 8).

Atomoxetine has a wide therapeutic window, but the risk of adverse effects may be increased among individuals who have variant *CYP2D6* alleles (9-11). Common adverse effects of atomoxetine therapy include a lack of response, weight loss, headache, and irritability. Psychiatric side effects may also occur; these include anxiety, depression, and the FDA-approved drug label for atomoxetine includes a boxed warning on the increased risk of suicidal ideation in children and adolescents treated with atomoxetine. Atomoxetine has not been adequately studied in pregnant women, therefore, pregnant or nursing women should not use atomoxetine unless the potential benefit justifies the potential risk to fetus or infant.

Unlike the stimulant drugs used to treat ADHD, atomoxetine has a delayed onset, and this should be taken into account during dose titration. An initial response may appear after one week, but typically, it takes 2–4 weeks for the full effect of atomoxetine on symptoms to be observed (3, 12).

Factors to be considered in determining the dose of atomoxetine include *CYP2D6* genetic variation (see below) and the child's weight. For children and adolescents who weigh less than or exactly 70 kg, the recommended starting dose is 0.5 mg/kg, which is then titrated upwards after a minimum of 3 days, to a target dose of 1.2 mg/kg. The maximum daily dose should not exceed 1.4 mg/kg or 100 mg (whichever is less). For adults, children and adolescents who weigh more than 70 kg, the recommended starting dose is 40mg, the target dose is 80mg, and the maximum daily dose is 100mg (Table 1).

The drug label states the dosage of atomoxetine should be adjusted in individuals who are receiving drugs that inhibit CYP2C26 (e.g., paroxetine, fluoxetine, quinidine); or in individuals who lack CYP2D6 activity because they have 2 non-functional copies of the *CYP2D6* gene ("CYP2D6 poor metabolizers"). For these individuals, the initial doses are the same (0.5mg/Kg or 40mg, based on body weight), but the dose should only be increased to the standard target dose if the initial dose is well tolerated and symptoms fail to improve after 4 weeks (1).

The Cytochrome P450 Superfamily

The cytochrome P450 superfamily (CYP450) is a large and diverse group 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.

Gene: *CYP2D6*

CYP2D6 is involved in the hepatic metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. Importantly, CYP2D6 is also the main enzyme that metabolizes atomoxetine.

The *CYP2D6* gene on chromosome 22q13.2 is highly polymorphic. Over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is annotated with either normal, decreased or absent enzyme function (when functional status is known) (Table 5). The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (e.g., *CYP2D6* *4/*4), which subsequently is used to assign a phenotype (e.g., CYP2D6 poor metabolizer).

The *CYP2D6*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype. Other *CYP2D6* alleles considered to have normal activity include *2, *33, and *35.

Alleles that encode an enzyme with decreased activity include **10*, **17*, and **41*, and alleles that encode a non-functional enzyme include **3*, **4*, **5*, and **6*. There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **10* more common in Asians, and **17* more common in Africans (13).

Table 5. Activity Status of selected *CYP2D6* Alleles

Effect on enzyme activity	*CYP2D6* alleles
Normal function	**1, *2, *33, *35, *45, *46*
Reduced function	**9, *10, *17, *29, *41*
No function	**3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *19, *20, *21, *36, *38, *40, *42*

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

The *CYP2D6*10* variant is one of the most well studied decreased function alleles, in part due to its impact on atomoxetine therapy, and the breast cancer drug, tamoxifen. Individuals who have one or 2 copies of *CYP2D6*10* have lower than expected CYP2D6 activity and higher plasma levels of atomoxetine (and tamoxifen). This has led to CPIC making special dosing recommendations for individuals with diplotypes that contain *CYP2D6**10 for both atomoxetine (3) and tamoxifen (14). In addition, a *CYP2D6* Genotype-to-Phenotype Working Group recently revised the activity score of *CYP2D6**10 from 0.5 to 0.25 (15-18).

CYP2D6 Phenotype

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 more than 2 normal function copies of the *CYP2D6* gene are classified as "ultrarapid metabolizers," which accounts for 1 to 10% of individuals (1).

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). The translation of *CYP2D6* diplotype to phenotype based on the activity score system was recently reported by the CPIC and DPWG (Table 6) (18).

Approximately 6–10% of European Caucasians and their descendants are poor metabolizers, mainly due to the prevalence of no function **4* and **5* alleles. Compared to Europeans, individuals of Asian descent are more likely to be intermediate metabolizers due to the prevalence of decreased function alleles, most notably *10. Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. Similarly, Africans and African Americans are more likely to be intermediate metabolizers than Europeans because of the prevalence of a wide range of decreased function variants (13, 19-21).

Table 6. CPIC Assignment of likely *CYP2D6* Phenotype based on Diplotype (2019)

Likely CYP2D6 metabolizer phenotype[b]	Activity score	Genotype[a]	Examples of *CYP2D6* diplotype
Ultrarapid	>2.25	An individual carrying duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN[c]
Normal	1.25 to 2.25	An individual carrying 2 normal function alleles or one normal function and one decreased function allele	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10
Intermediate	>0 to <1.25	An individual carrying one decreased function and one no function allele	*1/*4, *1/*5, *41/*41, *4/*10, *4/*41, *5/*9

Table 6. continued from previous page.

Likely CYP2D6 metabolizer phenotype[b]	Activity score	Genotype[a]	Examples of *CYP2D6* diplotype
Poor	0	An individual carrying only no functional alleles	*3/*4, *4/*4, *5/*5, *5/*6

[a] Assignment of allele function and citations for allele function can be found on PharmGKB: Gene Reference Materials for CYP2D6 (*CYP2D6* Allele Definition Table and *CYP2D6* Allele Functionality Table). For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* Genotype to Phenotype Table. Note that genotypes with an activity score of one are classified as normal metabolizers in the online *CYP2D6* genotype to phenotype table (22).
[b] See the *CYP2D6* Frequency Table for race-specific allele and phenotype frequencies (22) or see Gaedigk *et al* (23).
[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 diplotype into phenotype.
This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (3).

Linking *CYP2D6* Genetic Variation with the Risk of Side Effects and Treatment Response

Genetic variation in the *CYP2D6* gene has a major effect on atomoxetine pharmacokinetics. According to the FDA-approved drug label, for a given dose of atomoxetine, CYP2D6 poor metabolizers have a 10-fold higher area under the curve (AUC; a measure of exposure to a drug) and a 5-fold higher peak concentration compared with CYP2D6 normal metabolizers.

The increased exposure to atomoxetine in CYP2D6 poor metabolizers may lead to a higher rate of some adverse effects of atomoxetine therapy. The drug label cites a clinical trial where the frequency of different side effects is often higher in poor metabolizers compared with normal metabolizers (1, 10). However, some studies also report that the higher exposure to atomoxetine in CYP2D6 poor metabolizers may be linked to a greater improvement of ADHD symptoms (9, 24).

Several studies report that atomoxetine dosing based on *CYP2D6* genotype may lead to improved therapeutic outcomes (7, 25-28). Accordingly, the drug label provides dose adjustments for CYP2D6 poor metabolizers and states that laboratory tests are available to identify CYP2D6 poor metabolizers (1).

The drug label is silent on dose adjustments for individuals who have increased CYP2D6 activity ("CYP2D6 ultrarapid metabolizers"). These individuals may have a poor response to standard doses of atomoxetine because of lower plasma concentrations (1).

Genetic Testing

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

CYP2D6 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, and pseudogenes. The complexity of genetic variation complicates making a correct determination of *CYP2D6* genotype.

Targeted genotyping typically includes up to 30 variant *CYP2D6* alleles (over 100 alleles have been identified so far). Test results are 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 (14).

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 may 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 is defined by the sum of the 2 activity scores, which is usually in the range of 0 to 3.0:

- An ultrarapid metabolizer has an activity score greater than 2.25
- A normal metabolizer phenotype has an activity score of 1.25 to 2.25
- An intermediate metabolizer has an activity score of >0 to 1.25
- A poor metabolizer has an activity score of 0 (14)

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.

2020 Statement from the US Food and Drug Administration (FDA)

2.4 Dosing in Specific Populations

Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs — 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 capsules 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 capsules 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.

[...]

5.12 Laboratory Tests

CYP2D6 metabolism — Poor metabolizers (PMs) of CYP2D6 have a 10 fold higher AUC and a 5 fold higher peak concentration to a given dose of atomoxetine hydrochloride compared with normal metabolizers. Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of atomoxetine hydrochloride.

6.1 Clinical Trials Experience

[…]

[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, shown in square brackets, where necessary.

The following adverse reactions occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 normal metabolizer (EM) patients: insomnia (11% of PMs, 6% of EMs); weight decreased (7% of PMs, 4% of EMs); constipation (7% of PMs,4% of EMs); depression (7% of PMs,4% of EMs); tremor(5% of PMs,1% of EMs); excoriation

(4% of PMs, 2% of EMs); middle insomnia (3% of PMs, 1% of EMs); conjunctivitis (3% of PMs, 1% of EMs); syncope (3% of PMs, 1% of EMs); early morning awakening (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs); sedation (4% of PMs, 2% of EMs).

7.2 Effect of CYP2D6 Inhibitors on Atomoxetine

In normal metabolizers, inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6 to 8 fold and $C_{ss, max}$ is about 3 to 4 fold greater than atomoxetine alone.

In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

12.3 Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is

eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10 fold higher AUCs, 5 fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity (normal metabolizers). Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

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

2016 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 Poor Metabolizer

The genetic variation increases the plasma concentration of atomoxetine and thereby the risk of side effects.

Recommendation:

1. start with the normal initial dose, bearing in mind that an increase in this dose probably will not be required
2. advise the patient to seek contact if side effects occur (such as decreased appetite, vomiting, abdominal pain, constipation, insomnia, early waking, drowsiness, irritability, pupil dilation and itching)
3. if the medicine is effective, but side effects occur: reduce the dose and check whether the effect is conserved

   The plasma concentration of atomoxetine is a factor of 8-11 times higher for PM than for EM at the same dose.

CYP2D6 Intermediate Metabolizer

The genetic variation increases the plasma concentration of atomoxetine and can thereby reduce the dose requirement.

Recommendation:

1 in the event of side effects occurring and/or a response later than 9 weeks: reduce the dose and check whether the effect is conserved

  The plasma concentration of atomoxetine is a factor of 2-3 times higher for IM than for EM at the same dose.

CYP2D6 Ultrarapid Metabolizer

The genetic variation results in an increased conversion of atomoxetine to the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration. As the plasma concentration of the active ingredients decreases as a result, this gene variation can result in reduced efficacy.

Recommendation:

1. be extra alert to reduced efficacy of the treatment
2. advise the patient to contact their doctor in the event of inadequate effect
3. an alternative can be selected as a precaution. Clonidine is not metabolised by CYP2D6.

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

2019 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Tables 3 and 4 summarize the therapeutic recommendations for atomoxetine based on CYP2D6 phenotype in children and adults, respectively. Although not routinely ordered, patients may benefit from a single time point atomoxetine exposure check to guide therapy. Exposure check concentrations between 200 – 1000 ng/mL are generally considered to be "therapeutic", however for individuals with comorbidities a higher exposure target may be warranted, as was done in a study evaluating children with both ADHD and Oppositional Defiant Disorder. We propose that the plasma concentration exposure check be used with an individual's CYP2D6 genotype to help clinicians guide dose selection and titration as discussed below. Based on pharmacokinetic knowledge that CYP2D6 metabolism phenotypes influence atomoxetine peak concentration and half-life, Tables 3 and 4 propose that prescribers consider measuring peak concentrations 1 to 2 hours after dosing in known CYP2D6 UMs, NMs and IMs with high activity (activity score 1.0 without a CYP2D6*10 allele), 2 to 4 hours after dosing in CYP2D6 IMs with low activity (activity score 0.5) and in individuals with AS of 1 when the CYP2D6*10 allele is present, and 4 hours after dosing in PMs.

Very limited data exist for CYP2D6 UMs taking atomoxetine, but it is unlikely these individuals would achieve adequate serum concentrations with standard atomoxetine dosing. As discussed above, CYP2D6 non-PMs have a lower likelihood of treatment response as compared to CYP2D6 PMs. Thus, for CYP2D6 UMs and NMs, recommendations are to initiate standard atomoxetine dosing (see Table 3 and 4 for pediatric and adult dosing, respectively) and if no clinical response is observed after two weeks, consider obtaining a peak plasma concentration one to two hours after dose administration. If the peak concentration is less than 200 ng/ml, consider increasing the dose proportionally to approach 400 ng/ml. It is important to note that doses above 120 mg have not been extensively evaluated, although they may be necessary to achieve target concentrations in some patients. While CYP2D6 NMs with activity scores of 1 (without the presence of the CYP2D6*10 allele) have higher atomoxetine plasma concentrations compared to NMs with an AS of 2, the clinical significance of this difference is unclear. Thus, CYP2D6 NMs with an AS of 1 (without the presence of the CYP2D6*10 allele) should be treated similarly to CYP2D6 NMs with AS of 2.

CYP2D6 PMs, IMs, and NMs with an AS of 1 in the presence of the CYP2D6*10 allele have significantly decreased metabolism of atomoxetine, which may increase the risk of side effects. However, these individuals may also have greater improvement of ADHD symptoms and lower dose requirements as compared to non-PMs. Therefore, the recommendation for these phenotype groups are to initiate with a standard starting dose (see Table 3 and 4 for pediatric and adult dosing, respectively) and if there is an inadequate trajectory of symptom improvement after 2 weeks (in the absence of side effects), consider obtaining a plasma concentration two-four hours after dosing. If response is inadequate and side effects are not present, consider adjusting the dose proportionally to approach 400 ng/ml.

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

Nomenclature

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names / major variant	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A 4180G>C	NM_000106.5:c.506-1G>A NM_000106.5:c.1457G>C	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 delT Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least 2 functional variants: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.5:c.320C>T NM_000106.5:c.886T>C	NP_000097.3:p.Thr107Ile NP_000097.3:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.5:c.985+39G>A	Not applicable – variant occurs in a non-coding region	rs28371725

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 the variant 988G>A occurs with 2850C>T. (Cys296Arg).
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (29).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for *CYP2D6* alleles and other cytochrome P450 genes is available from the Pharmacogene Variation (PharmVar) Consortium.

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References

1. ATOMOXETINE capsule [package insert]. Pennsylvania, US: Teva; 2020. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4953df7b-ccdb-452c-8699-5fd7259609b4#LINK_560bd16e-0053-4dde-8d6b-542d8c428561
2. Royal Dutch Pharmacists Association (KNMP). Dutch Pharmacogenetics Working Group (DPWG). Pharmacogenetic Guidelines [Internet]. Netherlands. Atomoxetine – CYP2D6 [Cited Dec 2019]. Available from: http://kennisbank.knmp.nl [Access is restricted to KNMP membership.]
3. Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019. doi: 10.1002/cpt.1409. Epub 2019/02/26. PubMed PMID: 30801677.
4. Marian S McDonagh P, Kim Peterson, MS, Sujata Thakurta, MPA:HA, and Allison Low, BA. Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder. Drug Class Reviews. 2011(Final Update 4 Report).
5. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. J Clin Child Adolesc Psychol. 2018;47(2):199-212. Epub 2018/01/25. doi: 10.1080/15374416.2017.1417860. PubMed PMID: 29363986; PubMed Central PMCID: PMCPMC5834391.
6. Faraone SV. Report from the 4th international meeting of the attention deficit hyperactivity disorder molecular genetics network. Am J Med Genet B Neuropsychiatr Genet. 2003;121B(1):55–9. doi: 10.1002/ajmg.b.20047. Epub 2003/08/05. PubMed PMID: 12898576.
7. Yu G, Li GF, Markowitz JS. Atomoxetine: A Review of Its Pharmacokinetics and Pharmacogenomics Relative to Drug Disposition. J Child Adolesc Psychopharmacol. 2016;26(4):314-26. doi: 10.1089/cap.2015.0137. PubMed PMID: 26859445; PubMed Central PMCID: PMCPMC4876529.
8. Choi CI, Bae JW, Lee YJ, Lee HI, Jang CG, Lee SY. Effects of CYP2C19 genetic polymorphisms on atomoxetine pharmacokinetics. Journal of clinical psychopharmacology. 2014;34(1):139–42. doi: 10.1097/JCP.0b013e3182a608a2. PubMed PMID: 24346747.
9. Michelson D, Read HA, Ruff DD, Witcher J, Zhang S, McCracken J. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry. 2007;46(2):242–51. doi: 10.1097/01.chi.0000246056.83791.b6. PubMed PMID: 17242628.
10. Fijal BA, Guo Y, Li SG, Ahl J, Goto T, Tanaka Y, et al. CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial. Journal of clinical pharmacology. 2015;55(10):1167–74. doi: 10.1002/jcph.530. PubMed PMID: 25919121.
11. Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. Journal of neural transmission. 2015;122(1):5–28. doi: 10.1007/s00702-014-1300-5. PubMed PMID: 25200585.
12. Savill NC, Buitelaar JK, Anand E, Day KA, Treuer T, Upadhyaya HP, et al. The efficacy of atomoxetine for the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a comprehensive review of over a decade of clinical research. CNS Drugs. 2015;29(2):131–51. doi: 10.1007/s40263-014-0224-9. Epub 2015/02/24. PubMed PMID: 25698145.

13. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics. 2002;3(2):229–43. doi: 10.1517/14622416.3.2.229. Epub 2002/04/26. PubMed PMID: 11972444.
14. Goetz MP, Sangkuhl K, Guchelaar HJ, Schwab M, Province M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. Clin Pharmacol Ther. 2018;103(5):770-7. Epub 2018/02/01. doi: 10.1002/cpt.1007. PubMed PMID: 29385237; PubMed Central PMCID: PMCPMC5931215.
15. Cui YM, Teng CH, Pan AX, Yuen E, Yeo KP, Zhou Y, et al. Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele. Br J Clin Pharmacol. 2007;64(4):445-9. Epub 2007/07/06. doi: 10.1111/j.1365-2125.2007.02912.x. PubMed PMID: 17610534; PubMed Central PMCID: PMCPMC2048549.
16. Matsui A, Azuma J, Witcher JW, Long AJ, Sauer JM, Smith BP, et al. Pharmacokinetics, safety, and tolerability of atomoxetine and effect of CYP2D6*10/*10 genotype in healthy Japanese men. Journal of clinical pharmacology. 2012;52(3):388–403. doi: 10.1177/0091270011398657. Epub 2011/05/06. PubMed PMID: 21543662.
17. Byeon JY, Kim YH, Na HS, Jang JH, Kim SH, Lee YJ, et al. Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites. Arch Pharm Res. 2015;38(11):2083–91. doi: 10.1007/s12272-015-0646-z. Epub 2015/08/10. PubMed PMID: 26254792.
18. Caudle KE, Sangkuhl K, Whirl-Carrillo M, Swen JJ, Haidar CE, Klein TE, et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. Clin Transl Sci. 2020;13(1):116-24. Epub 2019/10/28. doi: 10.1111/cts.12692. PubMed PMID: 31647186; PubMed Central PMCID: PMCPMC6951851.
19. Gaedigk A, Gotschall RR, Forbes NS, Simon SD, Kearns GL, Leeder JS. Optimization of cytochrome P4502D6 (CYP2D6) phenotype assignment using a genotyping algorithm based on allele frequency data. Pharmacogenetics. 1999;9(6):669–82. PubMed PMID: 10634130.
20. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenet Genomics. 2007;17(2):93–101. doi: 10.1097/01.fpc.0000239974.69464.f2. Epub 2007/02/16. PubMed PMID: 17301689.
21. Yokota H, Tamura S, Furuya H, Kimura S, Watanabe M, Kanazawa I, et al. Evidence for a new variant CYP2D6 allele CYP2D6J in a Japanese population associated with lower in vivo rates of sparteine metabolism. Pharmacogenetics. 1993;3(5):256–63. Epub 1993/10/01. PubMed PMID: 8287064.
22. PharmGKB. Gene Reference Materials for CYP2D6 [Cited Available from: https://www.pharmgkb.org/page/cyp2d6RefMaterials
23. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med. 2017;19(1):69-76. Epub 2016/07/09. doi: 10.1038/gim.2016.80. PubMed PMID: 27388693; PubMed Central PMCID: PMCPMC5292679.
24. Trzepacz PT, Williams DW, Feldman PD, Wrishko RE, Witcher JW, Buitelaar JK. CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD. Eur Neuropsychopharmacol. 2008;18(2):79–86. doi: 10.1016/j.euroneuro.2007.06.002. Epub 2007/08/19. PubMed PMID: 17698328.
25. Brown JT, Bishop JR. Atomoxetine pharmacogenetics: associations with pharmacokinetics, treatment response and tolerability. Pharmacogenomics. 2015;16(13):1513–20. doi: 10.2217/PGS.15.93. PubMed PMID: 26314574.
26. Olson MC, Maciel A, Gariepy JF, Cullors A, Saldivar JS, Taylor D, et al. Clinical Impact of Pharmacogenetic-Guided Treatment for Patients Exhibiting Neuropsychiatric Disorders: A Randomized Controlled Trial. Prim Care Companion CNS Disord. 2017;19(2) doi: 10.4088/PCC.16m02036. PubMed PMID: 28314093.
27. Dinh JC, Pearce RE, Van Haandel L, Gaedigk A, Leeder JS. Characterization of Atomoxetine Biotransformation and Implications for Development of PBPK Models for Dose Individualization in Children. Drug Metab Dispos. 2016;44(7):1070-9. doi: 10.1124/dmd.116.069518. PubMed PMID: 27052878; PubMed Central PMCID: PMCPMC4931890.

28. Brown JT, Abdel-Rahman SM, van Haandel L, Gaedigk A, Lin YS, Leeder JS. Single dose, CYP2D6 genotype-stratified pharmacokinetic study of atomoxetine in children with ADHD. Clin Pharmacol Ther. 2016;99(6):642-50. doi: 10.1002/cpt.319. PubMed PMID: 26660002; PubMed Central PMCID: PMCPMC4862932.
29. Kalman LV, Agundez J, Appell ML, Black JL, Bell GC, Boukouvala S, et al. Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. Clin Pharmacol Ther. 2016;99(2):172-85. Epub 2015/10/20. doi: 10.1002/cpt.280. PubMed PMID: 26479518; PubMed Central PMCID: PMCPMC4724253.

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